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Modelling Cross-disciplinary Integration in FDA Multidisciplinary and Interdisciplinary Reviews for New Drug Products: A Phenomenological Descriptive Comparative Case Study

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MODELLING CROSS-DISCIPLINARY INTEGRATION IN FDA MULTI-DISCIPLINARY AND INTEGRATED REVIEWS FOR NEW DRUG PRODUCTS: A PHENOMENOLOGICAL DESCRIPTIVE COMPARATIVE CASE STUDY

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ABSTRACT

Cross-disciplinary integration is a key feature of interdisciplinary research and the collaborative form is often a desired outcome of Team Science endeavors. In 2019 the FDA began rolling out a new interdisciplinary approach to their cross-disciplinary assessment of marketing applications, with the key feature being integrated, collaborative review documents (Woodcock et al., 2020). FDA's assessment of new drug products to allow them to enter the marketplace is a critical translational activity to protect the US public's health that requires team-based integration and transparency (Woodcock, 2018). And, while increased cross-disciplinary integration through enhanced collaboration and communication is sought through this intervention, FDA and in fact the Science-of-Team-Science, arguably lack examples of a rigorous approach to the objective evaluation of integration.

Through a phenomenological descriptive comparative case study we identify, model, and analyze multiple instances of collaborative integration occurring in different FDA review teams using either their new interdisciplinary review or their traditional multidisciplinary review processes to evaluate the impact of the intervention to promote integration (Bugin, 2021). This study applies a framework of cross-disciplinary integration from the philosophy of Team Science using an input-process-output (IPO) model (O'Rourke et al., 2016). This framework is coupled with the FDA's structured benefit-risk framework for assessing the approvability of new drug products, and used to guide data collection and analysis, and the interpretation of integration (FDA, 2018).

Integration is observed in both review processes, confirming that FDA team-based new drug product marketing application reviews are indeed demonstrating collaborative cross-

disciplinary research activities per the cross-disciplinary integration framework. Furthermore, findings indicate that the cross-disciplinary integration framework and associated IPO model can be applied in the evaluation of collaborative cross-disciplinary integration, and that the method is sensitive enough to enable analytical comparisons. Through these comparisons, the study importantly demonstrates that the FDA's most recent improvement to its assessment of new drug product marketing applications, a new interdisciplinary review process with the use of more integrated documentation, is more integrative in comparison to the traditional multidisciplinary review process as illustrated in multiple integrative analyses and visualizations.

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Chapter 1 Introduction

Overview

The United States Food and Drug Administration (FDA) is charged with protecting and promoting the public health of the American people. The Center for Drug Evaluation and Research (CDER) within FDA does its part to fulfill this mission by ensuring the American public has access to safe and effective new drug products (FDA, 2015). In pursuit of this mission, CDER operates a regulatory program known as the New Drugs Regulatory Program that oversees the clinical research of investigational new drugs, assesses the safety and effectiveness of new drugs before they are legally marketed, and monitors their use in the marketplace to ensure the expected benefits of approved new drug products continue to outweigh the potential risks of their use in the United States (US). The assessment of safety and effectiveness of new drug products is therefore a critical function performed by FDA's CDER and necessary in the US healthcare system.

CDER's assessment of safety and effectiveness for new drug products is changing. In 2018, the Center Director for CDER, Dr. Janet Woodcock, stated the case for having more integration in the assessment of new drug products when she described upcoming changes to the New Drugs Regulatory Program:

> "Setting standards for approval and assessing innovative new drugs requires large and well-coordinated teams of highly trained professionals with many different types of expertise. CDER's Office of New Drugs (OND) has a staff of more than 1,000 individuals who work together in many ways. New drug development and approval also requires coordination across many offices within CDER, including the Office of

> Translational Sciences (OTS), the Office of Surveillance and Epidemiology (OSE) and the Office of Pharmaceutical Quality (OPQ). A central component of our proposed changes involves stronger integration of our talented staff so they can better work together – within and across offices, a concept we refer to as "integrated assessment". Previously, CDER reviewers would seek consults from specialists in other scientific disciplines (as issues were identified in the course of review). For greater collaboration, a cross-disciplinary team will be assigned to work on a new drug application at the outset" (Woodcock, 2018).

This vision marks an important milestone in the evolution of the assessment of new drug product applications, one that began more than a decade and a half ago surrounding public drug safety issues related to the withdrawal of Vioxx, a pain medicine for the treatment of osteoarthritis, in 2004. As a result of those issues, numerous internal organizational and cultural concerns related to the assessment of new drugs at the FDA were raised that led to the development of the 21st Century Review Initiative and efforts to improve benefit-risk determinations in the assessments of new drug products. The 21st Century Review Initiative, originally launched in 2008, included a set of processes and standards to address both quality and performance of "drug reviews that involve multiple offices" and promote a more organized, integrated, and accountable review of new drugs (FDA, 2018e). This approach is described extensively in the 21st Century Desk Reference Guide for New Drug Marketing Application Reviews (FDA, 2014).

The 21st Century Review processes and standards contributes to a highly coordinated team-based approach to conducting the review of new drugs. In this approach individual team members work independently but following a pre-determined process to review the new drug

product application then produce documentation of their assessments, known as a review. These individual reviews are often voluminous in size and contain redundant information across the review documents (e.g., repeated summaries of the same study, descriptions of similar issues) because each review document must stand alone.

At the end of this process a single individual, usually from the clinical discipline, known as the cross-disciplinary team lead would integrate the assessments from each individual document into a summary review document. This summary review document includes a completed benefit-risk framework (BRF) and a recommendation for the overall decision (or action to be taken) for the new drug product. This approach could most accurately be described as a multi-disciplinary approach to conducting the review of a new drug product application with a single integrator recommending a decision at the end. While integration is most certainly occurring in this approach, it is unclear if this integration is effectively cross-disciplinary or collaborative. Furthermore, this intensive, multi-disciplinary documentation and review process often obscures the underlying basis for FDA's decisions because information and insights would be spread out across the individual assessments and review documents of each individual team member in those separate, often voluminous review documents (McDonagh et al., 2013). The 2018 vision from Dr. Woodcock intends to enhance the key components of this now traditional approach to the review of new drug products and is part of FDA's continued commitment to the improvement of the new drug product review processes and the communication of its decisions (FDA, 2019h).

As mentioned earlier, the assessment of a new drug's benefits and risks, and the decision that the benefits outweigh those risks became the center of controversy following the very public postmarket safety issues related to the Vioxx drug withdrawal and other notable new drug

withdrawals in the early 2000s. In fact, many external stakeholders to the FDA believed drug withdrawals were a key indicator of FDA's failure to adequately weigh benefits and risks due to the occurrence of several withdrawals at that time (Institute of Medicine, 2006). The three most notable withdrawals in the early 2000s were Vioxx as has already been mentioned, Bextra, and Baycol/Lipobay. These three withdrawals led to a perceived erosion of confidence in FDA's ability to adequately assess drug safety and protect public health and made the agency's assessment of new drug risk the focus of major concern for the pubic and legislators (Committee on finance United States senate, 2004; Wysowski & Swartz, 2005).

As the most controversial and public of these withdrawals, Vioxx serves as a useful reference case for the greater focus on the benefit-risk assessment of new drug products. Vioxx was approved in 1999 for the reduction of signs and symptoms of osteoarthritis. Following several clinical studies examining gastrointestinal complications of the drug, additional cardiovascular adverse events emerged that changed the safety profile of the drug such that it was ultimately withdrawn voluntarily from the market in 2004 by its manufacturer, Merck (Wysowski & Swartz, 2005). This particular series of events would lead to a congressional hearing, an FDA commissioned report from the Institute of Medicine (IOM), and important legislative changes to FDA's authority in the Food and Drug Administration Amendments Act of 2007 (Committee on finance United States senate, 2004; FDA, 2007b; Institute of Medicine, 2006). In the IOM's report, IOM pointed out challenges at the FDA related to its safety culture, the science of safety, communications, and operations and management. One key takeaway for the FDA following the events that led up to the Vioxx drug safety crisis and the IOM's commissioned report was that FDA needed to develop and incorporate more quantitative or

semi-quantitative tools to aid the assessment of benefit and risk, which would help with the science of its decision-making, internal alignment, and communications (FDA, 2007b).

And so, beginning in 2013, the FDA began the implementation of a more structured approach to the benefit-risk assessment by implementing the structured Benefit-Risk Framework (BRF) (FDA, 2013). The BRF was a tool intended to facilitate a more balanced and consistent consideration of factors associated with benefits and risk during the new drug product review process and ensure transparency through improved communication of the FDA's decisions and decision-making process. The BRF adds structure to the determination of benefits and risks. And, builds on the origins of the review process for a new drug product to find a product "safe" and "effective".

Effectiveness is a regulatory definition that refers to the regulatory determination that is made through an assessment of clinical efficacy and other data of the potential benefits to patients associated with a new drug's use (FDA, 1998). This assessment is an important precursor to determining that the potential benefits to patients outweigh the known and possible risks to patients, otherwise considered the "safety" of a new drug (FDA, 2013). In totality, this assessment of benefits, and that benefits outweigh risks, otherwise known as the benefit-risk assessment, is the core decision to be made by FDA when approving a new drug product. The BRF therefore would facilitate this process in the FDA new drug product review by providing the FDA with a consistent, structured, semi-qualitative approach to focus the assessment process and analyze the benefits and risks in the final benefit-risk determination.

The structured approach to decision-making that the BRF provides also facilitates clarity and consistency in the way FDA communicates its decisions by intending to more clearly articulate the FDA's assessment of evidence and uncertainty related to its decision. These

decisions are made by a signatory, a leader from the clinical discipline, who has the authority, delegated from the Secretary of Health and Human Services, for approving a new drug product (FDA, 2018d).

Initially, CDER implemented the BRF through its incorporation into the clinical discipline's review and the final summary review of the application authored by the signatory authority of the FDA team. Other members of the FDA team would still complete their own disciplinary reviews and document these reviews in individual review documents. This multi-disciplinary approach to conducting the benefit-risk assessment and determiniation, with distal integration led by a single discipline, had its challenges and may not have fully realized the goals of implementing the BRF across the entire new drug product review process and across all disciplines.

In 2017, as part of the New Drugs Regulatory Program Modernization, a multi-year, multi-phase improvement initiative, CDER began designing and planning for the implementation of a more interdisciplinary process for the review of new drug products with an integrated, team-based approach to its review process and documentation from the start (Woodcock, 2018). The BRF is an integral component of this new approach and in fact serves again as a framework for the FDA team members to collaboratively integrate the insights gleaned from their assessments into a more comprehensive assessment of benefit-risk. This in turn was expected to contribute to more robust, integrated team-based decision-making and documentation (Woodcock et al., 2020).

As noted earlier, the FDA's traditional review process follows an approach to cross-disciplinary team science that is multidisciplinary, where team members coordinate to bring together their individual disciplinary/professional perspectives, knowledge, data, information,

and methods but do not change the individual disciplinary components (Thompson Klein, 2014; Wagner et al., 2011).With the existing FDA "multidisciplinary review" process, the integration of insights from across disciplines may occur, but occurs late in the review process when individual disciplinary reviews were completed, often resulting in only a small subset of the team being involved in the integration process and decision-making (FDA, 2014). FDA's new "integrated review" process proposes a more collaborative approach that uses the BRF, a shared conceptual framework, to orient the team's assessment process and documentation from the onset of their work rather than late in the review process (Woodcock, 2019).

As part of the New Drugs Regulatory Program Modernization, the FDA also initiated a reorganization of the CDER offices involved in the review of new drug products (FDA, 2019g). The reorganization is part of the FDA's broader strategy to promote scientific leadership and enable more integrated assessments by creating greater therapeutic alignment across the offices and strengthen cross-functional interactions (Bugin et al., 2020). It is expected that the improved alignment will contribute to more efficient internal review processes, including those that contribute to collaboration and integration in the integrated review, and external interactions with stakeholders in new drug product development (FDA, 2019i).

With the shift to more collaborative and integrated approaches to conducting and documenting assessments, the amount of documentation produced by FDA new drug product assessment teams has also decreased. Individual disciplinary analyses and assessments are still documented in the integrated review, in discipline-specific appendices, but reference information, such as study descriptions and results are shared by team memebers, thereby reducing redundant documentation. This decrease in the overall quantity of documentation is a point of contention or concern for FDA critics, with some even claiming that key information or

knowledge from the review process is lost in the Integrated Review (Herder et al., 2020). With the release of the first example of this new review process and template, some have criticized FDA for decreased transparency (Silverman, 2019). Demonstrating and communicating to stakeholders that FDA's new integrated review process and documentation maintains its expected rigor and depth—is truly more integrative, and not just less documented—will be important for maintaining FDA's credibility and transparency (Woodcock et al., 2020).

Lastly, the shift to greater integration and cross-disciplinary collaboration in new drug product application assessments conducted by the FDA is more aligned to preceding research and development process of new drug products that informs these applications. New drug research and development includes numerous activities from an intensive cross-disciplinary process in its own right, which includes clinical and nonclinical investigations of safety and tolerability of new drug products and the exploration and confirmation of efficacy or effectiveness (Burley & Park, 2005; FDA, 2018c). The development process unfolds over many years and incorporates clinical trials conducted through the drug development phases from small phase 1 studies in healthy volunteers to large, multi-center phase 3 confirmatory studies in patients (DiMasi et al., 2016; Hwang et al., 2017). Ensuring FDA has a similarly matched cross-disciplinary collaborative process to assess the diversity of data and information submitted seems therefore critical.

Statement of the Problem

The FDA assessment of marketing applications for new drug products is a critical translational research activity on the biomedical research continuum (Caruso et al., 2014; Drolet & Lorenzi, 2011). FDA's decision is necessary for safe and effective new drug products to enter

the U.S. marketplace and become subsequently incorporated into clinical practice. FDA forms cross-disciplinary teams to conduct these assessments, and these teams follow standard procedures and processes for their assessments and decision-making (FDA, 2014). Traditionally, this assessment requires multiple disciplines to work separately but in a highly coordinated way to share, verify, validate, and ultimately integrated their findings related to the submitted scientific data and information. With a shift in FDA's review process from this traditional multidisciplinary approach to a more integrative interdisciplinary approach, with the "Integrated Review", the teams must collaborate from start to finish with the intent to integrate their assessments (Woodcock et al., 2020). Such integration processes can be challenging for multiple reasons, such as those described by Michael O'Rourke and colleagues, including the number of disciplines involved, the types of inputs into the process, and the nature of the integration itself (e.g., connecting, mixing, transforming) (2016).

This highly collaborative, end-to-end integration can be considered an especially thorough form of cross-disciplinary research (Klein, 2012). Such extensive cross-disciplinary integration is necessary to make CDER's assessments of greater quality and ensure the assessments contribute to robust decision-making. Due to the changes in process and procedures, including for documentation, resulting from the implementation of the Integrated Review, external stakeholders of the FDA have concerns over a loss of knowledge and information (Herder et al., 2020). Without an understanding of the nature of collaborative cross-disciplinary integration occurring in CDER's new drug product assessment, the FDA may have challenges in evaluating its efforts and defending its new approach to team assessments.

The key phenomenon involved in cross-disciplinary research is integration and has been defined or characterized in different ways over the years by cross-disciplinary researchers

(Bammer, 2013; Bergmann., 2012; Klein, 1990; Newell, 2001; O'Rourke et al., 2013; Repko & Szostak, 2014). In the context of the FDA's assessment of a new drug product, FDA team members assess premarket evidence (inputs) from multiple disciplinary or cognitive domains then combine the insights from their individual assessments around various dimensions (outputs) of benefit and risk in the BRF to form integrated assessments. This input to output process of collaborative integration closely aligns with the framework for cross-disciplinary integration developed by Michael O'Rourke and colleagues (O'Rourke et al., 2016). Such a framework could inform the modelling of collaborative cross-disciplinary integration in FDA review teams' products and their processes. Modelling integration in collaborative FDA new drug reviews would enable the FDA to better document the integration in new drug product reviews, enabling stakeholders to better understand the process that led to a final regulatory decision on a new drug product, and what information or knowledge was involved in the integration. Finally, being able to confirm and/or trace the integration process is critical to FDA's internal management of information and decisions related to precedents, contributes to transparency in FDA's decision-making, and communicating the bases of FDA decisions to all stakeholders (i.e., FDA knowledge management) (FDA, 2019h).

Furthermore, a greater understanding of the underlying collaborative cross-disciplinary integration process in the FDA's regulatory review of new drug marketing applications, particularly the new integrated review is needed to evaluate the success of the new integrated review and develop practical guidelines or supporting resources (i.e., training) that would promote integration. In addition, by creating a model of the integration in FDA reviews, both new and old, the FDA could better explain the integration process and confirm that changes in

documentation have achieved an increased degree of integration in addition to the reduction in redundancy.

Beyond the FDA, understanding what integration looks like and how it occurs in collaborative, cross-disciplinary research has been the focus of researchers of science teams and interdisciplinary science for decades (Klein, 1990; National Research Council, 2015; O'Rourke et al., 2013; Repko, 2006; Wagner et al., 2011). Researchers and practitioners alike understand that better knowledge of the processes and conditions in which integration occurs and how to measure it are key to being able to further the effectiveness of our team science activities since it has been found that interdisciplinary teams require certain skills and abilities at the individual, team, and organizational level to be effective. These skills and abilities depend on the degree and nature of the integrative processes (Salazar et al., 2012; Stokols, Misra, et al., 2008a).

Due to the knowledge gap that exists regarding the interdisciplinary integration process that occurs within FDA new drug product assessment teams, FDA is hampered in its ability to defend its new approaches to team-based assessments and to develop practical guidelines and trainings for its teams to promote the effectiveness of its team-based assessments of new drug products. Most importantly, FDA is limited in its ability to evaluate the success of its recent improvement initiatives under the New Drugs Regulatory Program Modernization that aim to promote more integrated assessments without a clear way to evaluate integration in pre- and post-implementation new drug reviews.

Purpose and Research Questions

This research was conducted using a phenomenological descriptive comparative case study of new drug product assessments using either the new integrated review process and team-based

template, or the traditional multidisciplinary review process and individual review templates. This research study also involves the development of an approach to modelling the process by which integration occurs in collaborative, cross-disciplinary FDA new drug product reviews and a greater understanding of how collaborative cross-disciplinary integration occurs. The focus of the research is primarily at the *meso* level of the teams and the processes that affect their integration. More specifically, the unit of analysis is the FDA review team and discrete instances of collaborative cross-disciplinary integration that occur related to benefit-risk review issues. The research questions are:

1. What are examples of integration in a "multidisciplinary review" and an "integrated review" of an FDA new drug product?
2. What are the specific differences in integration between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?

As discussed in the introduction, a conceptual framework, the BRF, was created to structure the decision-making process for new drug product application assessments. But the process of integrating insights and evidence from multiple team members to inform a now much more collaborative benefit-risk assessment process in the integrated review is a new use and not well understood by the FDA. Without an approach to evaluate collaborative cross-disciplinary integration, the FDA will be unable to promote efficient and effective team processes that contribute to effective integration and robust decision-making. The FDA needs a strong understanding of integration in order to design training and guidelines for staff to promote greater team effectiveness in the completion of integrated assessments of new drug products, support the evaluation of improvement initiatives aimed at creating and supporting more

integrated assessments, and promote greater transparency to external stakeholders on the FDA's assessment and decision-making process.

In addition, the Science-of-Team-Science includes numerous theoretical and conceptual models of cross-disciplinary integration and collaborative cross-disciplinary, but none are geared towards the practical evaluation of integration. The lack of a measurement tool for integration limits the Science-of-Team-Science in its quest to better understand the key factors that influence team science.

Statement of Potential Impact

Creating a model of collaborative cross-disciplinary integration in FDA new drug product reviews, both the multidisciplinary review and integrated review, enables a greater understanding of the team processes and other factors that influence integration, a key outcome for the FDA. The ability to assess integration in a more rigorous, analytical way allows FDA to evaluate the implementation of the new integrated review, measure performance of teams, compare its new approach to previous approaches, and address concerns from stakeholders related to otherwise superficial changes to the outputs of the review processes.

In addition, the models of integration found in both an integrated review and multidisciplinary review helps identify the key points or features in the integration process that are distinctly different between the two approaches, as well as those that are working well and those that may need additional support for teams to achieve them. Such knowledge is critical for the FDA to achieve its strategic objective of having a truly integrated assessment. The modelling approach developed as part of this research may also be used to define the integrative processes

of FDA review teams in other contexts, such as the assessment of safety signals in pre-market and post-market development.

The FDA review of new drug products requires teams of scientific, medical, legal, and regulatory experts to collaborate in the review of evidence of safety and efficacy generated in the premarket development of a new drug product and benefit-risk decision-making. The evidence generation process of drug development is in itself a cross-disciplinary phenomenon, involving numerous disciplines and domains (Ettouati et al., 2013; Settleman & Cohen, 2016; Stojanovic & Kessler, 2011). It is natural that the FDA take similar cross-disciplinary approaches in its assessment of this evidence. That the FDA assesses information produced by pharmaceutical company sponsors generated by their cross-disciplinary teams of scientific, manufacturing and commercial experts during the premarket development of new drugs, makes knowledge gained from this study generalizable beyond FDA teams. And, the outcomes of this shift at FDA will be impactful to the pharmaceutical industry and researchers given the importance of making and communicating effective benefit-risk decisions in those contexts as well (Settleman & Cohen, 2016; Stojanovic & Kessler, 2011)

Lastly, the use of a theoretical framework from the Science-of-Team-Science to model collaborative cross-disciplinary integration in FDA new drug product reviews is a robust practical application of this model and subsequently a huge contribution to the literature on interdisciplinary theory and the Science-of-Team-Science. By having an established practical model of integration that highlights the “moving parts” in the collaboration researchers, including those at the FDA, can identify in a systematic way how to ensure, influence, and control the collaborative cross-disciplinary integration process.

Theoretical Foundation and Conceptual Framework

This study is primarily guided by a framework from the Science-of-Team-Science, specifically a philosophical framework for cross-disciplinary integration (O'Rourke et al., 2016). In addition to this philosophical framework for cross-disciplinary integration, a typology of integration in interdisciplinary research from Julie Thompson Klein offers a qualitative way to distinguish between the traditional multidisciplinary forms of integration and those expected in the integrated review (Thompson Klein, 2014). Finally, the BRF for US FDA regulatory new drug decision-making is used as a conceptual framework to operationalize the philosophical framework for cross-disciplinary integration in the context of a new drug product review (FDA, 2018a).

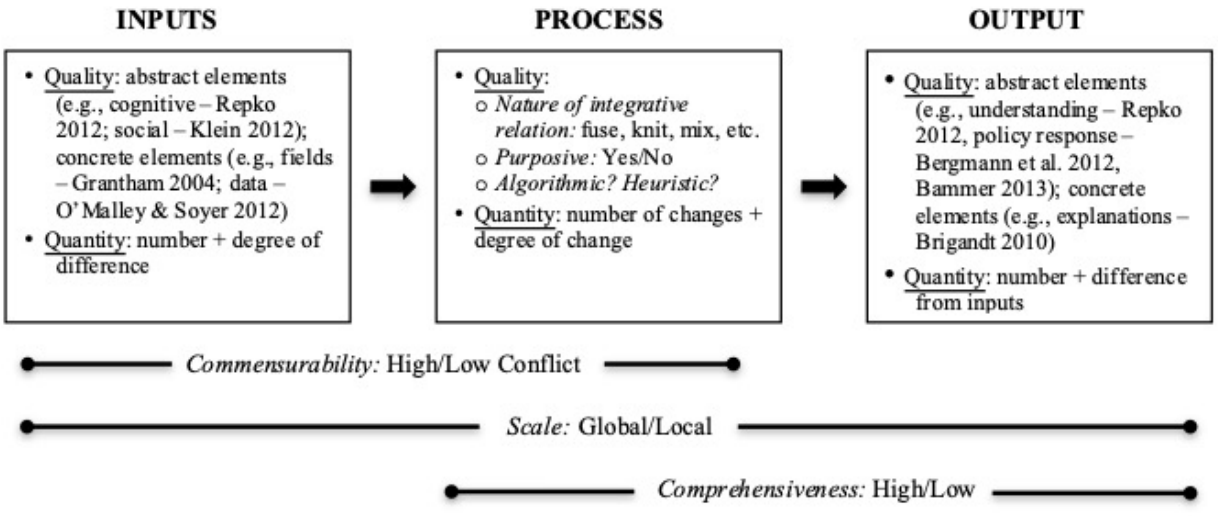


Figure 1: Cross-disciplinary Integration Framework

(O'Rourke et al., 2016)

In Figure 1, above, O'Rourke et al. describe a framework for integration using a "generic combination process" (O'Rourke et al., 2016, p. 67). In this combination process, inputs are

combined, and the output is produced. This combination process from input to output can be characterized by examining the quality and quantity of inputs, the process, and the outputs. Once characterized, the combination process, or “integration”, can be modelled using as an Inputs > Process > Outputs chain or logic model. In Figure 2, below, the framework for cross-disciplinary integration from O’Rourke et al. is operationalized with contextual elements from the BRF that guides a new drug product assessment. For example, in the figure below the known potential disciplines from a new drug product assessment have been outlined as clinical, statistics, clinical pharmacology (clin pharm), pharmacology/toxicology (PTOX), quality, or regulatory. These disciplines are responsible for inputs into the cross-disciplinary integration process. To illustrate the contextualization further, the below figure includes examples of potential inputs that you might find in a new drug product application and in the benefit-risk framework for the assessment. In this figure, one can conceptualize how the framework for cross-disciplinary integration can be used to model integration in a new drug product assessment.

Discipline	Type	INPUTS • Quality of Inputs (concrete vs abstract) or disciplinary origin/expertise required • Quantity of Inputs of each type or discipline	PROCESS • Degree and nature of integrative change to input Low-connecting High-transforming • Purposive changes: Yes/No • Number of changes to an input	OUTPUTS • Quality of the Outputs (concrete vs abstract • Quantity of Outputs (e.g., conclusions made on integrated review issues) • number of discrete outputs • degree of difference from inputs
Clinical, Statistics	Data (concrete)	Patient Experience Data	Clinical outcomes assessment integrated with clinical to inform clinical meaningfulness of results	
Clinical, Statistics, ClinPharm	Data (concrete)	Efficacy and Safety Studies and Data		Integrated analysis of benefits and risks
Clinical	Assessment (abstract)	Clinical Condition and Underlying Pathophysiology		
Clinical, Statistics	Assessment (abstract)	Patient Experience and Clinical Meaningfulness of Treatment Effect	Assessment of efficacy of clinical studies from statistics and clinical integrated to inform effectiveness	Assessment of Benefits
Clinical, ClinPharm, PTOX	Assessment (abstract)	Pediatric Use Information		
ClinPharm, Clinical	Data (concrete)	Clinical Pharmacology Study(s) and Data		Benefit Issues
PTOX, Clinical	Data (concrete)	Nonclinical Pharmacology/Toxicology Study(s) and Data	Data from nonclinical and clinical pharmacology studies integrated to inform dosing	
Clinical, PTOX	Assessment (abstract)	Pregnancy and Lactation Information		
All	Assessment (abstract)	Labeling		Labeling
All	Assessment (abstract)	Design of Study(s)		
Regulatory	Assessment (abstract)	Legal or Regulatory Drug-specific Issues	Data from nonclinical and clinical studies integrated to inform safety profile	Regulatory Precedents
Clinical, Safety	Assessment (abstract)	Safety Assessment and Profile		
Clinical, Safety	Data (concrete)	Safety Data		Safety Issues
Quality	Data (concrete)	Manufacturing Facility Information and Inspection Information	Clinical pharmacology, nonclinical, and CMC information integrated to inform quality and formulation information, including dosing and administration	
Quality, PTOX	Data (concrete)	Drug Substance/API Information		Assessment of Risks and Risk Management
Quality, PTOX	Data (concrete)	Drug Product and Formulation Information		
Quality, ClinPharm, PTOX	Assessment (abstract)	Product Attributes		

Figure 2: Analytical Framework for IPO Model of Integration in New Drug Product Reviews

Together these theories and frameworks come together to create a conceptual and analytical framework on which this study is centrally guided. In conjunction with the goals of the study and the research questions, an overall study design emerges; see figure 3, below. In this figure a Maxwell diagram of study alignment details the alignment of the research questions, conceptual frameworks, study goals, and methods (Maxwell, 2013). The goals of the study are to characterize the integration occurring in FDA's new drug product review teams and then explore differences in integration through a comparison of a traditional multidisciplinary review and an integrated review. These goals are furthered by targeted research questions on the integration in FDA new drug product reviews and the differences in multidisciplinary and integrated reviews. The conceptual frameworks discussed earlier provide the necessary tools, lens, and theories to both collect data, conduct analyses, and interpret the analyses necessary to answer the research questions. A phenomenological philosophy, constructivist ontology, qualitative epistemology, and descriptive case study methodology most naturally aligns with these goals and the research questions for this study, as discussed more below. And, lastly, the validity of this study is enhanced through randomization and blinding, triangulation, and the researcher's experience with new drug product reviews.

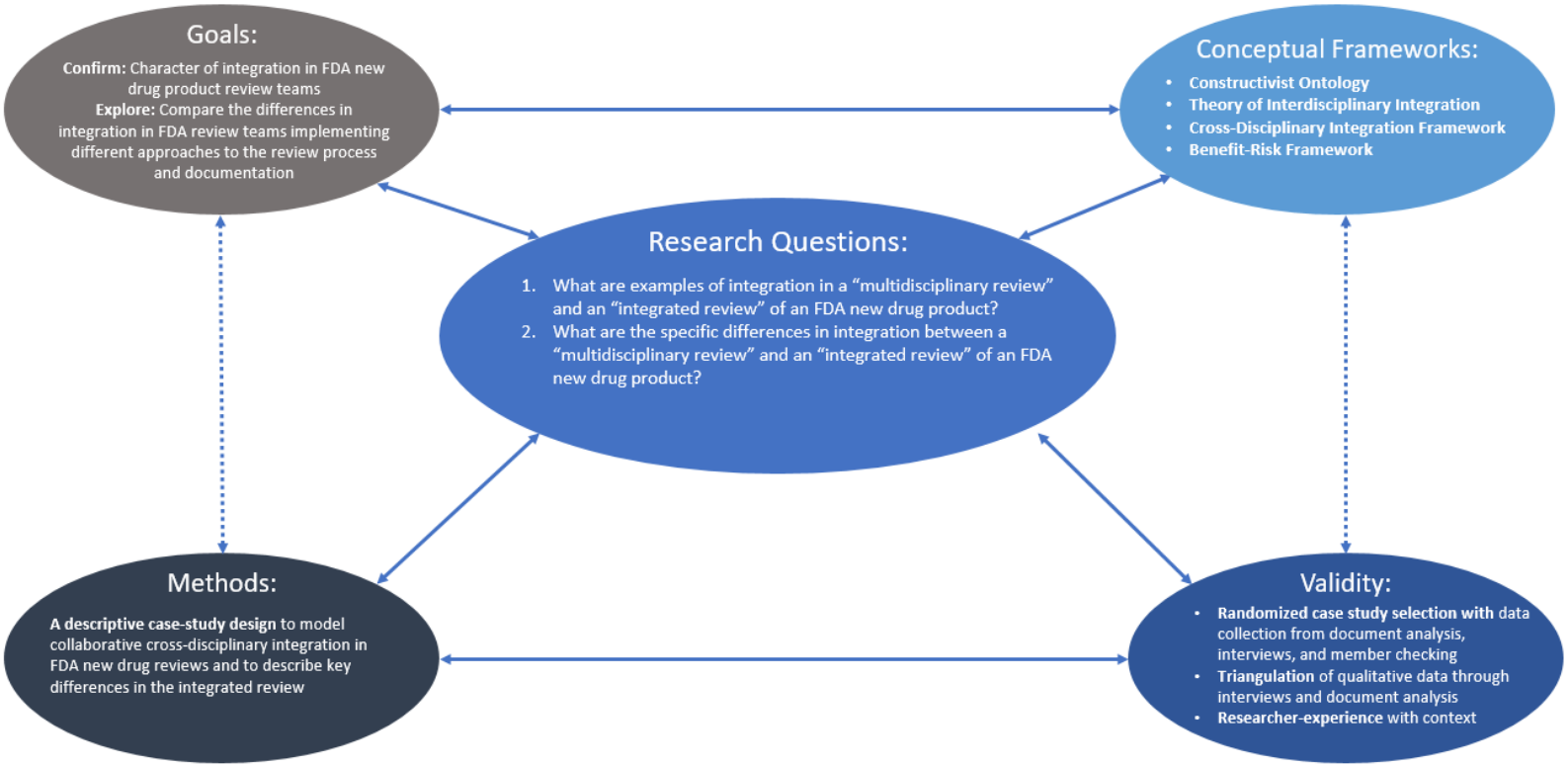


Figure 3: Study Alignment
(Maxwell, 2013)

Summary of the Methodology

This study is a qualitative descriptive comparative case study of a traditional FDA multidisciplinary review and a new FDA integrated review of a new drug product marketing application to model instances of collaborative cross-disciplinary integration and identify differences and similarities in the integration in the two cases. The study was conducted through a combination of the document analysis of final FDA review team documentation, semi-structured interviews with review team members of each case, and a member checking of the integration examples. The data collection from the document analysis is guided by the cross-disciplinary integration framework (O'Rourke et al., 2016) and the BRF (FDA, 2018b), which allows the content of the review to be analyzed as relevant to an instance of integration around a key benefit-risk review issue and coded as either inputs, outputs, or process related. Semi-structured interviews and member checking with the cross-disciplinary team members involved in integration will further inform the process variable of the framework of integration. Data collected, guided through the cross-disciplinary integration framework, will be modelled logically as inputs > process > outputs chains for further analyses.

Through the document analysis and interviews, descriptive elements of each case are catalogued, including details about the teams (e.g., size of team, composition of team), the new drug product being reviewed (e.g., new molecular entity, combination product, small molecule), and the assessment itself (e.g., length of documentation, final decision). These case descriptions inform the contextual parameters of the IPO framework and when combined with data on the key variables of the integration process gathered from the document review allows each case of integration to be thoroughly described and modelled, enabling comparisons.

Limitations

This study is focused primarily on modelling the phenomenon of collaborative, cross-disciplinary integration that occurs within an FDA review team conducting either a multidisciplinary review or integrated review. As such the study may not clearly define or describe other aspects of the FDA review process, such as communication, team dynamics, or scientific methods of analysis used. Also, while the FDA review process for a multidisciplinary review and integrated review is generally well-defined, it may not be consistently followed with fidelity and the effectiveness of the process may reflect individual or team characteristics (i.e., differences) rather than process characteristics. For this reason, it may not be possible to make conclusions about the resulting differences in integration as solely attributable to the multidisciplinary process or the integrated review process, but it may be possible for the interviews to help characterize fidelity. In addition, examining two cases with different teams, different processes, and additional differences in context (e.g., drug products reviews, therapeutic areas, scientific issues), may affect to the generalizability of some findings related to cross-disciplinary integration in FDA reviews.

Additional limitations of this study are the sample size and sample selection. Only two cases were selected for this study and therefore the selected samples may greatly influence the findings. Furthermore, because the integrated review is a newly implemented process there was a small pool of completed integrated reviews to choose at study start time. And, with the transition to integrated reviews, the pool of recently multidisciplinary reviews available was also decreasing. Selection was guided by a priori inclusion and exclusion criteria, described in detail in Chapter 3. In addition, because reviews can take a long time to complete and some time may have passed before the review team is contacted in the study, review team members may have

limited recall of the review. This limitation is mitigated using document analysis, which leveraged review documentation for the analysis that would have been completed at the time of the review and not the time of this study.

Lastly, this researcher is considered a member of senior leadership within the organization responsible for managing new drug review processes and is seen as someone responsible for the implementation to the new integrated review process therefore having a vest interest. This may influence subject participation and potentially bias the findings due to lack of transparency or accuracy of interviews due to power-status and trust issues. In addition, the research may have implicit biases related to the new integrated review process and documentation template. While these risks will be carefully monitored and managed, it may result in potential limitations in interpretation of the results To address any implicit biases, these are captured in a subjectivity statement in this document and the informed consent to make the potential biases explicit (Lincoln, Y.S., Guba, 1985).

Definitions of Key Terms

- *Benefits*: "The helpful effects you get when you use them [medicine], such as lowering blood pressure, curing infection, or relieving pain." (Department of Health and Human Services & Food and Drug Administration, 2018)
- *Benefit-Risk Framework (BRF).* A structured approach for drug benefit-risk assessments conducted by FDA, that serves as a tool to convey the basis of FDA's regulatory decisions in drug approvals (FDA, 2013).
- *Commensurability***:** Assessment of integrable the inputs are (i.e., their difference or conflict between) (O'Rourke et al., 2016).

- *Comprehensiveness*: Assessment of how comprehensive the output(s) reflect or include the inputs (O'Rourke et al., 2016).
- *Cross-disciplinary Research.* Approaches to research that combine disciplines in various degrees from multidisciplinary to transdisciplinary (O'Rourke & Crowley, 2013).
- *Discipline***:** FDA defined disciplines for the different members of the review team for a new drug product marketing application, and are defined in the 21st Century Review Desk Reference Guide (FDA, 2014).
- *Effectiveness*: Effectiveness is a regulatory definition that refers to the regulatory determination of or for a new drug product that is made on the basis of clinical efficacy and other data (Food and Drug Administration & FDA, 1998).
- *Integration.* The process and product of cross-disciplinary research that relates to the bringing together of inputs from multiple disciplines and creating a new whole, whether that be a simple combination of the parts into the whole or some change to the inputs and therefore some reduction of the inputs into the final output (O'Rourke et al., 2016). Integration can manifest across the range of cross-disciplinarity, although minimally in the case of multidisciplinary research.
- *Interdisciplinary Research.* Approaches to cross-disciplinary research that integrate, and potentially change, separate disciplinary perspectives, knowledge, data, information, and methods to create a more comprehensive overall view or understanding of a complex issue (Thompson Klein, 2014; Wagner et al., 2011).
- *Integrated Review*: The Integrated Review is the name of a newly proposed approach to the review of new drug product applications that involves a team-based,

interdisciplinary approach to the assessment of the application and an integrated, issue-focused review of the application (FDA, 2019h).

- *Multidisciplinary Research*. Approaches to cross-disciplinary research that juxtapose disciplinary/professional perspectives, knowledge, data, information, and methods but do not change the individual disciplinary components (Thompson Klein, 2014; Wagner et al., 2011).
- *Multidisciplinary Review*: The traditional FDA approach to conducting a review of a new drug product application (i.e., NDA, BLA) that involves the coordinated individual disciplinary review of the application is referred to as a multidisciplinary review (FDA, 2014).
- *New drug products.* A new drug product is a pharmaceutical product that contains a new molecular entity or an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or has been previously marketed as a drug in the United States (FDA, n.d.).
- *New drug review process:* The review activities required for new drug application abd biologic licensing applications, including the procedures and requirements described in both the FDA's "Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMP)", and PDUFA agreements (FDA, 2014, 2018d).
- *Safety:* The potential risks, or patient's adverse effects to new drugs, to patient health from the use of a new drug as labeled per the Federal Food, Drug, and Cosmetic Act (FDCA) (Federal Food, Drug, and Cosmetic Act, 1938).

- *Transdisciplinary Research.* Research that is interdisciplinary and addresses complex, broad societal problems and involves non-academic stakeholders (Frodeman et al., 2017). And/or research that involves either the creation of a new interdisciplinary field or a "transcending" of disciplines (O'Rourke et al., 2013).
- *Scale:* Assessment of how many disciplines or disciplinary input types involved and the overall impact (i.e., global--the entire application vs local--a specific problem/issue) (O'Rourke et al., 2016).

Chapter 2 Review of the Literature

Introduction

This literature review aims to describe the available literature related to drug development and FDA's benefit-risk assessment of a new drug product, the Science-of-Team-Science, cross-disciplinary research, and collaborative cross-disciplinary integration. The literature on drug development and FDA new drug product review provides important contextual information for the application of theories and frameworks from the Science-of-Team-Science research on collaborative cross-disciplinary integration. The review of literature from the Science-of-Team-Science explains approaches to measuring or studying collaborative cross-disciplinary research and the specific phenomenon of collaborative cross-disciplinary research, *integration*, that is the focus of this study. Lastly, literature on the phenomenon of cross-disciplinary integration is presented to identify the current state of research on the matter, gaps in existing evidence, and elicit the most appropriate tools or methods to study integration in this context.

Literature searches to inform the review of each domain use a combination of key terms and wildcards and are conducted across multiple databases to ensure adequate breadth of search, including Scopus, CINAHL, PubMed, and Mendeley. Searches were limited to English language publications, but the year range was not limited due to the paucity of research found initially in these domains. In addition, searches are included for literature related to the FDA new drug product review required searching federal websites and regulatory documents. Search methods and keywords are listed in Table 1, below.

Table 1: Literature Search Strategies for key Domains

Domain 1: FDA Assessments	Domain 2: Science-of-Team-Science	Domain 3: Cross-disciplinary Research
• FDA AND new drug* OR drug* AND assessment* OR review* • translational research AND FDA AND new drug OR new drugs OR drug* AND assessment OR assessments OR review* • translational research AND drug development	• interdisciplin* • cross-disciplin* • translational research AND interdisciplin* • translational research AND cross-disciplin* • collaborative OR collaboration AND interdiscipline* OR cross-disciplin* • Team Science • Science of Team Science • Collaboration Science • measurement AND interdisciplin* OR cross-disciplin* • measurement AND Team Science OR Collaboration Science	• integration AND interdisciplin* • integration AND cross-disciplin* • integration AND collaboration • integration AND collaborative interdisciplin* OR cross-disciplin* • measurement AND integration AND interdisciplin* OR cross-disciplin* • measurement AND interdisciplinary integration

* this symbol denotes a wildcard to include the multiple variations of disciplinarity or pluralities

Literature that fell outside of these domains was included when it included a key piece of supporting evidence for another aspect of the literature review (e.g., integration in philosophy) or provided useful context for this study. Literature was also considered for inclusion in this literature review based on certain evidentiary thresholds, in the following order: prior literature reviews or systematic reviews, followed by studies, books or book chapters, editorials and commentaries, and finally web postings or other grey literature. This hierarchy is motivated by a heuristic of evaluating the strength of scientific evidence that is routinely leveraged by biomedical researchers and those practicing evidence-based medicine research (Burns et al., 2011). It is worth noting that strong literature reviews exist in the domain of cross-disciplinary research, collaborative, cross-disciplinary research, Team Science and the Science-of-Team-Science and these enabled rapid identification of strong and seminal literature (Choi & Pak, 2006; Mâsse et al., 2008; National Research Council, 2015; Stokols, Misra, et al., 2008a). Citation mining and authorship influence in the space was used to further guide selection of literature. Full text copies of all identified literature were obtained and then loaded into

Mendeley, a free reference manager and an academic social network produced by Elsevier (Elsevier, 2008). Literature was reviewed and annotated in Mendeley, and in some cases the Mendeley network was leveraged to identify additional relevant literature through its social network and citations network features.

Drug development & FDA new drug review

New drug products are developed by pharmaceutical companies, academic medical centers, etc. via series of research and development activities that occur over a great number of years and an even greater number of scientific and clinical studies. According to literature, in totality this has been characterized as a process that takes anywhere from 5-15 years, involves dozens of studies and experts, costs hundreds of millions of dollars, and is wrought with high failure (DiMasi et al., 2016). In addition, this drug development process is cross-disciplinary—it requires that dozens of scientific, medical, commercial, and regulatory experts to collaborate regularly to translate an early basic scientifically plausible innovation to something for use at the patient's bedside (Settleman & Cohen, 2016). At the 2005 Keystone Symposium on "Meeting the Challenges of Drug Discovery", keynote speaker Leslie Brown described a new multidisciplinary set of goals for the drug development process: "use the right technology to find the right drug modulating the right target in the right patient" (Burley & Park, 2005, p. 1). These drug development goals have evolved over the years and included a greater emphasis on the culture of an organization's clinical research and commercialization programs, which relates to effective decision-making in the process (Cook et al., 2014), demonstrating a growing appreciation for the individuals and teams that make the process possible. This literature illustrates the cross-disciplinary nature of the drug development process and the complexity of the problems to be solved. These goals feed into a complex, multi-step sequential process, with

numerous activities including, but not limited to, the discovery of novel drug candidates, preclinical animal and toxicology research, conducting clinical studies (e.g. Phase 1, 2, and 3), submitting regulatory documents (e.g., Investigational New Drug [IND] applications, New Drug Application [NDA]), and initiating post-approval commitments (Ettouati et al., 2013). This process is described in Figure 4, below.

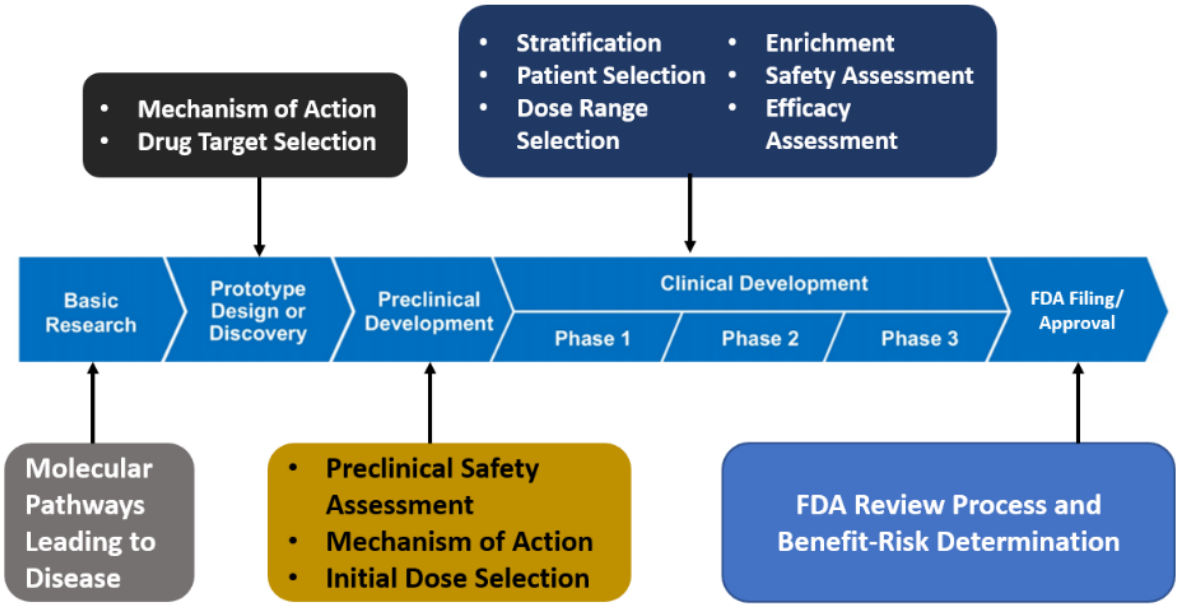


Figure 4: Drug Development Process

The outcome of this cross-disciplinary process for the research and development of a new drug is the generation of knowledge and evidence to support its safety and effectiveness in clinical practice. The requirements of the research and development process and the evidence that must be submitted to FDA to support its assessments are outlined by the Food Drug and Cosmetic Act (FD&C), FDA regulations, specifically title 21 of the Code of Federal Regulations sections 312 and 314 (Part 314 — Applications for FDA Approval to Market a New Drug, 2002; Part 312 - Investigational New Drug Application, 2004), and the many guidance documents generated by FDA review staff. The evidence generated from a product's development program

is compiled by a collaborative cross-disciplinary team into a marketing application, referred to as a New Drug Application (NDA) for a new chemical entity or a Biologics Licensing Application (BLA) for an original biologic product (Ciociola et al., 2014; Ettouati et al., 2013; FDA, 2014; Stojanovic & Kessler, 2011). These marketing applications can contain dozens of studies and thousands of pages of information and data.

A variety of disciplines are leveraged to design and conduct the studies during drug development. These studies generate evidence of the product's treatment effect (e.g., efficacy), its effects in the patient and effects of the patient's body on the new drug (e.g., pharmacokinetics/pharmacodynamics) and patient's safety of the product at various doses, in a very specific patient population under intensely controlled settings (Fielding, 2014). While a variety of disciplines' expertise is needed in drug development, the disciplines must work together towards a common goal that is to develop evidence to support a target product profile for the investigational new drug product, similar to key elements of a draft prescribing information (FDA, 2007a). The target product profile represents the features of a drug that need to be characterized during development to ensure the new drug product will be safe, effective, and competitive on the market (Breder et al., 2017).

As studies are completed and important milestones in the new drug research and development process are reached, massive amounts of data and information are summarized and submitted to decision-makers, such as pharmaceutical executives and health authorities, for ongoing review, feedback, and decision-making. This summarization or synthesis process goes beyond any single discipline and even the multidisciplinary interactions needed to generate evidence. It requires a more comprehensive understanding of a product at this late stage of

development and this understanding requires a certain cross-disciplinary integration of insights formed during the new drug research and development process (Ettouati et al., 2013).

Furthermore, the commercial and regulatory decisions, such as should a product move forward to phase 3 confirmatory testing or should a product be made available on the US market, respectively, require transcending the disciplinary ontologies and methodologies involved in the new drug research and development process to make a final determination, or judgment, of the new drug product's benefits and risk. These processes for decision-making are frequently referred to as benefit-risk assessments and attempts have been made to improve these assessments with structured frameworks due to the complexity of the decision (Walker et al., 2015). The complexity of benefit-risk assessments comes from not only the multitude of sources of inputs for data and information into the benefit-risk frameworks but also the necessary integration and evaluation that is required (Walker et al., 2015). These benefit-risk decisions and the inherent integration requires a collaborative approach as research has found that the inability to collaborate and communicate across diverse functions may lead to suboptimal decision-making (Stojanovic & Kessler, 2011). Literature therefore demonstrates that the drug development process and the ultimate benefit-risk determination are both cross-disciplinary and collaborative.

While the pharmaceutical industry and others are primarily leading the drug research and development process, the FDA is ultimately responsible for ensuring that new drug products marketed in the U.S. are safe, effective and of high quality (FDA, 2015). This is arguably a translational activity and therefore a brief review of translational research is necessary. Translational science or translational research is focused on how scientific knowledge is translated from basic science and discovery to public health impact (Drolet & Lorenzi, 2011). A

more narrow view suggests the truly translational activity occurs only in the gaps in the translational continuum between different forms of research (Austin, 2018).

In the Drolet and Lorenzi conceptualization of translational research, the activities of both the FDA and Sponsors of new drug products during drug development fit neatly in the basic and clinical research spaces, but it is the FDA's assessments of a marketing application that are truly boundary spanning. These assessments conducted by the FDA must be completed before a new drug product can be marketed in the US and it can used in practice. Therefore, in the Austin conceptualization the work of the FDA to assess clinical and basic research information and make benefit-risk assessments clearly exists in and even spans the gap between basic research and clinical practice.

Returning to the FDA's assessment of a new drug product, this assessment occurs when the drug development program concludes the generation and compilation of substantial evidence, both laboratory, clinical and in some cases social, to support the product's safety and effectiveness (Food and Drug Administration & FDA, 1998). This compilation of evidence is submitted in the form of a new drug application (NDA), or in the case of therapeutic biologics a Biologics License Application (BLA), to the FDA for a determination of safety and effectiveness (FDA, 2018c). The determination of adequate safety and effectiveness marks the "approval" of the product. This "approval" may appear simple on its face given that a standard or definition of 'substantial evidence' of safety and effectiveness is provided simply in regulations (Part 314 — Applications for FDA Approval to Market a New Drug, 2002) but it is worth noting that the evidence to meet this standard will be from various sources (e.g., animal research, clinical research, laboratory research, qualitative research), related to multiple attributes of new drug products or the diseases they are intended to treat can vary greatly, and ultimately it is the totality

of this evidence that must be carefully weighed in the context of its intended use. This careful weighing is known as a benefit-risk assessment (Ciociola et al., 2014).

The assessment of benefits and risks has been described as a careful examination of several factors, such as therapeutic context, the evidence submitted, uncertainties, FDA's regulatory options, and values of and tradeoffs between benefits and risks (Duke Margolis Center for Health Policy, 2019). Therapeutic context relates to the context in which the new drug product will be used, including the unmet needs of patients and the seriousness or severity of the disease the drug is intended to treat. "Evidence" of safety and effectiveness was discussed above.

Uncertainties result from the inevitable incompleteness of evidence that is generated during development and submitted in a marketing application, which will require scientific, medical, and regulatory judgment to determine if a benefit-risk determination can be made despite this uncertainty. FDA has regulatory tools to address the uncertainty inherent in new drug product applications and decisions, such as requiring additional clinical studies after approval, safety labeling, and risk evaluation and mitigation strategies (Darrow et al., 2017). Due to the variety of sources of evidence and the inherent uncertainty in clinical research and drug development, coupled with the FDA's assessment strategies, the benefit-risk assessment is a complex decision (McDonagh et al., 2013; Myers & Moore, 1987).

Core to making the decision to approve a new drug product is the benefit-risk assessment and this assessment is not a purely research endeavor. It leads to determination that has major implications on patient and population health. The benefit-risk assessments and the decisions they support have received much attention over the years from the public, FDA, industry, and Congress due to some of the ambiguity in these standards of safety and effectiveness. Drug withdrawals in the early 2000s led to the reignition of public claims that the FDA was too close

with industry and was favoring speedy approvals over public safety (Institute of Medicine, 2006). As a result of these public claims, the FDA commissioned an Institute of Medicine committee report to independently assess the FDA's "system for evaluating and ensuring drug safety postmarketing" (Medicine, 2006, pg 3, Box S-1). The committee described the assessment process as follows:

> "It is impossible to know everything about a drug at the point of approval because drugs' mechanisms of action are complex, and because the clinical testing that happens before approval is generally conducted in controlled settings in defined, carefully selected populations that may not fully represent the wide range of patients who will use the drug after approval, some chronically, and in combination with other drugs. Thus, the understanding of a drug's risk-benefit profile necessarily evolves over the drug's lifecycle. CDER staff who review regulatory submissions, such as new drug applications, must strike a delicate balance in judging the drug's risks and benefits, and whether the need for more study to increase certainty before approval warrants delaying the release of the drug into the marketplace and into the hands of health care providers and their patients." (Medicine, 2006, pg 17)

FDA would release a report in response to the commissioned report a year later calling for a number of improvements, including more quantitative or semi-quantitative tools to aid the assessment of benefit and risk (FDA, 2007b). In the same report, the FDA would also acknowledge the importance of using "an interdisciplinary team approach to assessment" (FDA, 2007, pg 3).

It would take many years to develop these benefit-risk assessment tools due to the complexity and delicate nature of the assessment and the importance of the decisions they

inform. During the congressional hearing on Vioxx in 2004, the deputy director of the Office of New Drugs aptly said:

> "…all drugs pose some safety risk, and that some drugs pose a greater risk than others. But there is no magic formula for deciding what drug is the biggest risk of all. If there were a magic formula, our jobs would be very much easier… Every drug has risks and benefits, and it is important not to get so focused on the risks that one forgets to look at the benefits. In evaluating any individual medication, our job is to do just that."
>
> (Committee on finance United States senate, 2004, pg 63)

This quotation clearly articulates the challenge FDA faces in its assessments of benefit and risk. It would take more than five years, beginning shortly after the withdrawal events from the early 2000s, for regulators from the US and Europe to develop more structured benefit-risk frameworks for the assessment of benefits and risks. In 2009, the European Medicines Agency released its report on its Benefit-Risk Methodology to inform regulatory decisions about medicinal products, after its working group's three year effort to review methods of benefit-risk assessments and practical application (EMEA, 2009). Also in 2009, FDA would begin considering a similar structured assessment, which would be finalized and implemented in 2013 (FDA, 2013). Industry faced similar challenges and during this time period began its own effort to develop an improved benefit-risk assessment. In 2005, the Pharmaceutical Research and Manufacturers of America (PhRMA) convened an action team, the Benefit Risk Action Team (BRAT), to develop a new framework for benefit-risk assessment (Coplan et al., 2011). Five years later, the BRAT would release its own framework.

Due to the ambiguity in the statutory requirements for evidence of safety and effectiveness and FDA's regulations and guidance, external stakeholders regularly question the

standards for evidence used by the FDA and demand greater understanding of the bases of FDA's decisions (Downing et al., 2014). To promote clarity and transparency of its decision-making process, FDA implemented its structured benefit-risk framework directly in the review process in 2013 (FDA, 2013). This was the culmination of much work to help characterize how evidence and uncertainty related to a new drug's safety and effectiveness was assessed by the FDA (Caruso et al., 2014). As of 2018, this framework is used by more than 87% the FDA review teams in all new drug product assessments, with a desired utilization rate of 100% (FDA, 2018b). FDA review team members assess information submitted in the NDA or BLA, to characterize the evidence and their uncertainties about key concepts of the benefit-risk determination.

The assessment process for a marketing application entails a verification and validation process of the design of the research, conduct of the research, and the analyses (FDA, 2018c). This process is conducted by an FDA review team of multiple disciplines. The FDA review teams responsible for the assessment of these marketing applications are formed following the receipt of a new drug product application to the Office of New Drugs in CDER. Initially, a regulatory project manager and a clinical team leader are assigned based on the therapeutic area for the product. These two co-leads of the review team then form a team of reviewers with specialized expertise to assess the evidence submitted in the marketing applications. Because the team will formulate insights about the new drug product's benefits and risks, it is important that these teams include multiple, but relevant, disciplines and that they collaborate effectively.

In addition to the evidence generated during the development program of a new drug product, the regulatory assessment is also informed by additional factors, including: the severity of the underlying condition, patients' unmet medical needs, uncertainty about how the premarket experience with a new drug will extrapolate to real-world use and whether known and potential

risks are manageable. The Food and Drug Administration's assessment and the decision the assessment supports must also be in accord with the earlier mentioned FD&C Act and regulations, and to some extent prior guidance or precedents from earlier regulatory decisions.

This verification and validation process of the evidence can be time consuming depending on the scale of the development program and the complexity of the product or disease. Evidence can be generated from any number of scientific domains, but primarily biological and clinical. FDA review teams are carefully composed of subject matter experts from across multiple disciplines in order to assess evidence from the appropriate disciplinary perspective (e.g., a toxicologist to review animal toxicology studies, clinical pharmacologist to review human pharmacology data). Following the marketing application assessment, individual FDA review team members can characterize the evidence and uncertainties that contribute to the FDA's conclusions related to the key dimensions of the benefit-risk framework. In this way, the FDA benefit-risk framework helps structure the review team's assessment across each factor and dimension of the benefit-risk framework (Duke Margolis Center for Health Policy, 2019). This integration process is critical for making and communicating FDA's benefit-risk decisions in its assessment of new drug products.

During the assessment of the sponsor's marketing application information, issues may be identified related to product or its key attributes and dimensions of the benefit-risk determination, such as its benefits, risks, or quality related to manufacturing processes of the new product, such as the final manufactured product's purity and potency. Such issues require cross-disciplinary collaboration of the team to fully understand the issue. For example, a robust signal of drug induced liver injury (DILI) may be identified in an animal toxicology study and a similar signal, albeit less certain, is found in a large clinical study. To fully understand the animal signal,

the pharmacology/toxicology experts must fully understand the animal study and subsequent pathology of the DILI signal, and translational implications for humans. The clinical reviewer, a physician, must understand the design of the clinical study and the context in which the clinical signal was identified. Both experts must work collaboratively to determine the importance of the DILI signal and to characterize potential risks to patients (Avigan et al., 2014). In these ways, the assessment of new drug products is cross-disciplinary in nature. Insights and conclusions formulated during the assessment and review process are then integrated by the team to inform a cross-disciplinary assessment known as the benefit-risk integrated assessment (FDA, 2018b), as part of the BRF. This integration process is managed by the cross-disciplinary team leader, often but not always a clinical team leader, and the regulatory project manager.

In conclusion, the review of a new drug product by the FDA is cross-disciplinary in nature and involves both an assessment of evidence generated by a long and complex drug development process and an assessment of benefits and risks, that requires an integration of insights from multiple disciplines, to inform the decision that a product is safe and effective before it can be approved. This decision by the FDA on a new drug product marks an important bridging of the translational gap between clinical research and clinical practice (Austin, 2018).

Cross-disciplinary Research

The next domain in this literature search is cross-disciplinary research, a key method deployed in Team Science, and has been increasingly recognized in translational research for its ability to generate solutions to complex problems that cannot be solved by a single discipline alone (Klein, 1990). This form of research involves drawing upon the insights or inputs of more than one discipline. More specific forms of cross-disciplinary research have been characterized. These more specific characterizations are frequently referred to as multidisciplinary,

interdisciplinary, and transdisciplinary (Klein, 1990; Repko & Szostak, 2014; Klein, 2014). While each specific form differs in several ways, a key differentiating factor, and relevant to this research, is how insights are integrated. In the case of multidisciplinary research, the inputs from two or more disciplines are brought together but do not necessarily change or result in something new. On the other hand, interdisciplinary research involves a more involved integration of inputs or insights into a more comprehensive output or understanding (Newell, 2001).

Transdisciplinary research was introduced as a further refinement or enhancement of cross-disciplinary research that transcends the disciplinary bounds of both multi- and interdisciplinary research, with definitions that at times are confusing (Rosenfield, 1992). In the *Oxford Handbook of Interdisciplinarity*, transdisciplinary research is primarily referred to as interdisciplinary, but stress is placed on the importance of addressing the most complex and broad societal problems and involving non-academic stakeholders (Frodeman et al., 2017). In some definitions of cross-disciplinary research transdisciplinary research is one that involves either the creation of a new interdisciplinary field or a "transcending" of disciplines (O'Rourke et al., 2013). In any case, it is important to note that while all forms of cross-disciplinary research may be conducted by a single individual, this form of research may also be conducted by teams. For the former, many interdisciplinarians have over time created models and guidance for conducting individual cross-disciplinary research (Newell, 2001; Repko & Szostak, 2014).

In order to understand the study of cross-disciplinary research in teams, or *collaborative, cross-disciplinary research*, it is important to understand the broader field of team science. Collaborative, or team-based, research has been steadily on the rise since the early 1990s and has become a key feature of successful science programs (Stokols, Hall, et al., 2008). The shift from individually conducted science to more team-based science has been seen in literature

publications and citations since the 1990s (Jones et al., 2007). This is perhaps a byproduct of the increasing rapidity with which science evolved into greater specialized fields which would then necessitate those individual specialized sciences coming back together to solve complex problems. Also, public agencies and private foundations have increasingly promoted team science through funding initiatives and priorities (Stokols, Hall, et al., 2008). This growth of team science and investment in team science has sparked research into the effectiveness of team science, its antecedents, processes and methods, and the performance or outcomes (including value or impact) of it. The study of these features of team science has become known as the Science-of-Team-Science (SciTS).

The Science-of-Team-Science

Perhaps the first use of the term Science-of-Team-Science came with a conference organized by the National Institutes of Health in October 2006 (NCI, 2006). At this conference, SciTS was defined as:

> "[a] rapidly emerging field concerned with understanding and managing the circumstances that facilitate or hinder the effectiveness of large-scale research, training, and translational activities…" (NCI, 2006).

Following the discussions of this conference, this nascent field of study was further developed and described in an American Journal of Preventive Medicine supplemental issue (AJPM). It was in this issue of AJPM that several seminal articles on the SciTS were published (Hall et al., 2008; Mâsse et al., 2008; Stokols, Hall, et al., 2008; Stokols, Misra, et al., 2008a). The field would further grow through its first annual International SciTS conference in 2010 and the formation of an international society in 2018, the International Network for the Science of Team Science (INSciTS).

There are several subdomains or areas of research interest in the field of SciTS. These domains evolved from an original six groupings suggested by Stokols *et al* (2008b): interpersonal, intrapersonal, physical environmental, organizational, societal and political, and technologic. In 2011, Holly Falk-Krzesinski et al. conducted a concept-mapping evaluation of research in the SciTS field (Falk-Krzesinski et al., 2011). The following concepts were identified through the mapping exercise and would inform a future research roadmap in SciTS: "Definitions and Models of Team Science, Measurement and Evaluation of Team Science, Disciplinary Dynamics and Team Science, Structure and Context for Teams, Characteristics and Dynamics of Teams, Institutional Support and Professional Development for Teams, and Management and Organization for Teams" (Falk-Krzesinski et al., 2011, pg. 18). These concepts or domains of SciTS were thoroughly reviewed and updated in the National Academy of Sciences' 2015 consensus report titled, "Enhancing the Effectiveness of Team Science". This report was produced by a committee of experts from SciTS to "recommend opportunities to enhance the effectiveness of collaborative research in science teams, research centers, and institutes" (Council, 2015, p.3). When the 2015 NAS report was introduced it organized research around individual and team factors, including individual indicators of collaboration to team processes, such as cross-disciplinary research; team composition and assembly; education for team science; leadership of teams; and, institutional or organizational factors that contribute to team science. A new watermark would be achieved with the release of *"*Advancing Social and Behavioral Health Research through Cross-Disciplinary Team Science: Principles for Success", including a new set of domains for the state of the science ("Strateg. Team Sci. Success," 2019). Understanding these domains is important for this study, as it sets the stage and represents the

short but rich history of the science. But the key focus for this study is on one domain, that of cross-disciplinary integration and this is discussed in the next section of this literature review.

Before discussing cross-disciplinary integration, a brief review of what the other domains or subdomains of SciTS have in common is in order. The commonality is the focus on the measurement or investigation of key indicators and factors that influence the effectiveness of team science. The measurement or study of Team Science is after all what makes SciTS a new science or discipline. As a seminal example, Caroline Wagner and colleagues in 2011 conducted a comprehensive literature review of performance measures, management and evaluation of interdisciplinary research (IDR) in response to a request from the U.S. National Science Foundation (Wagner et al., 2011). Wagner attempted to establish metrics, but limitations were noted and further research at the time was still warranted.

Wagner *et al*.'s review also points out that at the time of writing, SciTS was for the most part focused on understanding the antecedent conditions, collaborative processes, and outcomes associated with Team Science and its impact. Several quantitative and qualitative approaches are discussed. Lastly, two important points or limitations are offered by Wagner *et al*. that are relevant for this study. First, that knowledge integration is a critical concept to incorporate in future research and second it must be recognized that this integration can occur both within a single mind and as part of a team. Integration continues to be described as one of the defining processes and outputs of Team Science, worthy of further research, and this further supports the impact of this research (Huutoniemi et al., 2010; O'Rourke et al., 2013; Repko & Szostak, 2014; Salazar et al., 2012; Science, 2014; Thompson Klein, 2014).

Several seminal articles in the SciTS space attempt to assess the outputs or outcomes/value of team science through a quantitative lens, whether for integration or other

characteristics of cross-disciplinary research. Some of these studies leverage bibliometric approaches, such as the work of Hall *et al.* that explored the bibliometric indicators of publications from research initiatives supported by the National Cancer Institute and the National Institutes of Health (Hall et al., 2012). This study marked a more focused and nuanced use of bibliometrics to assess the impact of Team Science. Bibliometrics can also be used to explore the role of scientific research networks on cross-disciplinary research, another potential antecedent or input, as detailed in Leydesdorff's 2018 work titled, "Betweenness and diversity in journal citation networks as measures of interdisciplinarity—A tribute to Eugene Garfield" (Leydesdorff et al., 2018). While bibliometrics offer a unique tool for evaluating Team Science it does not target integration directly.

Taking a more qualitative approach, surveys and interviews have also seen wide use in the SciTS field to explore both the individual factors or characteristics of researchers that promote Team Science (Lotrecchiano et al., 2016; Van Rijnsoever & Hessels, 2011) but also more comprehensive assessments of the conditions that either facilitated or challenged Team Science (Mâsse et al., 2008; Vogel et al., 2014). Building on this qualitative approach, several studies have even attempted to combine qualitative and quantitative elements to empirically evaluate Team Science. These mixed method approaches have been used to evaluate Team Science in proposals (Hall et al., 2008; Huutoniemi et al., 2010; Nichols, 2014) and even assess integration in dissertations on other interdisciplinary topics (Mitrany & Stokols, 2005). There are some important insights from these mixed methods approaches for this study.

First, in the research approaches of Hall, Huutoniemi, Stokols, and others, while exciting and relevant to integration generally, the integration is only indirectly measured by an investigation of number, type, and diversity of contributions to the research, such as the

disciplines or contributions of those disciplines to the research being studied. In fact, Huutoniemi *et al.*'s investigation of research proposals in the Netherlands uses integration, a defining characteristic of interdisciplinarity, to inform their typology, offering a useful sub-categorization of the integration as follows: "to analyze multiple kinds of empirical material", "to combine methods of several disciplines", and "to work on theoretical tools for integrative analysis" (Huutoniemi et al., 2010, p.84). next, and somewhat more pertinent to this study is research from the philosophy of science on integration and especially recent work on the application of philosophy in the facilitation of cross-disciplinary research (Eigenbrode et al., 2007; O'Rourke et al., 2016; O'Rourke & Crowley, 2013). This will be explored further in the next section on integration.

These comprehensive studies offer perspective on the breadth of research in SciTS and inform a worldview of SciTS used in this study. Understanding the breadth of research in SciTS helps to set this study in translational context as much SciTS research has led to the development of recommendations to promote collaborative cross-disciplinary research and communication (O'Rourke et al., 2013). The historic overview of SciTS is important context for this study but, a deeper understanding of the integration and integration processes involved in Team Science, particularly the theories and frameworks related to cross-disciplinary integrated are needed to inform this study. The literature supporting these theories and frameworks are described below.

Cross-Disciplinary Integration

The literature on cross-disciplinary research, which includes both interdisciplinary research and transdisciplinary research is rich. The literature specifically on the phenomenon of integration that is central to cross-disciplinary research is also rich and extensive, ranging from theoretical to more practical. Important early contributions to this knowledgebase came from

Maurice de Wachter in 1982 who discussed new approaches to problem-solving in bioethics that began to illustrate interdisciplinary integration (de Wachter, 1982). However, de Wachter focused the integration on inputs and outputs and essentially avoided the process by which the integration occurred. This model of interdisciplinary integration would find its way eventually into Julie Thompson Klein's thinking about integration that would be discussed in her 1990 review of interdisciplinary research (Klein, 1990). Information integration theory from Norman Anderson is another example of an early theory of integration that would influence the developing thinking on cross-disciplinary integration (Anderson, 1970) with an almost formulaic approach to integration suggested. Following Klein's discussion of integration in 1990 research and directions on integration would begin to formulate into 3 areas: interdisciplinary research integration (Newell, 2001; Repko, 2007), transdisciplinary research integration (Bammer, 2013; Bergmann., 2012), and integration for cross-disciplinary research, which would include both interdisciplinary and transdisciplinary research (Klein, 2012; O'Rourke et al., 2016).

Interdisciplinary research and the concept of synthesis or integration was described by the theorist William Newell in his "A Theory of Interdisciplinary Studies" (2001), as a formulaic process, building on the initial work of Klein to describe the interdisciplinary process (1990). It is important to note that this approach to interdisciplinary research is considered more individualistic than it is team-based. Newell stressed the important prerequisite of interdisciplinary research being that a problem was complex by articulating important connections between interdisciplinary research and complexity science, particularly the sheer necessity for interdisciplinary approaches to tackle problems of complex systems. The two major activities of the interdisciplinary research process were: "(1) draw on disciplinary perspectives and (2) integrate their insights through construction of a more comprehensive understanding"

with several sub-steps (Newell, 2001). Lastly, it is important to note that Newell believed this process could be performed by a single interdisciplinary researcher or interdisciplinarian. He would continue to refine his process for inclusion in a 2007 book chapter titled "Decision Making in Interdisciplinary Studies" (Newell, 2007). These steps are outlined below, and while they are useful in some of the theories they build on, such as common ground and integration, they are not entirely applicable to this study given the individual view:

1. Drawing on disciplinary perspectives
    - Defining the problem (question, topic, issue)
    - Determining relevant disciplines (including interdisciplines and schools of thought)
    - Developing a working command of the relevant concepts, theories, and methods of each discipline
    - Gathering all relevant disciplinary knowledge
    - Studying the problem from the perspective of each discipline
    - Generating disciplinary insights into the problem.
2. Integrating their insights through construction of a more comprehensive understanding
    - Identifying conflicts in insights by using disciplines to illuminate each other's assumptions, or by looking for different concepts with common meanings or concepts with different meanings, through which those insights are expressed
    - Evaluating assumptions and concepts in the context of the specific problem
    - Resolving conflicts by working towards a common vocabulary and set of assumptions
    - Creating a common ground

- Identifying (nonlinear) linkages between variables studied by different disciplines
- Constructing a new understanding of the problem
- Producing a model (metaphor, theme) that captures the new understanding
- Testing the understanding by attempting to solve the problem.

(Newell p.248, 2007)

Allen Repko is another interdisciplinarian who shared an interest in interdisciplinary research or interdisciplinarity. Repko similarly focused on integration and common ground as key components of interdisciplinary research conducted by interdisciplinary researchers, both individuals and teams (Repko, 2007). Repko's research added insights from cognitive psychology to the theory of common ground and implications for integration, notably relevant to this study was the implication that finding common ground as part of integration is a process as opposed to a method, and that the presence of integration can be used to differentiate multidisciplinary research from interdisciplinary research (Repko & Szostak, 2016).

In some cases a key dimension or focus of integration is that it takes on some form of social dimension or real-world application (Bammer, 2013; Bergmann., 2012; Klein, 2012). These forms of integration are typically found in transdisciplinary research where the focus of the research from the onset for the pursuit of social and scientific purposes (Bergmann., 2012). Bergmann also emphasized the importance of not only the expertise of multiple disciplines but the expertise of partners from the society as well. This model for integration in transdisciplinary pursuits was best characterized in the following conceptual model from the Institute of Social-Ecological Research (Jahn et al., 2012). In this model, transdisciplinary integration occurs in a completely different phase and serves a unique purpose, apart from interdisciplinary integration.

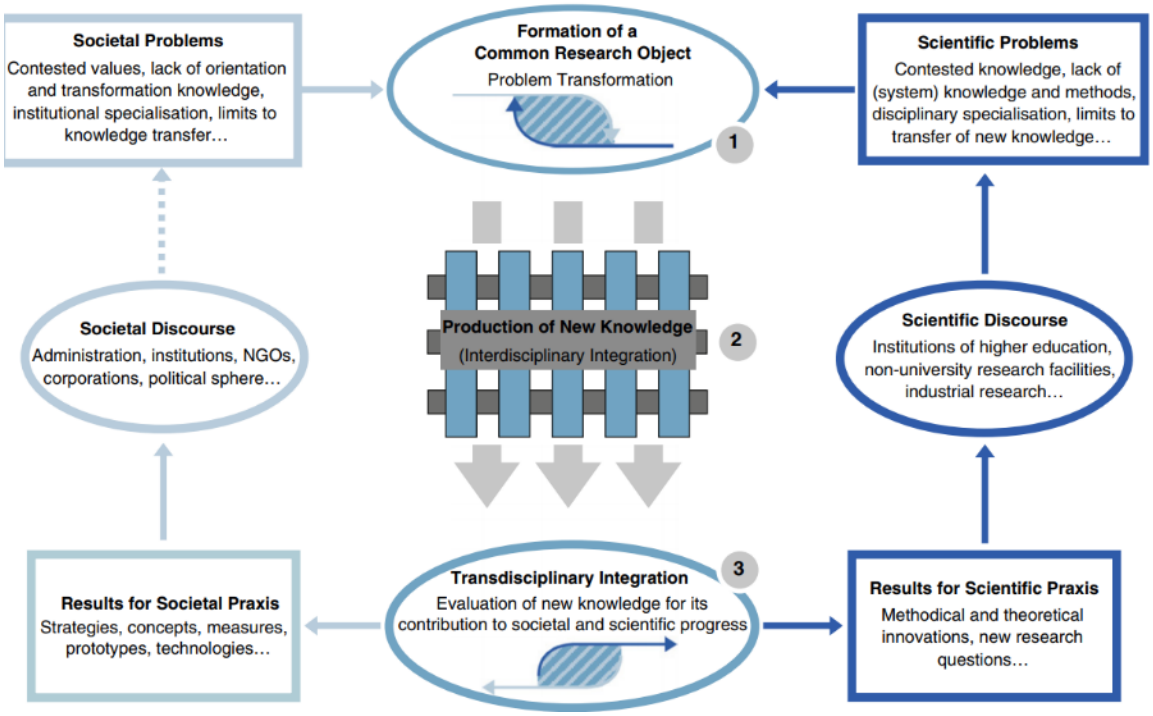


Figure 5: ISOE Transdisciplinary Research Process (Jahn et al., 2012, p. 5)

Bammer would add an important contribution to the understanding of integration with the characterization of integration as a planned process. However, a large distinction in Bammer's integration was that it would be expected to be primarily collaborative and involve experts working together (Bammer, 2013). In addition, Bammer describes two forms for this integration process, either as synthesis or as integration, and lastly adds a unique contribution to the concept of integration related to the management of the unknowns in decision-making and action. This last nuance of Bammer's transdisciplinary integration is relevant to the final decision made by FDA review teams given how uncertainty must be critically characterized.

While the research on interdisciplinary research and transdisciplinary research is important to understand as relevant to defining integration, they perhaps lack a universality or flexibility that could allow them to be easily applied to the context of this study, the FDA review

of a new drug product. In the review of literature on integration, the theories and frameworks of integration that are most relevant for this study were those that do not take on such an algorithmic or formulaic approach. The two theories that have broadest applicability, and by which this study is informed, come from the revised theory of cross-disciplinary research from Julie Thompson Klein (Klein, 2012) and a theory for cross-disciplinary integration that built on available theories of integration at the time from O'Rourke and colleagues (O'Rourke et al., 2016).

Klein in her 1990 book titled, *Interdisciplinary: History, theory, and practice* surveyed the vast field of interdisciplinary research and integration (Klein, 1990). The process of integration described by Klein in this book was stepwise and could take on either a "soft" approach – such as simply relying or referring to something from another discipline or a "hard" approach – where the tools and methods of other disciplines are leveraged. In this process, the interactions between disciplines were exemplified by different modes, such as "(1) borrowing, (2) solving problems, (3) increased consistency of subjects or methods, and (4) the emergence of an interdiscipline" (Klein, 1990, p. 64). The Klein (1990) model for integration included 12 steps that in summary cover the problem identification and definition, specifying what research and knowledge would be needed, and finally integrating, with close-out steps to confirm that the solution or answer to the problem is confirmed. Lastly, while Klein acknowledges that this process is rather algorithmic and stepwise, it is by no means linear and is subject to iteration. The key step of integration in Klein's step-wise model was 3b, "*integrating* the individual pieces to determine a pattern of mutual relatedness and relevancy" (Klein, 1990, p.189). This left much to be desired regarding how the integration is arrived at.

In the time following her 1990 book, Klein's theory and model of interdisciplinary integration would develop further as a result of her own continued research and the application of her theory by others (e.g., Newell). In 2012, Klein would publish a revised approach to interdisciplinary integration characterized by 4 principles:

1. "The Principle of Variance: No Universal Formula for Integration"
2. "The Principle of Platforming: Interaction Structure, Integration Potential, Fundament"
3. "The Principle of Iteration: Moving Back and Forth, Bootstrapping, Triangulation, Reflective Balance, and Weaving"
4. "The Principle of Communicative Rationality: Shared Language Culture, Social Learning, Translation-Negotiation-Mediation, Intersubjectivity" (Klein, 2012, p. 293-295).

These four principles applied to the theory of interdisciplinary integration would shed much light on the underlying process of integration, and speak more specifically to the inputs (e.g., communication) and outputs (e.g., mutual understanding) into the process. This is a significant insight and considered foundational in future theories of integration and in understanding the analytical framework for which this study is based. It is also important to note that Klein self-described the process at this time as no longer algorithmic, which opens the door to more dynamic, iterative and expansive approaches to integration (Klein, 2012).

As a result of research related to the Toolbox Dialogue Initiative, a new framework of cross-disciplinary integration would emerge that was more suitable to analyzing inputs, process, and outputs of the integration process (O'Rourke & Crowley, 2013). This framework would be further defined and described in 2016 by O'Rourke et al. and is most applicable to this study of

integration in FDA new drug reviews due to its emphasis on not just the final product or output of the integrative process but also the process by which integration occurs. Furthermore, the framework and Input, Process, Output (IPO) cross-disciplinary model associated with it is purported to have applications across the full range of cross-disciplinary integration (e.g., mutli-, inter-, and transdisciplinary integration). With the FDA new drug review potentially taking on either a multidisciplinary or interdisciplinary form depending on the review process, use of this framework of cross-disciplinary integration and its flexibility may be most appropriate for modelling it.

The IPO cross-disciplinary integration model lays out integration as a "generic" combination process, the details of which are determined by the specific contexts in which particular instances of integration occur" (O'Rourke et al., 2016, p. 67). In this "generic" process, inputs are combined, and the output is produced. This is much like any other IPO model or structure and is used in a wide variety of domains. The utility of IPO model from O'Rourke et al. is the conceptual framework it offers to understand integration in setting of collaborative cross-disciplinary research. It offers a sort of infrastructure for integration with variables and parameters with which to understand integration as a process and as a product. It also provides two dimensions, quality and quantity, along with an analytical framework, in which to organize "one's thinking" about the inputs, outputs, and integration process variables of the model, and "facilitate comparison" (O'Rourke et al., 2016, p.68). This analytical framework is described below:

Inputs/Outputs

- **Quality**: What is the character of the inputs/outputs? (Are they cognitive? Epistemic? Social? Are they abstract or concrete?) How do inputs into the process differ? How do outputs differ?
- **Quantity:** How many different kinds of inputs/outputs are there (e.g., inputs/outputs at different levels of organization, as in Brigandt (2010))? How many inputs/outputs of a particular kind (e.g., data sets, disciplines) are involved?

  (The quantity of inputs is also associated with the scope of the integration process under consideration. The quantity of inputs also begins to inform and is informed by the parameters of the IPO model, such as scale and comprehensiveness—discussed below.)

Process

- **Quality:** The integration puts or brings together inputs in some *integrative relation: "fusing", "melding", "amalgamating", "knitting", "linkage", "making sense together", "interconnection", and "harnessing differences"*, or a *disintegrative relation: "dissociation", "differentiation", and "boundary setting"*, or *combinational relation*: *"assembling".* Was the integration process purposive? Algorithmic? Heuristic or constructivist?
- **Quantity:** How many specific changes to inputs were required to produce the outputs? What degree of change (low: process leaves inputs alone but connects them v. high: process transforms inputs into something new or reconceived collectively when combined)?

Parameters

- *Scale (Global/Local)*:
  - What is the scale of cross-disciplinary integration?

    - Does integration operate globally (e.g., the domain level, such as all of biology), locally (e.g., data sets, specific problems), or somewhere in between (e.g., disciplines, fields)?

      *This will affect inputs, process, and outputs.

- *Commensurability (High conflict/Low conflict)*:
    - Are the inputs integrable, or must conflict be reduced before they can be combined?
    - Does the integration process leverage conflicting differences while transcending them?
    - Can integration take place if conflict is minimized?

      *This parameter will affect inputs and process.

- *Comprehensiveness (High/Low)*:
    - How comprehensive will the output be, relative to the inputs? For example, will the integration process result in a cross-disciplinary output that provides a more comprehensive view of a problem than the disciplinary inputs, or will it result in an innovative but focused cross-disciplinary output that is a "vector sum" of the inputs without being more comprehensive)?
    - This parameter will affect inputs, process, and outputs.

(O'Rourke et al., 2016, p. 69)

Leveraging this extensive theoretical and analytical framework from O'Rourke *et al* (O'Rourke et al., 2016), the integration occurring in the FDA new drug review process, whether that be a multidisciplinary or interdisciplinary process, can be modelled and subsequently

defined. And as mentioned earlier, this framework is best fit for this study due to its flexibility and customization with multiple customizable parameters and variables to analyze data across the integration process. While it remains to be determined if the IPO model of cross-disciplinary integration developed by O'Rourke *et al* is truly as universal as it is proposed, this study may in fact shed light on the application of this model and framework for collaborative cross-disciplinary research in a new context. In addition, the validation of a potentially universal framework for studying integration would add an important evaluation tool for cross-disciplinary integration, and the SciTS.

The final insight from the literature on cross-disciplinary integration comes from an assessment of collaborative interdisciplinary reasoning from Bethany Laursen (2018). Laursen refers to collaborative interdisciplinary reasoning as "the attempted integration of disciplinary contributions to exchange, evaluate, and assert claims that enable shared understanding and eventually action in a local context (Laursen, 2018, p. 81)". This definition of the integration process and its focus on the disciplinary contributions has great relevance and similarities to the IPO framework and proposed approach to modelling cross-disciplinary integration used in this study. To operationalize this definition and study collaborative interdisciplinary reasoning, Laursen leveraged a Sankey modelling approach to diagram the flow of the integration process.

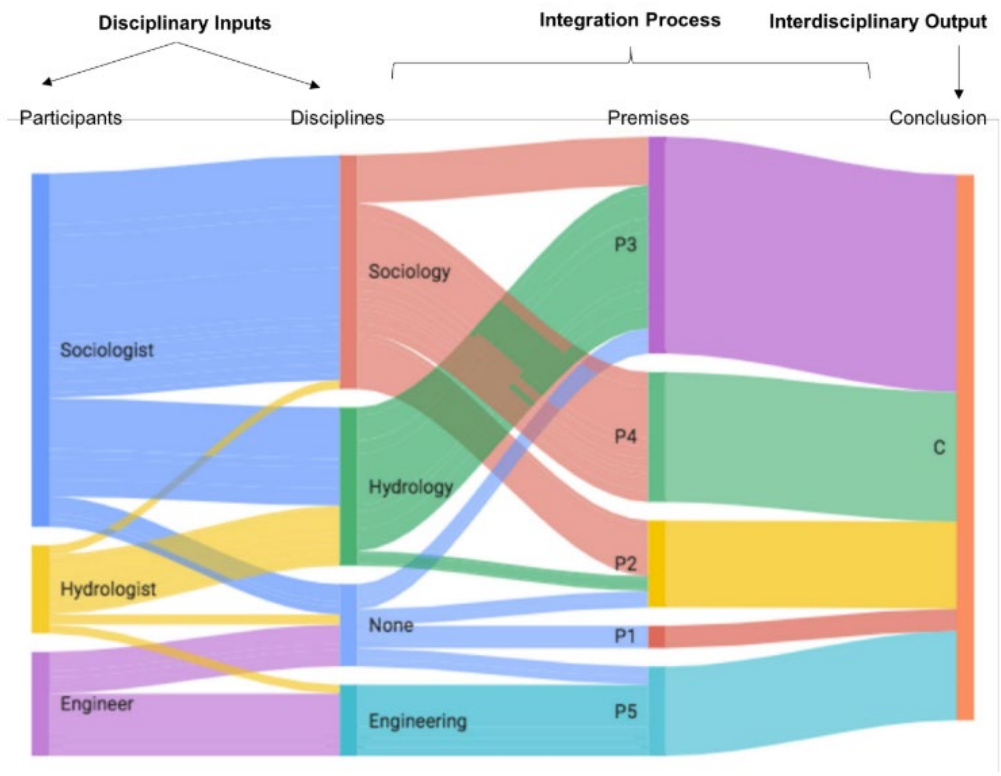


Figure 6: Sankey Diagram of Collaborative Interdisciplinary Reasoning
(Laursen, 2018, p. 86)

In the flow diagram of collaborative interdisciplinary reasoning, dialogue was analyzed to capture the flow of words from speakers to disciplines, premises, and conclusions. The number of words from a speaker would dictate the width of the originating flow and how they fed into the disciplinary contributions to a premise and subsequent conclusion can then be diagrammed. This approach helps illustrate the dynamism of the integration process. A similar approach could be used in this study to help diagram the disciplinary contributions to benefit-risk review issues and how those contributions (inputs) fed into process activities and subsequent outputs (recommendations or actions).

Inferences for Forthcoming Study

The domains discussed in this literature review inform the overall conceptual framework for this study that borrows knowledge from the context of FDA new drug product assessments to contextualize the IPO framework for investigating integration in cross-disciplinary research; See Figure 6. Additional knowledge and insights from cross-disciplinary and particularly collaborative cross-disciplinary research creates a foundation for explaining the importance of the types of key input and output variables, describing changes to inputs and outputs, and a theoretical framework for the understanding the integrative nature of the change process.

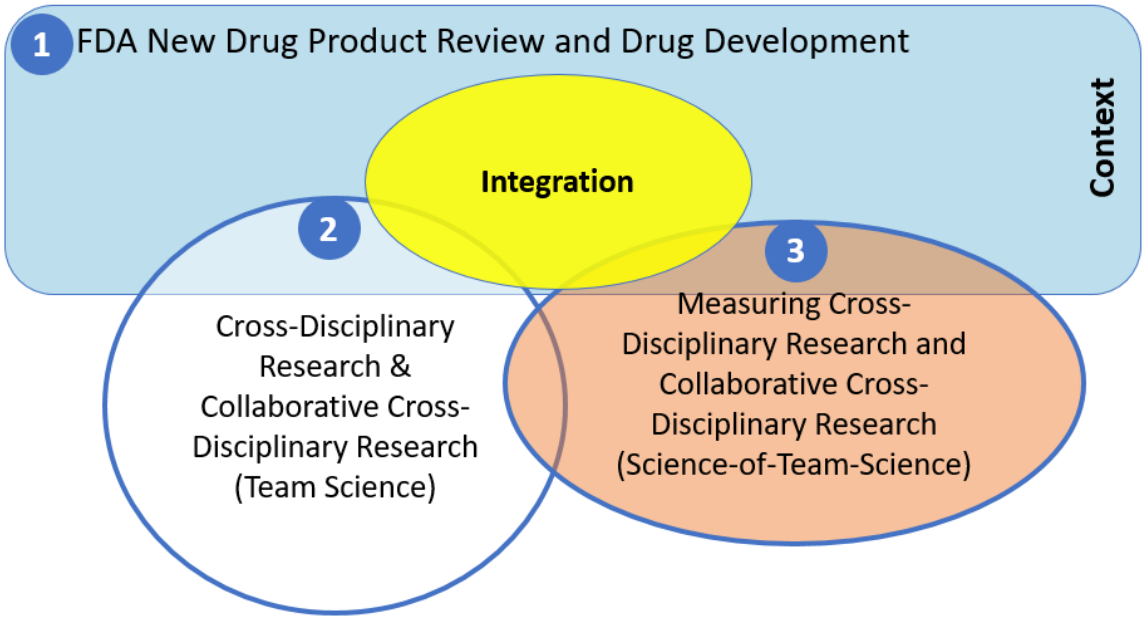
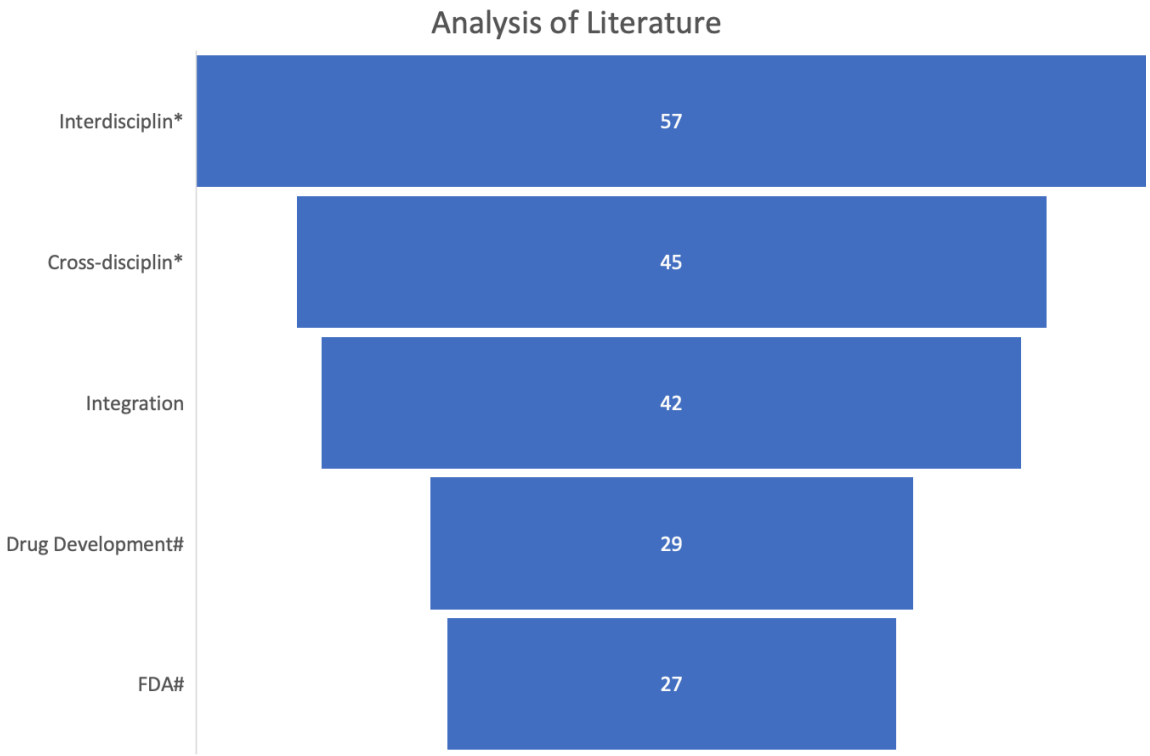


Figure 7: Key Literature Domains

Literature from the topics of interdisciplinary research and cross-disciplinary research was rich and informative. After reviewing for relevancy to this study, 57 articles related to interdisciplinary research and 43 articles, many overlapping, on cross-disciplinary research were included. As expected, a roughly similar number (41) of articles on integration in inter/cross-

disciplinary research were found as integration is considered a key characteristic of cross-disciplinary research.

When exploring assessments or measurements of integration there was a paucity literature available, and among the research identified the methods varied from study to study suggesting more work is needed. In the context domains of drug development and FDA benefit risk assessments, a much smaller number of references were identified and included. There is very little research on cross-disciplinary research in drug development and no research at the FDA on cross-disciplinary research, including integration. Figure 8 illustrates the quantity of literature included in the bibliography for this study.



% Does not include full analysis of literature library.
* Wildcard in search term.
# Includes previous search terms in addition.

Figure 8: Analysis of Literature[%]

From the literature (and gaps) identified, several insights for this study can be inferred. First, while literature exists on the new drug development process, and FDA's assessment of new drug product applications, little literature exists on the collaborative research or integration processes in the FDA's assessment. A tremendous amount of literature exists on the benefit-risk assessment of new drug products and FDA's framework for these assessments, the BRF. However, how this benefit-risk assessment or the BRF is translated into the FDA new drug product review processes and documentation has not been extensively discussed in literature. Secondly, integration is a key characteristic that occurs in collaborative cross-disciplinary research. While there is literature and research on integration in cross-disciplinary research, there is little on collaborative or team-based integration. This suggests that research on collaborative cross-disciplinary integration will be a useful contribution to the field of team science. Furthermore, there is very little literature or research on collaborative cross-disciplinary research at the FDA, and none on integration. Thirdly, the literature also suggests that the underlying phenomenon of the integration process may not yet be fully understood, at least not to the universal extent needed to reliably measure it across the diverse range of teams and team-based science activities that use it in cross-disciplinary research in Team Science. More specifically, the gaps appear to be either in attempts to measure integration in the products (outputs) of integration or the antecedents of the integration (inputs), without much focus on measuring the integration process itself. As such, a need exists to understand the complete picture of integration by exploring the process from end-to-end and measuring evaluation as both a process and an output. This need aligns to the goals of this study to understand the integration that is occurring in FDA collaborative cross-disciplinary research, and if it is even occurring. Lastly, the approach to the study and the conceptual framework are informed by the application of O'Rourke *et al.'s*

framework and IPO model of integration. The use of the IPO model as a conceptual framework is an ideal fit for this study because potential use as a "universal model" and subsequent adaptability to a variety of contexts (Laursen & O'rourke, 2019). More specifically, it is the ability of the model to handle multiple iterations levels of integration, across the full collaborative, cross-disciplinary experience rather than a single integration event.

Theoretical and Conceptual Frameworks

This study is guided by a series of theories and frameworks from the fields of cross-disciplinary research, Science-of-Team-Science, and regulatory decision-making for medical products. The first theoretical foundation for this study comes from Julie Thompson Klein's theory of interdisciplinarity and the core process of interdisciplinary work, integration (Klein, 1990). Klein's view of interdisciplinary research is that it is research that involves two or more disciplines and involves a greater degree of integration than purely disciplinary or multidisciplinary work. Such a continuum of integration for thinking about research can be useful in assessments and in fact Klein and her collaborators have done just that in previous research. In the 2010 study conducted by Huutoniemi, Klein, Bruun, and Hukkinen (Huutoniemi et al., 2010), an empirical approach to analyzing the interdisciplinarity of research proposals was described, including a typology of interdisciplinarity that included:

- Encyclopedic multi-disciplinarity
- Contextualizing multi-disciplinarity
- Composite multi-disciplinarity
- Empirical inter-disciplinarity
- Methodological inter-disciplinarity

- Theoretical inter-disciplinarity

The application of such a continuum of cross-disciplinary research to an empirical analysis of the research proposals was guided by four elements: background and objectives, expertise and implementation, results, and significance. The continuum is represented in Figure 9, below. The continuum that represents this theory serves as a useful guide for this study, because it suggests certain forms of integration that might occur in different degrees of integration, which might be expected in FDA's new drug product reviews, which are self-described as either multidisciplinary or interdisciplinary. More specifically these elements, and the continuum that they exist in, helps provide "signposts" by which to characterize the transformation of inputs to outputs in an integration process.

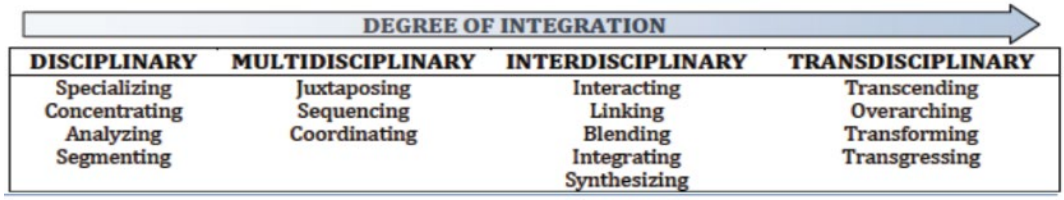


Figure 9: Continuum of Cross-Disciplinary Research

(Thompson Klein, 2014)

The next theoretical framework that is core to this study is one related to the phenomenon of integration in interdisciplinary research. Over the years the concept of integration has been an integral component of interdisciplinarity and has been discussed and researched by many theorists, such as Newell, Repko, Klein and Bammer (Bammer, 2013; Frodeman et al., 2017; Klein, 1990, 2012; Newell, 2001; Repko, 2007). In 2016, Michael O'Rourke, Stephen Crowley, and Chad Gonnerman of the Toolbox Dialogue Initiative developed a philosophical and more practical theoretical model of integration (O'Rourke et al., 2016). This framework offers a schematic parameterized inputs-process-outputs (IPO) model for cross-disciplinary integration; see Figure 10, below.

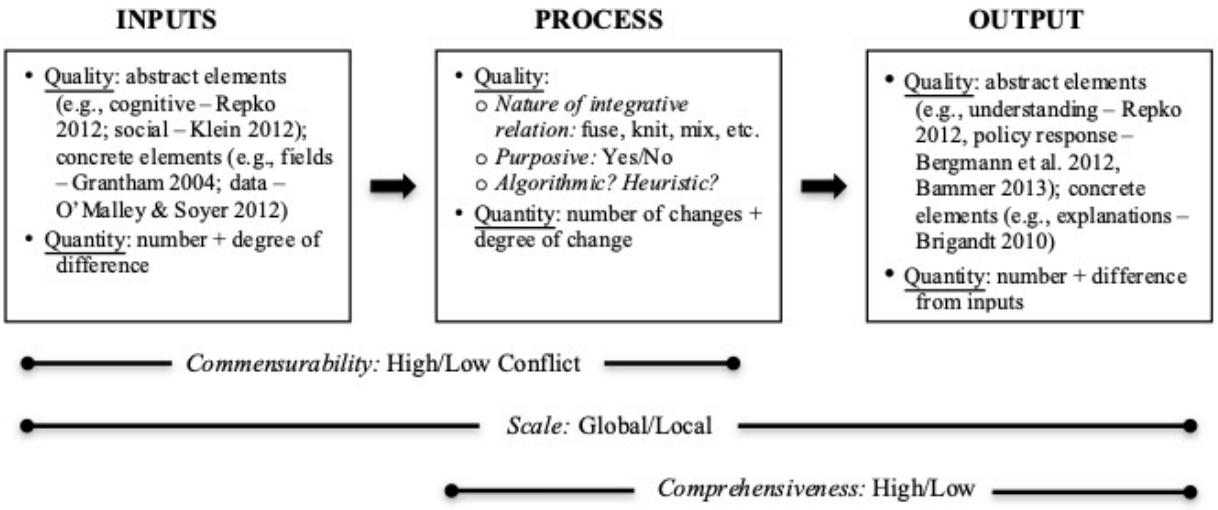


Figure 10: Cross-disciplinary Integration IPO Model

From this theoretical framework, several variables related to the inputs, process, and outputs of an integration process can be defined, such as the quality and quantity of the inputs, the process, and the outputs. These variables will become the basis of an analysis of integration in FDA new drug product reviews. In addition, the contextual parameters of scale, commensurability, and comprehensiveness allow the model to be used more universally at different levels of cross-disciplinary research and to better characterize the integration.

In order to use O'Rourke *et al.*'s 2016 parameterized IPO model of cross-disciplinary integration as the basis of an empirical analysis of integration in FDA new drug product reviews it must be contextually adapted. The inputs to FDA new drug product review can vary greatly depending on the development program but tend to be generated from and assessed by the following FDA disciplines: clinical, clinical pharmacology, nonclinical pharmacology/toxicology, biostatistics, pharmaceutical quality, regulatory/legal, and experts on gathering patient experience. The outputs of the integration process are organized around the

evidence and uncertainty related to four dimensions of the US FDA BRF (FDA, 2018a). The BRF is shown in Figure 11, below.

Benefit-Risk Integrated Assessment		
Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Figure 11: US FDA Benefit-Risk Framework

The BRF has become a tool for FDA new drug product review teams to process evidence and create common ground to support decision-making. In addition, through its structure, it has become the basis by which the integration of disciplinary insights occurs. The rows in the BRF outline the key dimensions of the assessment, related to the therapeutic context (i.e., analysis of condition and current treatment options) and the product-specific assessments of benefit and risk and risk management. The columns differentiate between the evidence and uncertainties that are pertinent to the benefit-risk assessment and the FDA's conclusions and reasons supporting the strength of evidence and the potential significance of findings or review issues (Duke Margolis Center for Health Policy, 2019). Lastly, an integrated assessment of benefits and risks brings together all the dimensions and considers whether the evidence and uncertainties for the benefits outweigh the risks for a favorable decision in the context of treatment.

The May 2019 Discussion Document outlines several key considerations for FDA's benefit-risk assessment which could serve to guide the document collection and thematic analysis of inputs and outputs in the completed BRFs of both multidisciplinary and integrated reviews (Duke Margolis Center for Health Policy, 2019). See reproduced table below.

Table 2: Potential codes for BRF analysis

BRF Section	Key Considerations	Common Sources of Uncertainty
Analysis of Condition	• Context of use for proposed indication: intended medical use, target patient population • Relevant clinical aspects of the condition • Patient-focused disease burden	• Ability to define target population • Complexity of disease (e.g., effect on understanding drug's mechanism of action) • Extent of patient input on disease burden
Current Treatment Options	• Goals of current standard of care • Efficacy and safety of available therapies • Burden of treatment (e.g., administration) • Aspects of disease burden not addressed by current therapies	• Patient utilization of treatments • Extent of evidence about therapies not FDA-approved for the indication • Extent of patient input on unmet needs
Benefit	• Strengths/limitations of clinical trial data: potential implications for assessing drug efficacy • Clinical relevance of the study endpoints: ability to measure or predict clinical outcomes of importance to patients • Demonstrated results and their clinical significance, informed by: • Magnitude, duration of treatment effects • Nature of benefit (e.g., disease modifying, symptom reduction) • Distribution of effects in the study population • Potential effect on future clinical outcomes (e.g., death, organ damage) • Ability to predict which patients may benefit • Ability for patient/provider to assess individual benefit • Patient perspectives on benefit • Generalizability of the clinical trial evidence to the to-be-marketed patient population in the postmarket setting	• Program or trial design; e.g., less than two randomized controlled trials, use of single arm-designs, use of observational data • Statistical uncertainty • Relationship between study endpoint and clinical outcomes • Extent of patient input on the significance of expected benefits • Populations not included or underrepresented in clinical trials • Quality and integrity of data
Risk and Risk Manage-ment	• Strengths/limitations of safety evaluation: potential implications on assessing drug risks • Serious adverse events or safety signals—clinical significance and remaining uncertainties, considering: • Magnitude, duration, severity of harms • Reversibility of harm (e.g., upon cessation of treatment)	• Size and extent of safety population; background rate of adverse event in the treated population (e.g., trials may be underpowered to identify all safety risks) • Understanding of the relationship between safety endpoints and clinical outcomes • Potentially susceptible patient groups (e.g., elderly, patients with co-morbidities) not included or underrepresented in clinical trials

	• Distribution of harms in the study population • Potential effect on future clinical outcomes (e.g., death, organ damage) • Ability to predict which patients may be at risk • Ability to prevent, detect, and mitigate harms • Patient perspectives on risks • Adverse effects (e.g., nausea) that could affect tolerability or adherence • Potential impact of product quality or device issues on effectiveness or safety • Additional safety issues considering how prescribers and real-world use in the postmarket setting may differ from the clinical trial setting • Effectiveness of strategies to manage risks	• Quality and integrity of data • Challenges or barriers to quality health care delivery • Untested risk management strategies • Potential differences between the development batch of the drug versus commercial scale
Conclusions Regarding Benefit-Risk	• How therapeutic context affects threshold for benefits and tolerance for risk and uncertainty • Benefit and risk values and tradeoffs, including patient perspectives • How the product, if approved, may enhance the treatment armamentarium • Importance of unresolved uncertainties • Need for labeling (e.g., boxed warning) or REMS to support favorable benefit-risk assessment • Need for postmarketing evidence to address uncertainty	• Extent of patient and other inputs on benefit and risk values and tradeoffs • Ability to generate the desired evidence of safety or benefit (e.g., through randomized control trials or observational studies) in the postmarket setting

A new theoretical model that contextualizes the IPO model for FDA new drug product reviews was created to support the conceptual framework of this study, see Figure 12, below. This model is based on regulatory documents that describe the new drug product review processes, both traditional and newly proposed, and information from the FDA-Duke Margolis Center for Health Policy Discussion Document to support the May 2019 workshop titled, "Benefit-Risk Assessment Throughout the Drug Lifecycle" (Duke Margolis Center for Health Policy, 2019). As illustrated in this new theoretical model of integration in new drug product reviews, inputs to the process can originate from a multitude of disciplinary domains, and these inputs then contribute to more comprehensive insights about the new drug product, such as the product's benefits and risks. For example, clinical efficacy data of statistical significance

generated from robust clinical trials may be considered alongside data on patient experience with the new drug product, thereby by forming a more comprehensive understanding of the benefit of the product that is both statistically significant and clinically meaningful. This process by which inputs (i.e., assessments of benefits and risks) come together and ultimately lead to a benefit-risk assessment is through an integration process that is informed by the BRF.

As discussed previously, the nature of the combination process, or integrative nature to be more specific, can be understood using the theory of interdisciplinarity and then further characterized by examining the quality and quantity of the inputs, process, and outputs (O'Rourke et al., 2016; Thompson Klein, 2014). Because the IPO model from O'Rourke et al. is considered universally applicable framework that can serve to model integration in multiple contexts, but it must be contextualized for the collaborative, cross-disciplinary activities involved in new drug product review. As the BRF serves as the framework and anchor for new drug product review teams it offers a useful set of elements to contextualize the IPO mode (e.g., disciplines or cognitive domains, data types). A theoretical model of how these theories and models come together to support the complex lens through which this study will be conducted is offered below, in Figure 12.

In the next chapter, a qualitative comparative case study design will be described that addresses the outstanding gaps in knowledge related to how collaborative, cross-disciplinary integration occurs in FDA new drug product reviews. This study is intended to not only describe the processes by which the FDA review team assessments are translated into a benefit-risk assessment, and overall determination, but also characterize the nature of collaborative cross-disciplinary research that may be occurring in FDA review teams. In both areas, very little research exists. Beyond the FDA new drug product reviews and the review teams that generate

them, the study will also contribute to a growing body of knowledge related to integration in collaborative cross-disciplinary research, including a method for reliably evaluating integration.

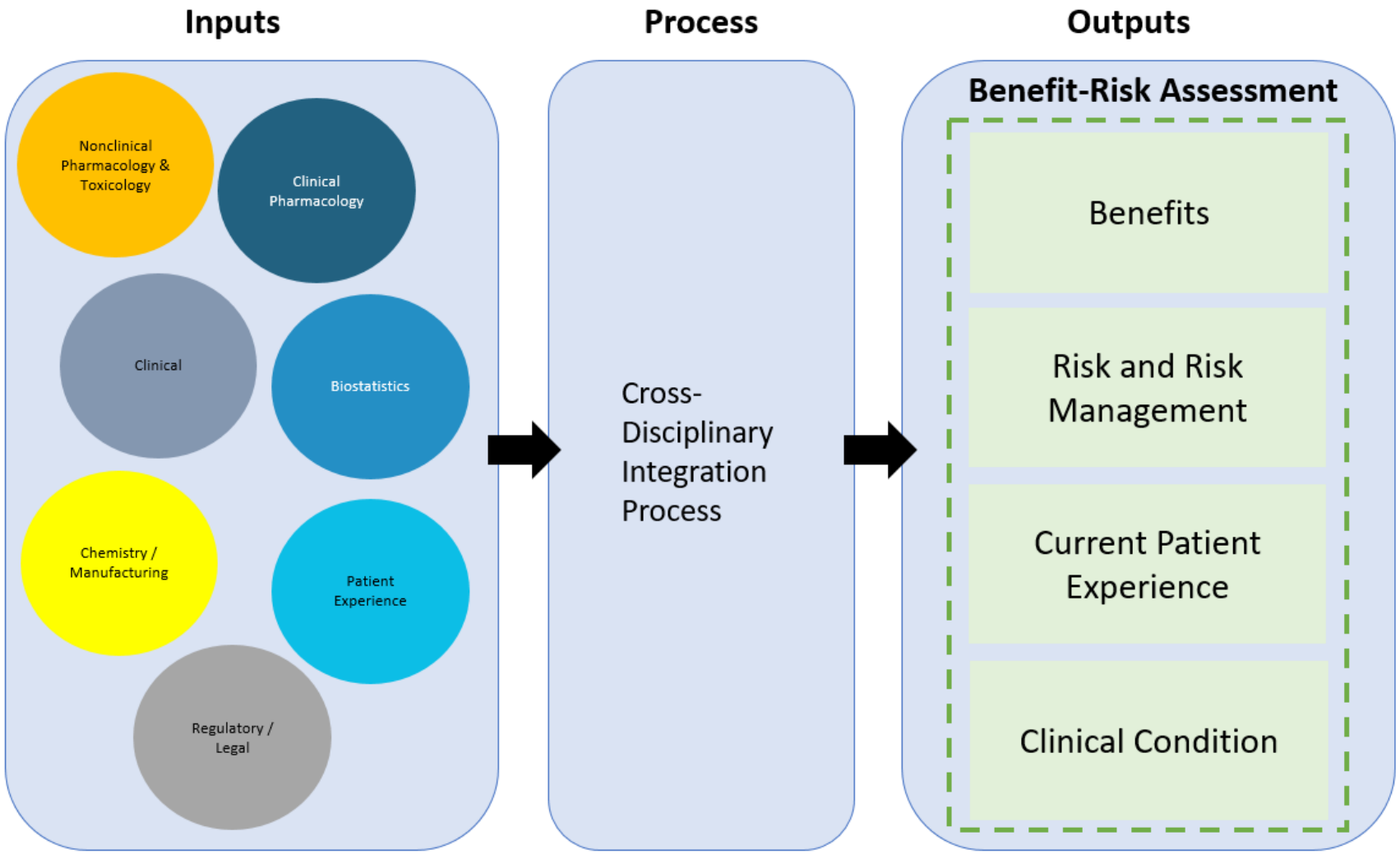


Figure 12: Theoretical Model of Integration in New Drug Product Reviews

Chapter 3 Methods

Overview of Methodology

As discussed previously, while Integration is a desired outcome in FDA's new integrated assessment approach, how this integration occurs is unknown. The Science-of-Team-Science offers some insight into how to evaluate integration, including potential frameworks, but a pragmatic and contextualized instrument for FDA does not exist. This study aims to characterize integration within FDA new drug product reviews, a collaborative cross-disciplinary research activity, using a contextualized cross-disciplinary integration model. The qualitative comparative case study methodology best aligned with the purpose and research questions of this.

Integration in collaborative cross-disciplinary FDA team science is a phenomenon of process that occurs between the individuals on the FDA review team over the course of the review and to understand this phenomenon from the perspective of the review team members a phenomenological approach is needed (Creswell & Poth, 2016). The comparative case study design allows for the purposeful selection of cases that would be expected to include integration enabling comparisons of integration between two different approaches to FDA new drug review (Creswell & Poth, 2016), the new integrated review and the multidisciplinary review. In addition, the case study design allows for the replication of the procedures used for data collection and analysis in two cases to enhance credibility and reliability of findings. As a reminder, the research questions are:

1. What are examples of integration in a "multidisciplinary review" and an "integrated review" of an FDA new drug product?
2. What are the specific differences in integration between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?

A case study is a qualitative research method where a researcher explores a program, event, activity, process, or one or more individuals in depth with multiple forms of data collection (Creswell & Poth, 2016). The specific case study method deployed in this study is a descriptive case study, sometimes referred to as an *intrinsic case study* by Creswell (2016). The descriptive case study approach is needed to describe the cases (i.e., new drug product reviews) and the examples of integration in a sufficiently robust way to allow comparisons to be made between the two approaches to the FDA new drug product review (e.g., traditional "multidisciplinary review" vs new "integrated review"). In this descriptive case study, three forms of data collection are deployed: document analysis of completed work products of the team (i.e., reviews), semi-structured interviews with select members of the team that are found to have contributed to integration in the reviews, and a member checking following the interviews to validate the data collected.

That the phenomenon of cross-disciplinary integration in FDA new drug product reviews can be understood through a descriptive case study is based on a constructivist ontology, or view of reality, that suggests that the interpretations of those experiencing a phenomenon are key to understanding it. This ontology is best aligned to an epistemology that the qualitative descriptive case study fits in, which is that the world is constructed through a person's lived experiences (Creswell & Poth, 2016). The constructivist ontology and the qualitative epistemology are rooted in this researcher's view that the collaborative integration process is heavily dependent on the experiences of the individuals that contribute to the process, not just the final outputs or the inputs into the work. This study design and the richness of data collected ensures the research questions can be answered fully because data is collected for multiple dimensions of the case and

of the integration that occurs, allowing the integration process to be modelled and compared in each case.

Through the document analysis of completed FDA new drug product reviews, descriptive elements of each case are catalogued, including details about the teams (e.g., size of team, composition of team), the new drug product being reviewed (e.g., new molecular entity, combination product, small molecule), and the assessment itself (e.g., length of documentation, final decision). Key variables of the integration process can be described quantitatively and qualitatively through a thematic coding and analysis process informed by the IPO model of O'Rourke et al. (2016) by way of the document analysis. The nature of the integrative process by which the inputs become the outputs can be difficult to interpret from the document analysis alone, since changes may occur at different times or in cycles over the course of the new drug review process. Therefore, semi-structured interviews of team members are conducted to identify how integration occurs (i.e., the quality or nature of the integration, such as combine, mix, transform) and participants' perceptions of how the integration is taking place, which can indicate whether the integration was purposeful and deliberate. Member checking with team members interviewed post-analysis is leveraged to check the validity of the integration(s) as modelled. An alignment of the research questions, epistemology, research methods, and the rationale for their selection is described briefly in the Table 3, below.

Table 3: Research Alignment

Research Question	Research Methods and Techniques	Rationale
1. What are examples of integration in a "multidisciplinary review" and an "integrated review" of an FDA new drug product?	Document analysis, semi-structured interviews, and focus groups (Bowen, 2009; Miles, Matthew B., 1994)	Minimally invasive; efficient and aligned to retrospective analysis; individual perception captured

2.	What are the specific differences in integration between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?	Intrinsic, descriptive, and comparative case study analysis (Creswell & Poth, 2016; Seawnght & Gerring, 2008)	Modeling integration in two richly descriptive cases allows a comparison between the two cases, specifically a comparison of the components that affect integration

Qualitative Inquiry

The primary line of qualitative inquiry in this research is that of a descriptive case study using a document analysis, semi-structured interviews of select team members, and member checking of the interviewed team members, which is one of Creswell's eight validation strategies for qualitative research (Creswell, 2014; Creswell & Poth, 2016). The richness and depth of detail from a descriptive case study approach allows the integration processes in each case, either FDA's new integrated review or the traditional multidisciplinary review, to be thoroughly described and modelled, which in turn allows for the differences between the two approaches to be compared.

Document analysis is a systematic analysis process for qualitative research that relies on evaluating documents (Bowen, 2009). Document analysis was chosen because the primary research question involves identifying analyzing integration in instances of FDA benefit-risk review issues of new drug products, and these review issues are required to be documented in the team's review documents. In addition, the review documents are prepared in standardized ways, following set processes and procedures, which makes a document analysis more effective and efficient (Corbin & Strauss, 2008). Similar studies of FDA review documents have been successfully conducted through document analysis, such as the FDA's commissioned study of BRF adoption (FDA, 2018a). The standardization in review documents also increases the likelihood that the final reviews are reliable reflections of the integration process because the

context or cases in which these documents are created are of a similar nature. Lastly, document analysis is a low-cost way to obtain empirical data in an unobtrusive and nonreactive way (Bowen, 2009). Furthermore, the O'Rourke et al. IPO model of cross-disciplinary integration, an operational/analytical lens for thinking about integration, lends itself to a document analysis since the primary variables related to the inputs and outputs can be quantitatively described and qualitatively coded from the final review documents and the parameters (e.g., scale, commensurability, and comprehensiveness), which help with making comparisons across cases, can be identified from the document analysis.

As mentioned above, semi-structured interviews and member checking with select team members, identified through the document analysis are conducted to understand and confirm, respectively, the "nature of integration" that occurred in the two cases. Combining the document analysis with semi-structured interviews and focus groups of the team members not only provides additional data for the modelling of integration, specifically that related to process, but also helps to triangulate the data. Through triangulation of data, evidence is generated from multiple methods to boost credibility and reliability of the data collected (Creswell, 2014). Triangulation is achieved by combining data on the two cases from document analysis with data from the semi-structured interviews and then validating the data from the two member checking focus groups.

Figure 13: Triangulation of Data

Research Procedures

Study design and settings

As previously mentioned, this study uses a descriptive case study design to explore integration in two specific cases of FDA new drug product reviews using document analysis, semi-structured interviews of select team members involved in identified instances of integration in the document analysis and focus groups for member checking. The setting of this study was the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) headquarters in Silver Spring, MD. Data was collected through qualitative document analysis, interviews, and member checking focus groups of FDA review staff.

Access to the review documents for the initial analysis for this study is through the publicly available Drugs@FDA database. Access to participants is provided through the researcher's status as an employee of CDER. Document analysis was conducted both onsite at FDA and offsite using a secured laptop computer with controlled access that uses two-factor authentication (i.e., password and a RFID-enabled ID badge). The setting of the semi-structured interviews was virtual due to the COVID-19 pandemic and these interviews were audio-recorded, transcribed, and combined with field notes captured electronically on a secured iPad

(iOS13) via tablet notations converted to Adobe PDF. Any recordings, transcriptions, or PDF notes from interviews are electronically stored on a local, secured laptop computer with a backup to a password protected external hard drive with 128-bit AES encryption with a 256-bit key. This secured storage includes consent documents and the results of the data collection and analysis.

Participants: Inclusion and Exclusion

The sampling frame for this study is of the completed reviews and the review team members for the completed reviews of new drug product reviews between May 2019 and May 2020. Two pools are created from the listing of completed, publicly available reviews in this 12 month window based on whether they used the multidisciplinary review or the integrated review approach. The two pools of cases were then screened and curated based on the following Inclusion/Exclusion criteria:

Inclusion:

- 505(b)(1) New Drug Applications
- 351(a) Original Biologics Licensing Applications
- New Molecular Entity (NME) or Original Biologic due to the increased complexity associated with such novel products and their development programs, which would be expected to require greater cross-disciplinary collaboration and integration

Exclusion:

- Any supplemental New Drug Applications
- 505(b)(2) New Drug Application that relies on previous FDA findings of safety and effectiveness, and may have a fewer than average number of review staff or disciplines involved
- 351(k) Biosimilar Biologics License Application

Cases are purposively selected from these two pools of completed, publicly available review documents—a strategy to improve transparency, increase credibility through reproducibility, and minimize risks to disclosure of information. There were 60 applications in total in the sampling frame. Of the 60 applications, 5 applications were interdisciplinary (integrated review) applications. From the initially screened pools of cases, cases were assigned a random number and one case from each group was selected at random using a randomizer. This random selection of cases minimized bias even though the selection is purposive (Seawnght & Gerring, 2008).

Of the applications randomly selected from the two pools, the review team members were identified. These review team members were contacted with a recruitment communication via email to ascertain interest and willingness to participate. A copy of this recruitment email can be found in Appendix 1. The initial case selected randomly from the multidisciplinary review pool was ZEPOSIA. For this potential case, the researcher failed to obtain enough interested review team members to participate in the interviews and the case was considered a screen fail. Another multidisciplinary review, RINVOQ, was randomly selected and subsequently passed screening with enough review team members agreeing to participate.

This selection process was discussed and reviewed with another member of the research team before potential case participants were contacted. The final selection of cases was confirmed following screening of participants for the semi-structured interviews. This dual screening ensures eligible cases are selected and that access to participants for interviews can be ensured.

Because the FDA review documents generated by the two teams used in this case study were publicly available documents anonymity cannot be maintained, which carries some risk.

However, all attempts were made to maintain confidentiality of the participants participation in this study through safeguarding of collected data and reporting of any findings without attribution, and where possible in aggregate form. It may be possible to link feedback related to an instance of modelled integration from a case back to participants due to the descriptive nature of the integration model (e.g., descriptions of the inputs, outputs, and process) and the description of the case itself due to the inclusion of team member information in public review documentation, including their discipline and organizational affiliation. Risks of such breaches to confidentiality, while likely minimal and not more than normal, were thoroughly conveyed to participants through the informed consent process.

It is possible that this risk led some participants to decline to participate in the case of ZEPOSIA. It was also possible for the participants' choice to participate was affected by the role or status of the principal researcher in this study. The principal researcher has held a leadership role in the development and implementation of FDA's new integrated review and other organization development projects as part of the New Drugs Regulatory Program Modernization (FDA, 2019h). To address this risk of coercion, a subjectivity statement was included in the informed consent, see Appendix 2, and is discussed later in this chapter.

Document Analysis

Data collection from the document analysis was conducted on review documents generated by the FDA review teams conducting the review of a new drug product. The documents targeted for document analysis are a rich source of insights and data on the integration process that contributes to the benefit-risk determination because they include not only the final benefit-risk determination but the bases of this determination, including documentation of the review staffs' assessments of evidence and uncertainty of key benefit/risk

issues, and therapeutic context that contributed to the determination. All data collected through document analysis and interviews or focus groups was included in NVivo 12 for Mac, a qualitative analysis software platform (QSR International, 2019). As noted above, document analysis is a systematic analysis process for qualitative research that relies on evaluating documents (Bowen, 2009). The document analysis in this case involves an iterative qualitative coding of the key variables and parameters of integration (Miles, Matthew B., 1994).

The source document for the document analysis in the interdisciplinary case is the 'Integrated Review' in its entirety since this document reflects the collective work product of the team. For the traditional multidisciplinary review case, multiple documents will need to be sourced: first, the Summary Review, which in some ways reflects an "integrated" review, then the individual reviews from the key review disciplines that make up the review team in that case, typically clinical, nonclinical, statistics, clinical pharmacology, and quality.

The data targeted for collection in the document analysis is related to the defining characteristics of the integration process, viz., the inputs, outputs, and integration process itself, along with the parameters. Data collection was operationally guided by an analytic framework, the O'Rourke et al.'s IPO framework of cross-disciplinary integration. This framework was then contextualized by the researcher's experience with new drug product reviews and recent public discussions related to the benefit-risk framework.

After downloading, the documents were loaded into NVivo 12 for Mac. In both cases, the document analysis process was iterative. The first review enables familiarization with the content and thus promote a more effective document review (Bowen, 2009). In this first review, documents were collected and categorized based on their title and other high-level descriptors. In the next review, all documents were scanned briefly to confirm contents and familiarize the

reader with the documents' contents. Following the scan, key documents were reviewed in more detail. It is during the detailed review that content is identified or coded thematically as either related to "inputs", "process", or "outputs", and other key parameters of each case. It is through this iterative document analysis and coding process that the contents of the document become data for qualitative study (Creswell & Poth, 2016).

The documents were analyzed in NVivo to initially identify instances of integration by reviewing the documents for benefit-risk review issues (i.e., issues with the application that impacted approvability or the benefit-risk determination) and then coding these issues with a code, such as CYP3A4 Issue. CYP3A4 refers to the Cytochrome P4503A enzyme complex is that is critical to much of drug metabolism (Wilkinson, 1996). If any evidence or basis of the review issue is cited, such as a submitted study, dataset, or data analysis, this was coded as an input. The final recommendation for regulatory action was also noted and coded as an output.

Document analysis was targeted initially to improve efficiency and given that the review documents can be quite voluminous (i.e., greater than 300 pages in length). In the case of the Integrated review, this targeting entailed reviewing the executive summary section and the interdisciplinary assessment section to identify review issues that impacted the benefit-risk determination. For the multidisciplinary review case, the Summary Review in its entirety was reviewed in addition to the executive summary of each individual disciplinary review, where a disciplinary BRF was sometimes found. For the interdisciplinary review case, additional data on the inputs would be described in the integrated assessment section of the Integrated Review and its appendices. For the multidisciplinary review, the individual disciplinary reviews needed to be reviewed to collect additional data on the inputs.

The inputs and outputs associated with each review issue were further coded, based on the document analysis, as either concrete or abstract. And the disciplines associated with the input or output were coded. An input or output is considered concrete if it includes tangible, physical elements, such as data, literature, or analyses. Conversely, an output is considered abstract if it is cognitively based, such as a perspective, an expert opinion, insights, or conversation/discussions. The inputs and outputs were coded based on the FDA defined disciplines for the different members of the review team who were responsible for originating the input or who would be responsible for reviewing or assessing the input. In some cases, multiple disciplines were responsible for either identifying the input or contributing to the review/assessment of the input. If there was mention of activities that were conducted following the identification of the issue and that led to the final regulatory action, then these items were coded in the document analysis as a "process".

Inputs in this framework include both the disciplines and the antecedents of a regulatory decision or benefit-risk determination. These inputs can be concrete and tangible, such a dataset, literature article, or new drug applicant's analysis, or abstract such as a review team member's experience or assessment of submitted data/information. Outputs reflect the final regulatory decision or action taken, such as a recommendation to not approve an applicant's proposed claim or that additional labeling is required. Outputs can be either concrete or abstract, such as in the previous example where the former example (i.e., the recommendation to not approve a proposed claim) is abstract and the latter example (i.e., requirement for new labeling text) is concrete. The process by which inputs are changed by the review team before they become the output is more active or action oriented. For example, these process steps might be discussions, more integrated analyses or assessments conducted by more than one discipline.

Through the analytical framework guided document analysis, inputs are identified and additionally characterized by their quality and quantity. Outputs are similarly catalogued and characterized. The variables associated with the inputs were the degree of difference in inputs, which was defined as difference either in the source, disciplines involved, or type. For the process activities of each review issue, the analysis captured whether the process activities were purposive (i.e., pre-planned or built-in process/workflow steps). This assessment of purposiveness was based on available documentation related to the multidisciplinary review and the new integrated review. Most features of the integration "process" element could be collected via the document analysis, but that the semi-structured interviews were needed for this component of the framework.

The integrative relationship of the process activities, or change to inputs, was assessed as either Integrative, Disintegrative, or Combinatorial, relying on descriptions of these relationship from O'Rourke *et al* 2016:

- **Integrative -** brings together inputs in some way for an irreversible integration
- **Disintegrative -** changes aimed at breaking an input down into its constituent parts or to differentiate between the inputs
- **Combinatorial -** an assembling or combining of inputs but is of low change to the inputs (i.e., stacking)

The degree of change in inputs (found in process) were also assessed as a measurement of how the process changed the inputs from low to high, such as a simple combining of inputs vs a process where the inputs are unrecognizable in the integrative output (i.e., something new is created). In addition to the degree of change in inputs, the degree of difference between the final output(s) and input(s) was assessed. Lastly, the integration parameters from the O'Rourke *et al* framework were captured for each review issue/instance of integration as described below.

Parameters of each case were collected through the document analysis to facilitate contextualization of the two cases and any identified instances of integration and enable comparisons.

- **Commensurability:** assessment of integrable the inputs are (i.e., their difference or conflict between)
- **Scale:** assessment of how many disciplines or disciplinary input types involved and the overall impact (i.e., global--the entire application vs local--a specific problem/issue)
- **Comprehensiveness:** assessment of how comprehensive the output(s) reflect or include the inputs

Semi-Structured Interviews

As noted earlier, additional data collection comes from semi-structured interviews of select team members. Select team members were interviewed to provide additional data to support the analysis of the integration process, specifically to describe what was integrated and how it occurred. The use of semi-structured interviews is important because it may be difficult during document analysis to objectively describe the integration "process" variables or to describe it from the document review alone. Team members are selected for the semi-structured interviews based on the instances of integration initially identified through the document analysis and were expected to include the clinical reviewer, nonclinical reviewer, clinical pharmacology reviewer, statistician, and quality (chemistry) reviewer. These five stakeholder groups are routinely involved in the review of new drug products and are considered the 'primary' review disciplines.

The interviews are semi-structured because they utilize a set structure and standard, open-ended questions to guide the conversation and using a set structure ensures conversations are both productive with regard to data collection but also replicable across the two cases and future research (Creswell, 2014; Miles, Matthew B., 1994). The use of open-ended questions in a semi-structured interview allows the team members to freely express their perception of the integration process (Creswell, 2014). The interview guide was informed by data collected via the document analysis leading to concurrent data collection and analysis, subsequently making the data collection and analysis process more efficient and allows for gaps in data collection to be identified and resolved earlier (Miles, Matthew B., 1994).

The semi-structured interview follows a set of process that includes an opening from the interviewer to orient the participant to the study and the interview process, then a series of standardized, open-ended questions (Spradley, 2016). Probes or prompts are used to stimulate deeper introspection and sharing from the participant, as needed (Miles, Matthew B., 1994). Total length of the interview was planned for 60 minutes and is outlined in a planned interview guide, below. However, as noted in Chapter 4, the interview guide was adapted into a PowerPoint presentation due to the virtual nature of the interviews, see Appendix 3.

Once rapport was established, the interview would focus on (1) confirming the identified application-specific benefit-risk review issues and (2) obtaining a thorough description of the integration process for each review issue. Since the document analysis represented an independent (outside) perspective, it was important to give the participants an opportunity to identify gaps in the initial list of identified instances of integration before proceeding with descriptions of the integration process for the preliminary list. This was done via a *specific* grand tour question to have the participant describe their role, the overall review of the application, and

any review issues. During this process, the researcher can cross-check against the list of preliminarily identified review issues to confirm or revise the list. Then for each review issue a *mini-tour* grand tour question is used to have the participant describe the end-to-end integration process that occurred for the review issue in their own words. Probing questions are used to ensure critical features of the integration process, guided by the O'Rourke et al. IPO framework, are described. At the conclusion of the interview, the participant is thanked, advised of status of study, and expected completion date. The interview was audio-recorded using Zoom, subsequently transcribed via Rev.com, and combined with field notes in NVivo 12 for Mac for data analysis.

Planned Semi-Structured Interview Guide

Application-specific Review Issues

This first question is intended to get the participant to describe in their own words the application-specific review issues that were found in the application review:

Grand Tour:

1. Can you tell me about your role and about the key application-specific review issue(s) that you and your team found in your review of this application that impacted the benefits, risks, or benefit-risk assessment?

Mini-Tour:

Outputs

2. Where did you and your team document the review issue(s) in the Multidisciplinary or Integrated Review?
    - How did you decide where to document the review issue(s)?
    - Did you or someone from the team take the lead in documenting the review issue(s)?
    - Was the approach to the assessment of the review issue discussed as a team? Did you or the team document the approach in the review documents?

Integration for Review Issues

For the review issues identified by the participant work through the following process questions:

Inputs

3. How did you or your team come to identify the review issue?
    - Who initially identified the review issue?
    - What role did you play in identifying the review issue?
    - What information or data was reviewed that led to the identification of the issue?
    - Was there a discussion in a meeting or with a team member regarding the issue as it was being identified?

4. What information, data, analyses, or discussions did you leverage to work through the review issue?
    - Which disciplines or experts were involved in the review of these information, data, or analyses?
    - Which disciplines were involved in the discussions of this review issue?

Process

5. What strategies did you use to resolve review issue and what was the impact of the review issue on the benefit-risk determination?
    - Who on the review team worked on the review issue?
    - Were the steps taken to resolve the review issue planned (e.g., deliberate)?

6. How did you work through the review issue in an integrated way?
    a. What information, data, analyses, or discussions did you or the team use?
    b. What meetings did you have to discuss the issue?
    c. Did you have to work with the Applicant?

7. How would you describe the incorporation of your inputs and contributions into the final documentation of the review issue in the Multidisciplinary or Integrated Review?

Member Checking

Following the semi-structured interviews a member checking activity was conducted to validate the descriptions of integration identified through the document analysis and semi-structured interviews (Creswell & Poth, 2016). Member checking was done through the creation of IPO models of the review issues that include collected data on the Inputs, Process, and

Outputs. Originally, this member checking was to be conducted in person in a focus group. But, due to the pandemic these models were circulated with the interview participants via email. The reference models utilized a visual of integration, a logical IPO model, illustrated in the figure below. The purpose of providing models of integration to the interview participants is to validate the inputs, outputs, and integration process. Any feedback on the integration models will be collected and included in NVivo for incorporation in finalize analysis and interpretation.

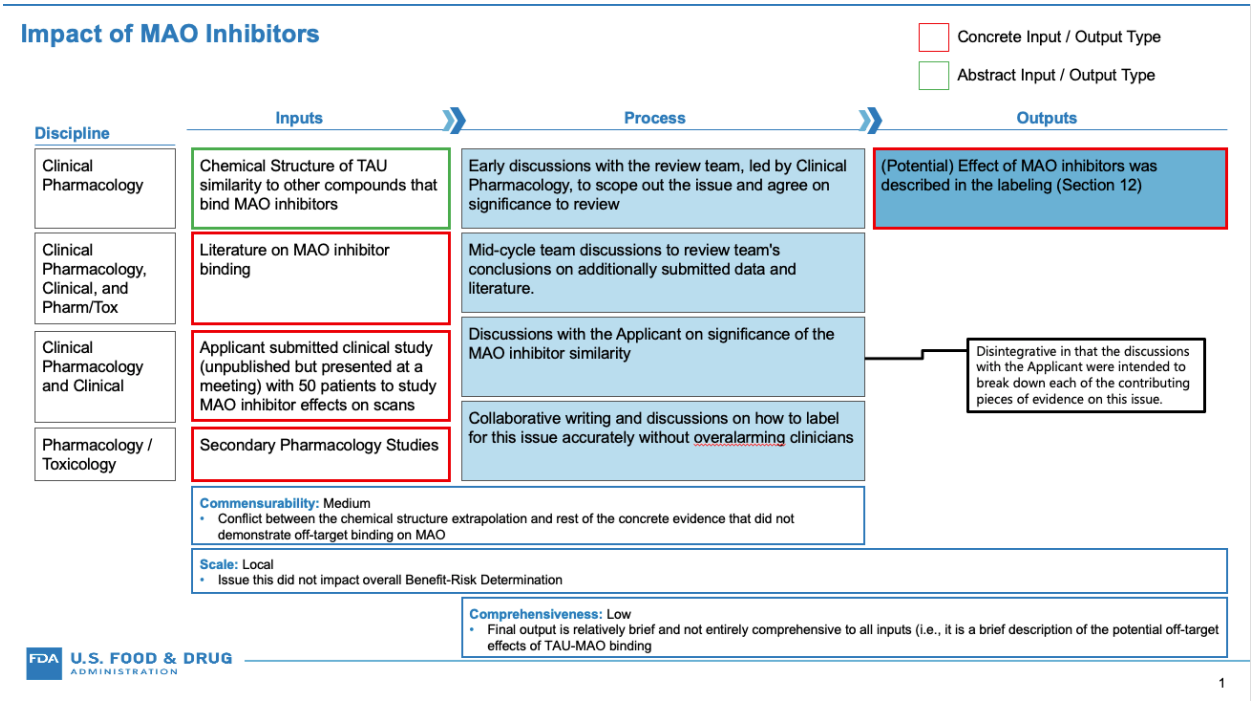


Figure 14: Member Checking Model Example

As mentioned earlier, the combination of data collection from the document analysis, semi-structured interviews, and member checking helps to triangulate the data collection and provide the richness of data needed for a descriptive case study of each review. All three methods of data collection were guided by the operationalization of the O'Rourke et al. IPO model into guiding questions to ensure alignment. See Table 6, below for a description of the variables of interest in the data collection, including relevant guiding questions, and sources of data collection.

Table 4: Operationalizing the O'Rourke et al IPO Model

Variables	Guiding Questions	Sources
Inputs and Outputs including a description	Is the input or output a concrete piece of evidence (e.g., data or results from a study or analysis)? Or, is it an abstract insight or concept from a cognitive domain (e.g., an expert opinion or recommendation)?	Document Analysis: Benefit-Risk Framework from Integrated Review or Summary Review
	Discipline: Disciplinary origin or expertise required for the input	Document Analysis: Integrated Assessment and Appendices of Integrated Review or Individual Disciplinary Reviews
Process	Integrative relationship between inputs and outputs (*Qualitative*)	Document Analysis: Benefit-Risk Framework from Integrated Review or Summary Review
	Purposive change: Yes/No	Semi-Structured Interviews
	Number of changes to an input	Semi-Structured Interviews Document Analysis: Integrated Assessment and Appendices of Integrated Review or Individual Disciplinary Reviews
Parameters (e.g., Scale, Commensurability, Comprehensiveness)	• *Scale (Global/Local)* • *Commensurability (High conflict/Low conflict)* • *Comprehensiveness (High/Low)*	Document Analysis: Benefit-Risk Framework from Integrated Review or Summary Review Semi-Structured Interviews

Data analysis and synthesis

An embedded analysis was conducted to understand a very specific aspect of both cases in this study, the integration process related to key benefit-risk review issues. This qualitative analysis is thematic in nature but guided by the operationalized analytical framework from the underlying theory behind O'Rourke et al.'s framework of cross-disciplinary integration. As detailed above, the data collection and analysis of integration was guided by several guiding questions related to variables in the IPO model (e.g., type of input or output, nature of integrative relation) and dimensions of the BRF. These guiding questions and the dimensions of the BRF can inform emergent coding; see the tables below.

Table 5: Emergent Input / Output Code Categories Informed by BRF

Inputs	**Outputs**
Patient Experience Data	
Efficacy and Safety Studies and Data	Required labeling to convey or mitigate a risk
Clinical Condition and Underlying Pathophysiology	Benefits Issue: such as the approvability of a claim or dose
Patient Experience and Clinical Meaningfulness of Treatment Effect	Adequacy of Labeling to convey a risk or inform physciains
Pediatric Use Information	Safety Issues
Clinical Pharmacology Study(s) and Data	Assessment of Risks
Nonclinical Pharmacology/Toxicology Study(s) and Data	Risk Management Issues
Pregnancy and Lactation Information	Drug Quality Issues
Labeling	Drug Use/Utilization Issues
Design of Study(s)	
Legal or Regulatory Drug-specific Issues	
Safety Assessment and Profile	
Safety Data	
Manufacturing Facility Information and Inspection Information	
Drug Substance/API Information	
Drug Product and Formulation Information	
Product Attributes	

Table 6: Emergent Integrative Relationship Code informed by O'Rourke et al.

Integrative relation*:*	*mixing, linking, making sense together, and harnessing differences*
Disintegrative relation*:*	*dissociation, differentiation, and boundary setting*
Combinational relation:	a*ssembling, combining*

It is important to note that these codes are not *a priori,* or provisional, codes because they are not expected to be specific enough to describe the two cases. However, considering these as potential categories or types of emergent codes or tags in advance is a useful technique to jumpstart analysis (Saldaña, 2013). Coding is the systematic review of qualitative information and linking of data to ideas, and subsequently allowing all data related to that idea to be linked (Saldaña, 2013). Qualitative coding from both the document analysis and semi-structured

interview transcripts in both cases was used to identify instances of integration, including descriptions of the Inputs, Process, and Outputs in each instance of integration. This facilitates the characterization of representative models of integration (i.e., I>P>O chains) and enables analyses related to those models.

Once review issues and their inputs, outputs, and process items were coded, the guiding questions were used in a memoing process to advance thinking and create a record of the coding process (Creswell & Poth, 2016). This memoing process also helped create a more transparent process and could be revisited during the analysis and interpretation of results to improve understanding. The codes for inputs, outputs, process, parameters, and the themes identified from the analysis, when combined with the thorough descriptions of the two cases, offered a more complete rendering of the interdisciplinary integration process that unfolded in each FDA new drug product review (Creswell & Poth, 2016). This rendering or model of the integration process was used to analyze the similarities and differences of the integration process in the two cases.

In qualitative research, data collection and analysis can often overlap and proceed "hand-in-hand", even with the data synthesis steps (Creswell, 2014). Creswell's linear or hierarchical approach to data analysis was used in this study and involved building from the bottom up; however, it is important to point out again, that this process may unfold iteratively (Creswell & Poth, 2016). In addition, data collection and analysis steps occured concurrently at times and therefore overlap considerably. This can be beneficial for several reasons, including earlier identification of gaps, the agility to explore new hypotheses, and the production of interim reports, which can be used to guide other aspects of data collection (e.g., listings of inputs/outputs for use in semi-structured interviews) (Creswell & Poth, 2016; Miles, Matthew,

1994). These steps as they were planned to occur in this study, including their concurrent, iterative nature, are outlined in the figure below, adapted from Creswell (2014).

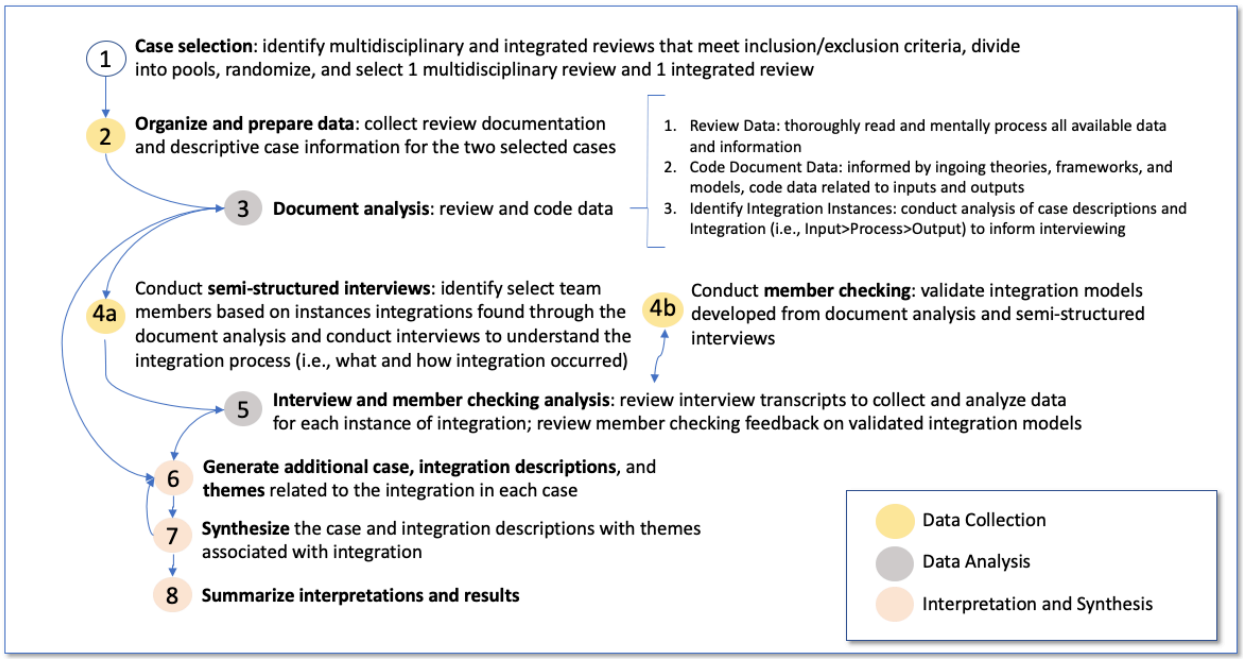


Figure 15: Data Collection & Analysis Process
(Creswell, 2014)

Steps 1 and 2 were described in the Study design and settings and Participants sections, respectively, above. Step 3 involves the document analysis and coding of data related to the key variables of this study (e.g., inputs, outputs, process, and parameters) and themes. Guiding questions and emergent codes informed by the O'Rourke et al. IPO model and BRF are described in Tables 6, 7, and 8, above. Step 4 involves the conduct of semi-structured interviews and focus groups for member checking, which was described above. Step 5 includes the analysis through coding of the transcripts from the semi-structured interviews and any feedback from the focus groups on the integration models from each case. It is possible that following both Steps 4 and 5, coded data needs to be re-reviewed to ensure emergent codes do not require modification.

Sub-step 3 of Step 3 is where the O'Rourke et al. IPO model and operationalized framework are first leveraged, as described in the data analysis section above. During this step,

coded data associated with variables of each instance of integration (e.g., inputs, outputs, process) and relevant parameters (e.g., scale, commensurability, comprehensiveness) were tabulated, described, and linked in Inputs → Process → Outputs (IPO) logic models. Semi-structured interviews provide data that completes these IPO models, with focus groups validating the models. Analysis of the IPO models of integration found in each case was a critical focus/unit of analysis in this study. Analysis and themes from Step 6 are further interrelated with other themes and descriptions of the two cases and IPO models in Step 7. Step 7 is where comparisons between the two cases can first begin to be made. Following Steps 6 and 7, it was necessary to revisit the coding. Lastly, the findings of the data analysis are summarized and interpreted for reporting of findings or results.

Reflections on strengths and weaknesses

The document analysis is not without limitations due to the subjectivity of the reader and interpreter of the data contained in the documents. In addition, because the documents were authored by different individuals or teams it is possible that biases of the authors were reflected in the documents and ultimately collected in the source data. Therefore the initial coding in the document analysis was thoroughly documented to ensure transparency and reproducibility, and reviewed by an independent researcher (Creswell & Poth, 2016). In addition, since the semi-structured interviews were conducted with only select team members from the teams based on the identified instances of integration or willingness to participate, it is possible that variations in the data or interpretations result directly from variations in these individuals and not the entire teams. The use of a semi-structured approach to the interview and a set list of questions,

including focus groups for member checking, helps to minimize this risk (Creswell & Poth, 2016).

Key strengths of this study resulted from the use of multiple methods of qualitative data collection and analysis. These strengths relate to efficiency by which the initial review can be completed, lack of reactivity and obtrusiveness involved in a document analysis, and triangulation. In other words, at the onset of the study, participants were not directly affected (Bowen, 2009) due to the data collection beginning with the document analysis. Given the availability of review documents another key strength of a document review is the ability to reproduce the study with future review documents, both internally and externally. Where the document analysis did not provide insufficient detail to complete the data analysis required to create the IPO models of integration in each review case, semi-structured interviews of the team members helps to minimize this weakness by providing additional perspectives and triangulating findings (Creswell & Poth, 2016). In addition, member checking to validate the integration models further triangulated the findings. As with all qualitative research approaches, it is possible that the researcher's bias impacted the document analysis and influenced participants. These biases were documented at the study start in a subjectivity statement and provided in the informed consent to all participants. This subjectivity is described below. This helps make explicit these biases (Lincoln, Y.S., Guba, 1985).

> The Researcher, Kevin Bugin, was the lead for the New Drugs Regulatory Program Modernization, which to date, has implemented a structural reorganization of the Office of New Drugs, which is the lead office for the review of new drug products, and created new, more efficient processes for review of INDs and NDAs/BLAs, including the interdisciplinary assessment of marketing application (i.e., Integrated Review), which is

of interest in this study. Given this close connection to the development of the integrated review, including the new interdisciplinary processes and documentation template, which was by design intended to create more integration, the research clearly has implicit biases for the new integrated review and expects to see greater integration.

In addition to the statement of subjectivity, several other methods were employed to counteract any potential biases. First, case selection for this study was guided by objective inclusion and exclusion criteria and a randomization process to avoid the preferential selection of cases. Secondly, an interrater was used for one round of the document analysis to confirm all review issues were identified and tagged without bias. A member checking of the review issues and the associated input, output, and process data was conducted to validate the data collection. And, lastly, with the multiple qualitative methods deployed, triangulation occurs which helps to minimize the impact of these biases by offering multiple data sources.

This study is focused primarily on modeling cross-disciplinary integration in two FDA new drug product reviews that were either multidisciplinary or integrated. As such the study may not clearly define or describe other aspects of the FDA review process, such as communication, team dynamics, or scientific methods of analysis and may not be extrapolatable to other review types (e.g., reviews of generic drugs, postmarket safety assessments). Such conclusions would require larger sample sizes since FDA review processes are conducted by humans and consistency may not always be achieved. However, examining two cases with different teams, different processes, and additional differences in context (e.g., drug products reviews, therapeutic areas, scientific issues), may contribute to the generalizability of findings to other FDA new drug product reviews given such differences routinely exist due to the uniqueness of the new drug product applications and review teams.

An additional limitation of this study is the sample size and selection, however, the approach to conducting this study (i.e., descriptive case study) does mitigate this limitation by providing a high degree of depth and detail on each case. Even so, with the selection of only two cases it is possible for unique qualities of these two cases, whether related to the focus of the review (e.g., the product or application) or the review team, may drive the findings. This is exacerbated by the fact that there was small pool of completed integrated reviews and multidisciplinary review to select during this transition period (e.g., phased implementation of the new integrated review replacing the multidisciplinary review. Selection was guided by inclusion and exclusion criteria mentioned above but was limited given the transition state of reviews from the traditional multidisciplinary review to the new integrated review. It was anticipated that at the time of study start there would only be a limited number of completed integrated reviews. And, over time, there will be fewer available multidisciplinary reviews. So, this was unavoidable.

Lastly, it is important to acknowledge that this research took place in the context of the COVID-19 pandemic—with this research study beginning in Spring 2020. While the entire world was certainly affected by the pandemic, the FDA review staff within the Office of New Drugs were especially impacted in that they saw major increases in workload both from the receipt of multiple applications for the use of repurposed and novel therapeutics to treat COVID-19, but also the handling of requests for regulatory discretion and flexibility for conducting clinical research during the pandemic (e.g., increased use of telemedicine), and assistance with mitigations risks to drug supply chains given the disruption in global supply and trade. This had at least three known effects on this research and potentially more. First, all interviews had to be conducted virtually. In some cases, participants did participate with video and in those instances

without video the rapport may not have been effectively established. Secondly, the plan for member checking had to accommodate the inability to conduct a live focus group. Instead, a series of email communications was used to validate the integration models for member checking purposes. Thirdly, the willingness of subjects to participate was likely driven by their availability or workload, which as noted above, was greatly impacted by COVID-19. As such, at multiple cases had to be screened before finding a case with a pool of subjects willing to participate. Lastly, this researcher was also heavily affected by the COVID-19 pandemic having been pulled into the US Governments Operation Warp Speed efforts to manage the Therapeutics Program.

Human Participants and Ethical Precautions

Risks for participation in the study and breaches of confidentiality

The risks to subjects participating in this study was minimal. Most of the data collection came from publicly available documents that may already contain subject identifying information. Potential risks to participants were somewhat minimized because the researcher did not engage directly with subjects and stronger measures to ensure confidentiality were taken (e.g., deidentifying subject names in documents included in the document analysis or using only publicly available documents). Given potential influence from the researcher due to status, such methods were an important study enhancement.

Minimal risk to subjects was possible from their sharing of information during interviews and could manifest in extreme cases as changes to their working conditions, such as peer or leadership perceptions of their performance or quality of work. However, this risk is expected to be minimal through the anonymized collection of interview feedback and masking of any review

team names and roles with pseudonyms or unique subject identifiers. There are no risks from breaches of confidentiality because information gathered is from publicly available documents, and as mentioned above, personally identifying information will not be collected.

Coercion due to researcher's position or status

As mentioned earlier, the researcher holds a position of status in the organization as the Director of Special Programs, with responsibilities that relate to driving the New Drugs Regulatory Program Modernization and other quality improvement initiatives. As such, the researcher may have been perceived in polarized ways (e.g., always looking for problems and creating trouble, or always improving work practices and helping others). In addition, the researcher has known close working relationships with FDA and CDER leadership that may be result in perceived power or influence over senior leadership. These position/status factors may have influenced participants' choice to participate and influenced their contributions during semi-structured interviews and/or member checking. It is expected that risks of coercion are low because subject selection was primarily through convenience sampling and did not require self-selection. In addition, by including a statement of subjectivity, or the researcher's interests and relationship to the participants will help mitigate these risks and ensure the participants are free from coercion. Furthermore, agreement to participate was possibly balanced by reverse coercion, or the unwillingness to participate due to the researcher's position or status.

Chapter 4 Results

Introduction

This study was a phenomenological descriptive comparative case study of the regulatory review of a new drug product marketing application that used either the traditional approach to the review (i.e., multidisciplinary review) or the new integrated approach (i.e., interdisciplinary review) at the FDA. The purpose of the study was to identify instances of integration related to benefit-risk review issues, if any, and more clearly define the differences and similarities in the integration process. The study employs a combination of document analysis, semi-structured interviews, and member checking to characterize the integration found within each case that centered around the collaborative cross-disciplinary review issues encountered by the review teams. Data collection and analysis are guided by a philosophical framework for the modelling of integration from O'Rourke *et al* and subsequent analyses (O'Rourke et al., 2016).

FDA's assessment of new drug products before they enter the marketplace is a critical activity to protect the US public's health and requires team-based integration and transparency (Woodcock, 2018). In 2019 the FDA began rolling out a new interdisciplinary approach to the assessment of marketing applications, with the key feature being integrated, collaborative review documents (Woodcock et al., 2020). As FDA makes this transition to implementing a more integrated approach to its review processes and documentation, there are tradeoffs and some external stakeholders have expressed concerns with a decrease in transparency and loss of knowledge (Herder et al., 2020). This study is being conducted to better understand how integration is occurring in the interdisciplinary approach and has occurred in the traditional FDA multidisciplinary reviews to guide the transition from multidisciplinary review to the new

interdisciplinary review, and perhaps help address external stakeholder concerns. The research questions are below.

Table 7: Research Questions and Methods

Research Question	Research Methods and Techniques
1. What are examples of integration in a "multidisciplinary review" and an "integrated review" of an FDA new drug product?	Document analysis, semi-structured interviews, and member checking (Bowen, 2009; Miles, Matthew B., 1994)
2. What are the specific differences in integration between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?	Intrinsic, descriptive, and comparative case study analysis (Creswell & Poth, 2016; Seawnght & Gerring, 2008)

The goal of research question one was to identify and model instances of integration of the cross-disciplinary review assessments in these two cases of collaborative cross-disciplinary research that were centered around key benefit-risk review issues. Benefit-risk review issues are issues are identified by the review team of a new drug product application that would impact the approvability of the application as submitted and lead to some form of regulatory decision or action related to the marketing of the new drug product. These review issues are rooted in a benefit-risk assessment and determination guided by the benefit-risk framework (BRF). A regulatory decision or action is the decision to approve or conversely not approve the marketing application and the subject product with an indication, a specific dose and administration, labeling, and any required postmarket studies and commitments. Benefit-risk review issues were the focus of this study because these are the "problems" that FDA new drug product review teams work through together in a cross-disciplinary fashion.

The goal of research question two was to then comparatively analyze the differences, both quantitatively and qualitatively, between the instances of integration identified using the

models of integration developed from the framework from the O'Rourke *et al.* for cross-disciplinary integration (O'Rourke et al., 2016).

Following IRB approval, data collection began with a screening process for eligible applications as discussed in Chapter 3. The screening process was used to identify cases with available review documents and individuals willing to participate and consent to the study. Following confirmation of participation from the review team, the documents for the associated application review were gathered from Drugs@FDA. Drugs@FDA is a public database that includes publicly available review documents for approved applications. The review documents used in this study can be found at the following links:

- RINVOQ https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=211675

- TAUVID https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=212123

For the RINVOQ (upadacitinib) case, the following review documents were collected:

- Clinical Pharmacology and Biopharmaceutics Review (FDA, 2019a)
- Clinical Review (FDA, 2019b)
- Non-clinical Review (FDA, 2019c)
- Quality Review (FDA, 2019d)
- Statistical Review (FDA, 2019e)
- Summary Review (FDA, 2019f)

For the TAUVID (flortaucipir F-18) case, only the following document was collected:

- Integrated Review (FDA, 2020a)

Following document collection, review documents were analyzed to identify benefit-risk review issues. Review issues were identified through a selection process that was informed by the BRF since review issues are approvability issues and approvability for a new drug is closely

linked to the benefit-risk determination. As discussed in Chapter 3, this was an iterative process that involved an initial review to build familiarity with the case and documents, followed by a coding analysis of review issues and subsequent coding of the review issue(s) for inputs, outputs, and process activities (O'Rourke et al., 2016). The BRF again informed analysis underlying the coding and development of the IPO models as the inputs could be identified through their connection to either evidence of benefit (i.e., efficacy) or of risk (i.e., safety), and any related uncertainties. The same was true for the identification of outputs, as these were directly connected to a key dimension of the benefit-risk determination documented in the application review.

Interview participants were then contacted to schedule the semi-structured interview and obtain informed consent. Due to the ongoing COVID-19 pandemic, all semi-structured interviews were conducted via Zoom with audio recording. Also, due to the COVID-19 pandemic and the nature of FDA review staff's work related to reviewing therapeutics for COVID-19, interviews took a considerable amount of time to schedule. Interviews took between 30 and 60 minutes and involved six review team members for the RINVOQ case and seven review team members for the TAUVID case. A PowerPoint slide deck was used to facilitate the interview. The slide deck included a few introductory slides on the research study, including its impetus, and then two slides to walk the participant through the semi-structured interview questions. This slide deck can be found in the Appendix 3. Audio recordings from the interviews were transcribed and then analyzed similarly for review issues, inputs, outputs, and process activities.

After coding the interview transcripts and the coding of the review documents, the transcripts and review documents were re-analyzed and re-coded for any additional detail or data associated

with newly identified inputs, outputs, or process activities. This iterative coding, analysis and interpretation process ensured that an accurate picture of each review issue and its integration could be collected. The final analysis step encompassed a review of codes with the O'Rourke *et al* framework for cross-disciplinary integration (O'Rourke et al., 2016) in mind. Then codes were inventoried and analyzed in a database of key variables of the inputs, process, and outputs from the O'Rourke et al. IPO framework. A snapshot of the completed data tables from the inventories, along with associated data, can be found in the appendices 4 and 5.

The IPO analysis and inventorying were used to inform logical models (i.e., Input>Process>Output) of the integration for each review issue. These models were created in PowerPoint and then distributed to interview participants for validation, or member checking. Responses were received from all participants and the generated models were considered validated.

The following sections describe each of the cases, associated review issues, and the integration found. Each section includes descriptive information on the application and new drug product, the review team, and the approach used (i.e., multidisciplinary, or interdisciplinary). Within each case, the review issues are discussed individually, including the integration seen. Qualitative data from the review documents and interviews are included to support the identification of review issues, and the inputs, outputs, process, and parameters of the integration. As a reminder, the IPO parameters are defined as follows:

- *Commensurability***:** Assessment of how integrable the inputs are (i.e., their difference or conflict between) (O'Rourke et al., 2016).
- *Comprehensiveness*: Assessment of how comprehensive the output(s) reflect or include the inputs (O'Rourke et al., 2016).

- *Scale:* Assessment of how many disciplines or disciplinary input types were involved and the overall impact (i.e., global--the entire application vs local--a specific problem/issue) (O'Rourke et al., 2016).

To help illustrate the integration within each benefit-risk review issue from the cases, a Sankey flow model was developed for each based on the IPO framework analysis and an diagraming approach from Laursen (2018). The colors in the Sankey diagram are arbitrary and are only intended to help the interpreter distinguish between the different disciplines (far left, in figure below) and their contributions to the inputs (second from the left), then the flow of inputs into process activities (second from the right) and lastly the flow of those process activities to the final output (far right). The width of the bars or flows is driven in part by the number of disciplinary contributions to the inputs, but mostly by the number of process activities these inputs were involved in. All disciplinary contributions and inputs were counted equally and so the larger the width of the input "flow" reflects mostly the degree to which this input was involved in the process activities. As Sankey diagrams were originally intended for the modelling of thermodynamic systems where energy was contained or conserved in the system, the remaining flow widths are all driven by the width of the Inputs and how these flow through the rest of the integration model.

An example from the TAUVID case for review issue 4 is shown below to help describe the mechanics and key features of what the Sankey diagram depicts. These diagrams are quite useful in demonstrating the dynamics of the integration that occurred.

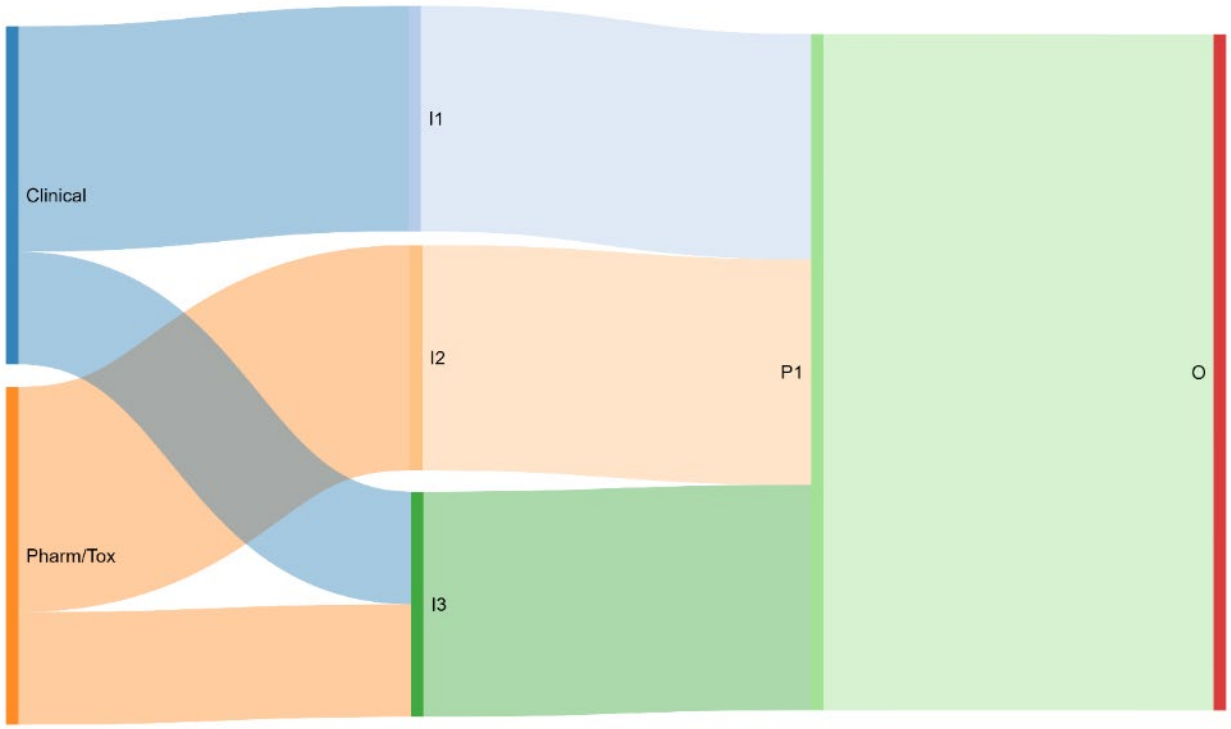


Figure 16: TAUVID Review Issue 4 Integration Model

In the review issue above, two disciplines contributed to a total of three inputs that then were involved in one process activity to arrive at a single output or conclusion of the cross-disciplinary integration for this review issue. As noted above, for these models the inputs are counted as equal parts and so are the originating contributions of the disciplines. The differences seen in the width of flows occur when disciplines contribute to more than one input or when inputs contribute to more than one process activity. In this example, because there was one process activity that incorporated all three inputs, these inputs had similar widths.

The section that follows the case descriptions includes results from comparisons of the two cases, including the applications, teams, review issues, and integration. In addition to cited in the sections below, underlying data (i.e., direct quotations from review documents and interviews)

supporting the results of the analyses can be found in appendices 4 and 5 alongside the integration inventories.

RINVOQ Case

Description of the multidisciplinary case

The multidisciplinary case for this descriptive comparative case study was the new drug application (NDA) 211675 for RINVOQ (upadacitinib) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The NDA was submitted by AbbVie, Inc. on December 19, 2018 and approved on August 16, 2019. The review was conducted with a priority review timeline of 8 months. RINVOQ (updadacitinib) is a new molecular entity (NME), oral small molecule inhibitor of the Janus associated kinases (JAK). While RINVOQ was still a new molecular entity there were two other JAK inhibitors approved at the time of review: tofacitinib (Xeljanz, NDA 20321, approved November 6, 2012) and baricitinib (Olumiant, NDA 207924, approved May 31, 2018).

The NDA for RINVOQ was reviewed in the Division of Pulmonary, Allergy, and Rheumatology Products. As RINVOQ was an NME, the signatory, in other words the final decision maker, for the application was the Office of Drug Evaluation II Director, who oversees the review division. The review team was made up of a regulatory project manager, a clinical reviewer, a statistical reviewer, a clinical pharmacology reviewer, two pharmacometrics reviewers, a pharmacogenomics reviewer, a nonclinical pharmacology/toxicology reviewer, and a dedicated quality team with a drug substance reviewer and supervisor, a drug product reviewer, a process/microbiology/facility reviewer, and a biopharmaceutics reviewer. Each discipline reviewer was also joined and closely supervised by a discipline team leader. It should be noted that while some of these disciplines may be similar, they are considered separate and distinct

within the FDA. For example, the clinical review discipline is focused almost exclusively on medical topics and clinical research design/conduct. Whereas clinical pharmacology is more interested in how the drug performs within the human body. For this application, as with many, the clinical or medical team leader served as the cross-disciplinary team leader. Of this large review team, the following disciplines consented to participate and were represented in the interviews: clinical, statistics, clinical pharmacology, biopharmaceutics, process/ microbiology/ facility, and nonclinical pharmacology/toxicology.

The RINVOQ review team utilized a traditional approach to conducting the review of this application, as defined by the 21st Century Desk Reference Guide for new drug product application reviews (FDA, 2014). This approach to the review of a new drug application involves a multidisciplinary review team working initially separately within disciplines to review the application, with team meetings at key milestones of the review, such as filing, mid-cycle, and wrap-up. The team writes individual discipline-specific review documents and then the cross-disciplinary team leader—sometimes in partnership with the signatories of the application—writes a summary review of the discipline-specific reviews to support the final regulatory decision. For the RINVOQ review, the discipline-specific reviews were completed between four and two months prior to the action on August 16, 2019, and the Summary review was completed on July 11, 2019, about one month before the action. These documents were targeted for document analysis and are listed below.

Table 8: RINVOQ Review Documents

Document	Length in pages
Summary Review	54
Clinical Review	243
Nonclinical Pharmacology/Toxicology	92
Clinical Pharmacology	138

Product Quality	38
Statistics	171

In the multidisciplinary approach, review teams come together during the first 30-60 days to align on the filing of the application, which is a determination that the application is materially complete and that it can be reviewed. Benefit-risk review issues and filing issues may be discussed at this initial meeting. The review team will come back together for a "mid-cycle meeting" at about the half-way point of the review to discuss major review issues that could affect approvability. The team will not come back together fully again until a "wrap-up meeting" towards the end of the review timeline, shortly after all discipline-specific reviews are completed. In some instances, closely related disciplines may meet separately to confer on specific issues (i.e., clinical and statistics on safety analyses, pharmacology/toxicology, and quality on impurities, etc.). Recommendations for the final decision are made by the review team members at this meeting, to inform the signatory's final decision. A schematic of the process and timelines for either a Standard or Priority review is found in the figure below (Standard review milestones in gray and Priority review milestones in red).

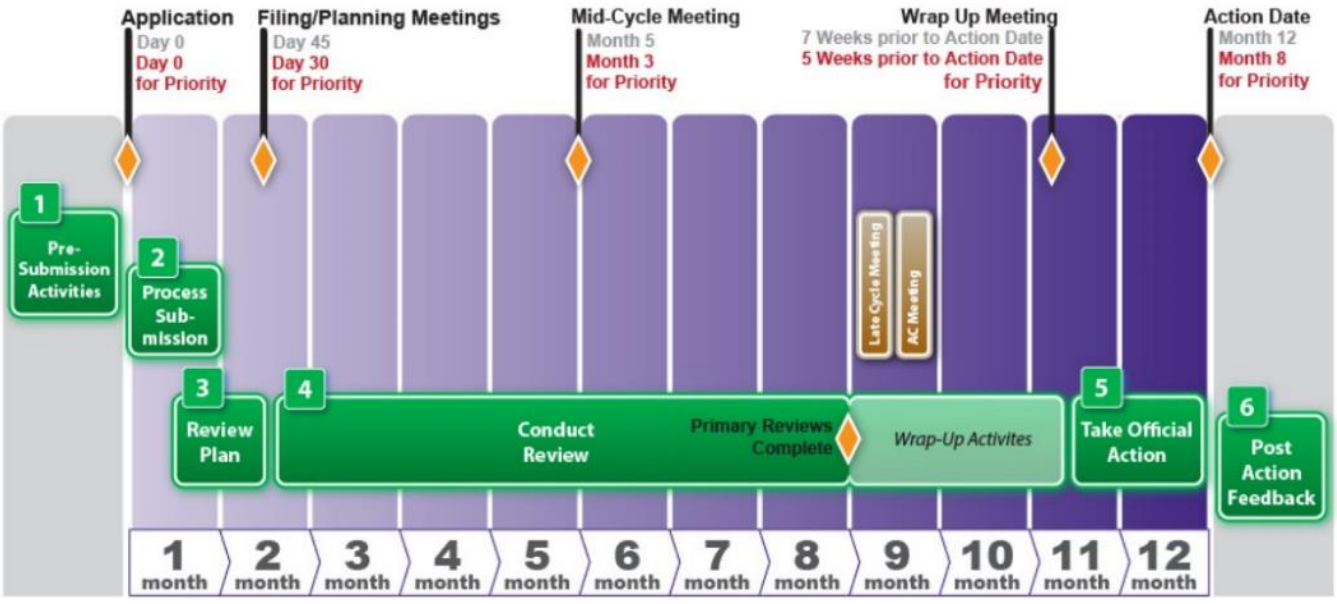


Figure 17*: Multidisciplinary Review Process (FDA, 2014, p. 51)*

Description of cross-disciplinary review issues identified

Over the course of the document analysis and interviews with select review team members, six cross-disciplinary review issues that had or could have had a regulatory impact on the application review decision were identified based on frequency of reference and emphasis of impact found in interviews. These six review issues were all considered resolved and therefore the cross-disciplinary review issue had a complete input to output process. The review issues and their mentions across the documents and interviews are listed below:

Table 9: RINVOQ Review Issues

Review Issue	**Coding Instances**
Embryofetal Issues	49
30mg vs 15 mg Issues	47
Formulation Bridging Issues	15
CYP3A4 Issue	10
Impurities Issue	6
JAK Class Safety Issue	6

Figure 18: RINVOQ Review Issues

The review issues in RINVOQ were described in mostly the same way across review documents, but because they were mentioned across multiple review documents it was difficult to confirm the significance of the review issues until the interviews could be analyzed, triangulating the importance of the issues. The following figure of the Formulation Bridging Issues, helps illustrate this point.

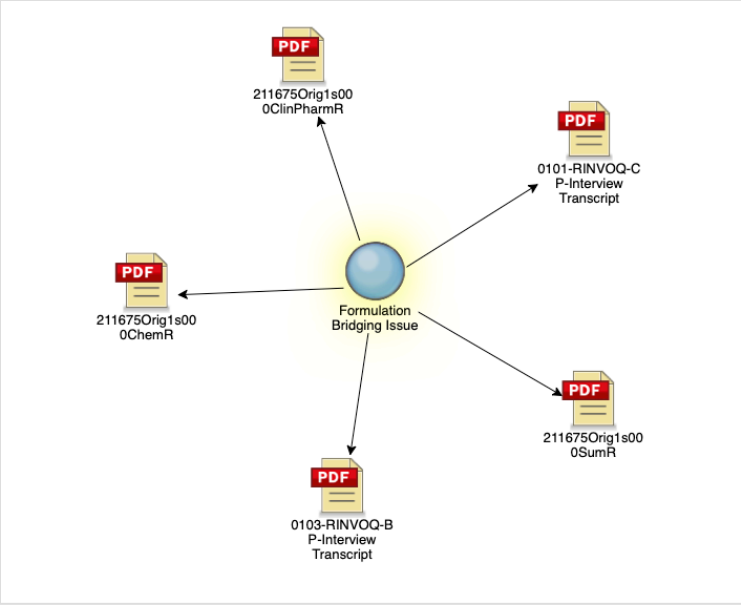


Figure 19: RINVOQ Formulation Issue Across Objects

Review Issue 1: 30 mg vs 15 mg Issues

The first review issue identified in the RINVOQ application was related to the two doses studied in the RINVOQ drug development program. Two doses, 30 mg and 15 mg, were studied over the course of development, including in five pivotal phase 3 studies, which were submitted in the NDA.

"Patients treated with UP A 30 mg consistently had a numerically higher proportion of patients with greater ACR50 and ACR 70 responses compared to the UP A 15 mg group;

however, given the relatively small increase in benefit, the degree of clinical meaningfulness is uncertain." (FDA, 2019f)

The review team had to carefully assess the safety and effectiveness, or benefit-risk profile, for each dose to establish if the benefits would outweigh the risks. This review issue included 3 inputs and involved 3 disciplines, which are listed in the table below.

Table 10: RINVOQ Review Issue 1 Inputs

Input #	Discipline	Input Description
1	Clinical Pharmacology	Exposure-Response Analysis
2	Clinical, Clinical Pharmacology, and Statistics	Integrated Safety Analyses
3	Clinical, Clinical Pharmacology, and Statistics	Results from Five Phase 3 Studies

These three inputs were considered concrete and relatively similar, with a low degree of difference across them, translating to a relatively high degree of commensurability. The first input was an exposure-response analysis conducted and described by the clinical pharmacology reviewer in their review document, along with their findings, as:

"Overall, results from Phase 3 studies and exposure-response analysis support the proposed 15 mg QD dosing regimen as it provides the optimal benefit-risk balance in patients with moderately to severely active RA" (FDA, 2019a)

The second input was an integrated safety analysis conducted by the medical and statistical reviewers. The statistical reviewer described the analyses as integrated as seen in the following statistical review document excerpt:

"Based on the integrated safety analyses during the placebo-controlled or MTX-controlled period, there was an observed dose response relationship for key treatment

emergent AEs such as infections, and serious infections, common to the JAK class." (FDA, 2019e)

The third and final input was the overall results seen across the five submitted studies in the RINVOQ application.

The three inputs for each dose were processed via additional analyses or assessments for safety, benefits, and then both individually and comparatively for benefit-risk. These activities are considered best practice or routine for reviews and since the disciplines conducted their analyses/assessments independently before bringing their findings together in order to make a consensus decision. Based on the analysis of the review documents and interviews, the process by which the individual findings were brought together was more a coordinated review of separate aspects by review team members to come to a combined decision. As such, the process activities were considered combinatorial with regards to their integrative nature. These process steps are listed in the table, below.

Table 11: RINVOQ Review Issue 1 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Analysis/Assessment of Safety at 15 mg and 30 mg independently (1, 2, 3)	Yes	Combinatorial
2	Analysis/Assessment of Benefit at 15 mg and 30 mg independently (1, 3)	Yes	Combinatorial
3	Comparative Analysis of Adverse Event Profile between 15 mg and 30 mg doses (1, 2, 3)	Yes	Combinatorial

While each process step represented some change to the inputs, the degree of change was low as the output of the process was expected by the review team and confirmed the applicant's

proposal to not market the high dose (i.e., 30 mg); see following quote from the medical reviewer interview:

> "It is worth noting that the safety analyses included comparisons of AEs between the UPA 15 mg and 30 mg doses but only the UPA 15 mg dose is being sought for approval by the Applicant."

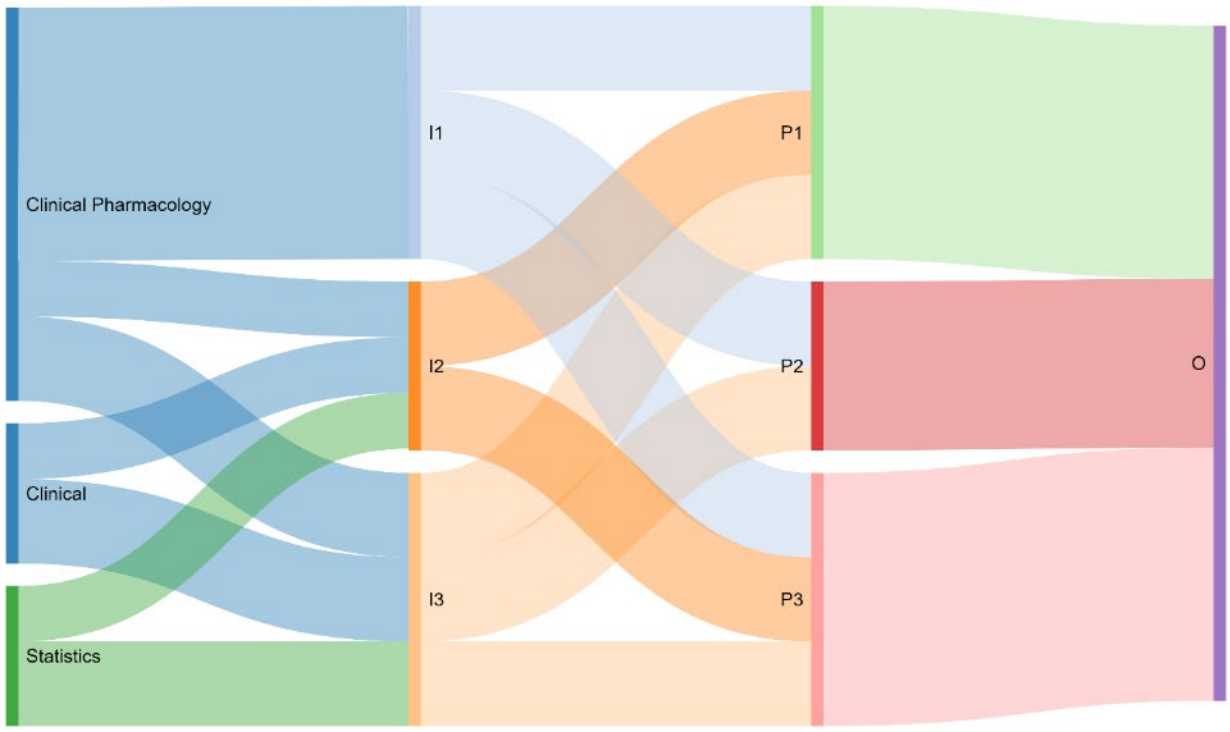
The integration of inputs in this review issue led to a single regulatory decision (output) that 15 mg dose was found to have favorable benefit-risk profile and approved by FDA, but 30 mg Dose was found to have an unfavorable benefit-risk profile. This output is considered concrete because it led to an action to approve the 15 mg dose and not the 30 mg dose. Or, as stated in the Summary Review document:

> "The benefit-risk profile of the upadacitinib 15mg dose is more favorable than the 30mg dose. The small incremental benefit of the 30mg dose does not outweigh the dose-related safety findings with the 30mg dose of upadacitinib." (FDA, 2019f)

This output is cross-disciplinary and includes all inputs making its integration comprehensive. And, this instance of integration is considered global given that the issue is relevant to the entire application. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in appendix 4.A.

Based on these data, the integration found in review issue 1 can be modelled as follows in the figure, below. As can be seen in the figure below, two of the process activities were inclusive of all inputs. Also, interesting in this diagram is the contribution of clinical pharmacology to all inputs and the addition of an input (input 1) that was entirely clinical pharmacology and the subsequent incorporation of this input in all process activities. This clearly indicates the extensive reliance on this discipline in the overall review issue.

Figure 20: RINVOQ 30 mg vs 15 mg Review Issue Sankey Integration Model



Review Issue 2: Formulation Change

The second review issue identified in the RINVOQ multidisciplinary case was an issue related to the adequacy of the bridging of data to support both a change in the clinical trial material formulation made during drug development from an Immediate Release to Extended Release Formulation and a change between Clinical Trial Material (CTM) used in the Phase 3 studies and for the To-Be-Marketed Material. This issue was initially identified by the following succinct statement in the summary review:

> "The phase 3 clinical trial formulation differs from the proposed commercial formulation." (FDA, 2019f)

As manufacturing changes, such as formulation changes, can alter the product's quality and performance in the clinical setting, providing the bridging data between such changes is considered to have important regulatory impact. This review issue included six inputs, all

concrete, and involved two disciplines, as listed in the table, below. The clinical pharmacology discipline contributed to four inputs related to the bioequivalence study, bioavailability study, and a population pharmacokinetics analysis. The analysis of the bioequivalence study was repeated by the clinical pharmacology reviewer, who noted in their interview that it was "critical … to repeat the data analysis". As with review issue 1, these inputs were similar in source, type, and findings making the commensurability or degree of similarity/congruence high.

Table 12: RINVOQ Review Issue 2 Inputs

Input #	Discipline	Input Description
1	Clinical Pharmacology	Bioequivalence Study
2	Clinical Pharmacology	Repeated Bioequivalence Study
3	Biopharmaceutics	Release Profiles
4	Biopharmaceutics	In Vitro Dissolution Study
5	Biopharmaceutics and Clinical Pharmacology	Bioavailability Study
6	Clinical Pharmacology	Population Based Pharmacokinetics Analysis

The six inputs for this review issue were processed in two activities, a presentation of results and a discussion of clinical significance with the review team. The results presentation is considered purposive as it is routine to present results from either the application or the reviewer analyses, whereas the discussion of clinical significance was more spontaneous or emergent and driven by the findings of the reviewer's assessment of the release profiles. The routine nature of the review team presentation was noted in the following quote from the clinical pharmacology reviewer:

> "I normally discuss with the team leader first to finalize the slides, and then we presented with the whole review team"

The results presentation was considered combinatorial as the bioequivalence study was mostly left to the Clinical Pharmacology team to evaluate and other disciplines relied on that

assessment—the same was true for the bioavailability study and Biopharmaceutics team. The discussion of clinical significance of the release profiles on formulation change was considered integrative because it required multiple disciplines to provide their perspective on the same data before a conclusion could be reached, as noted by the biopharmaceutics reviewer in the following interview quote:

> "…communications were between both clinical and clinical pharmacology teams in trying to make sure that the plus or minus 10% [in release profiles] is okay in terms of establishing the boundaries"

The process steps involved in review issue 2 are listed in the table, below.

Table 13: RINVOQ Review Issue 2 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Results presentation to the Review Team (1, 2, 3, 4, 5, 6)	Yes	Combinatorial
2	Discussion of clinical significance of the release profiles with the Review Team (3)	No	Integrative

The degree of change seen in the inputs during the process steps was low with only a combination of data from across all phase 3 studies to inform the population-based pharmacokinetics analysis. These two process steps led to the single regulatory decision (output) that the formulations were considered bioequivalent, including their release profiles:

> "Bioequivalence was established between the to-be-marketed ER tablets and the ER tablets used in Phase 3 studies", Clinical Pharmacology Review (FDA, 2019a).

This output was again cross-disciplinary, incorporating all inputs and disciplines, making the comprehensiveness of the integration high. However, this review issue was localized to the formulations and therefore had a local scale and considered abstract in that no change to the

proposed formulation or regulatory action was required. Additional supporting data, including excerpts from the review documents and quotes interviews can be found in the appendix 4.B.

Based on these data, the integration found in this review issue can be modelled as follows in the figure, below. While multiple inputs were observed in this review issue, as the model below illustrates, these inputs were mostly from a single discipline. However, the presentation of inputs at a review team meeting in process activity 1 (P1) was inclusive of most inputs. What is not indicated in this model is the integration in process activity 2 (P2), that occurred when the review team provided additional input to the biopharmaceutics discipline to inform the final recommendation.

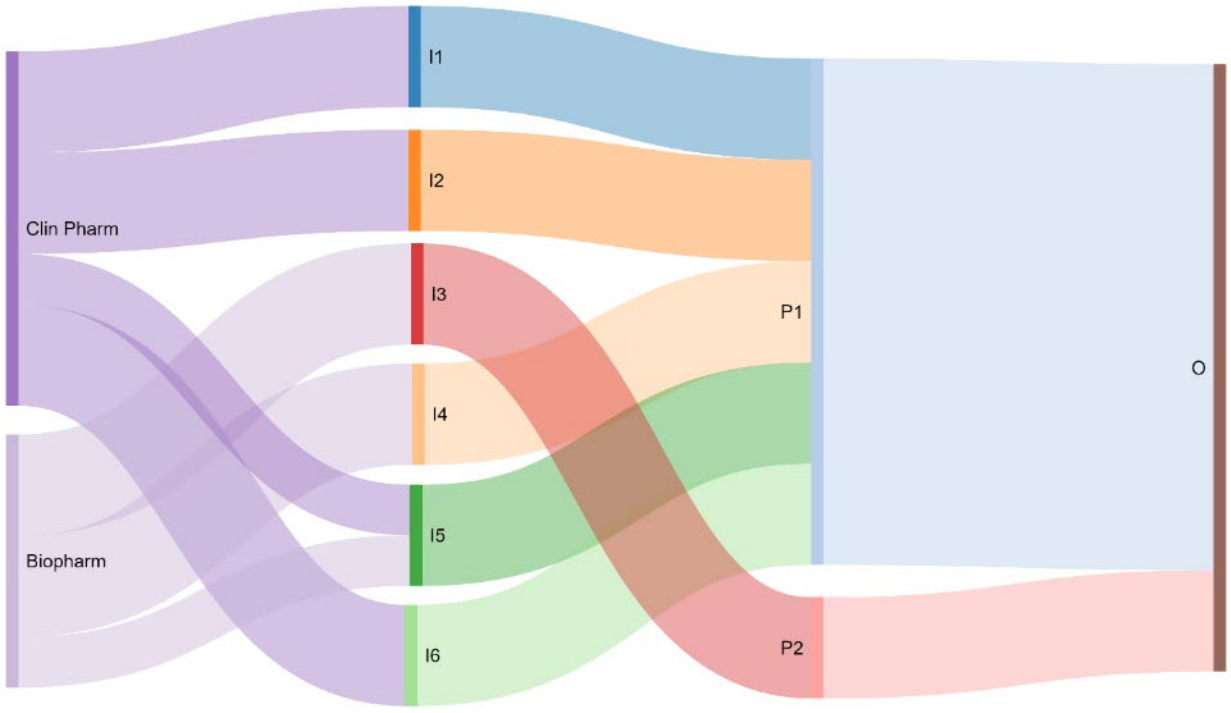


Figure 21: RINVOQ Formulation Change Review Issue Sankey Integration Model

Review Issue 3: Impurities

The third review issue identified in the RINVOQ multidisciplinary case was related to the impurities present in the finished drug product. This issue included one concrete input, which were data and information related to the set of impurities found in the product, and this rose to the level of a review issue due to the sheer number of impurities that needed to be assessed, as indicated by this quote from the interview of the pharmacology/toxicology team leader:

> "I guess the other complexity to this one was there was, compared to some applications, kind of a lot to sift through regarding impurities."

This input involved two disciplines and is concrete since it related to specific impurities, and their chemical structure, and the data and information related to them. As this was a single cross-disciplinary input, commensurability is not assessable. The input is described further in the table, below.

Table 14: RINVOQ Review Issue 3 Input

Input #	Discipline	Input Description
1	Pharmacology/Toxicology and Chemistry	Identified Impurities

This input was processed via three activities, two of which were purposive and considered routine for assessing impurities. However, due to the large number of impurities to be assessed, one process step was unplanned and added, that of a computational toxicology consult. As the pharmacology/toxicology reviewer worked through the nonclinical safety assessment of the impurities themselves this process step lacks any nature of change. The same can be said for the computational toxicology consult. This makes the integrative nature of the change not

applicable. The third process step involved routine collaboration with the chemistry team, as indicated by the pharmacology/toxicology team leader in their interview:

> "requires collaboration with the CMC review team",

As the additional collaboration was on the original input from the pharmacology/toxicology team, this was not considered an additional input. And the process activity was integrative due to the bringing together of perspectives from two different disciplines on the same input. These process steps are described in the table, below.

Table 15: RINVOQ Review Issue 3 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Nonclinical safety assessment conducted on the range of impurities (1)	Yes	NA
2	Computational Toxicology Consult was issued to evaluate the sheer number of impurities (1)	No	NA
3	Chemistry collaboration to review impurities (1)	Yes	Integrative

There was a low degree of change seen to the inputs in processing, and the final output was abstract in nature as the regulatory conclusion was simply that there were no safety concerns with the impurities, as noted in the summary review:

> "There are no safety concerns related to UPA impurities for the proposed dose, duration, and patient population" (FDA, 2019f)

This review issue was straightforward, but the collaboration, even if routine, between the pharmacology/toxicology and chemistry disciplines led to the cross-disciplinary nature of the output. And, it was comprehensive with the single input fully incorporated into all process activities and the output. With that said, this was a relatively localized issue and did not impact

review of the application outside of this issue. Additional supporting data, including excerpts from the review documents and quotes interviews can be found in the appendix 4.C.

Based on these data, the integration found in this review issue can be modelled as follows in the below figure. Process activities 1 and 2, while appearing equal to process activity 3, should be noted as not assessable for integrative nature due to only a single discipline perspective being brought to bear on the input in the process activity.

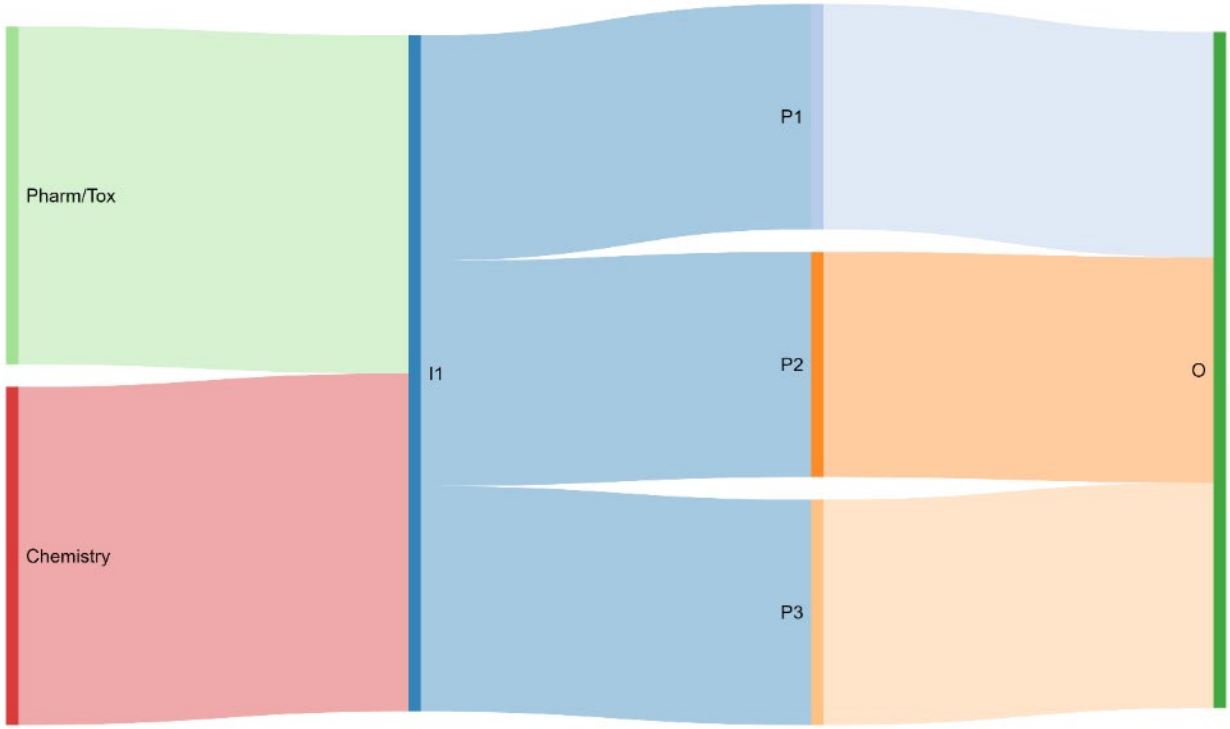


Figure 22: RINVOQ Impurities Review Issue Sankey Integration Model

Review Issue 4: CYP3A4 Coadministration

The fourth review issue identified in the RINVOQ multidisciplinary case was related to the effects of coadministration of the new drug product with other CYP3A4 inhibitors or inducers. This issue was identified by the clinical pharmacology discipline and was described as follows in the clinical pharmacology review:

> "Ketoconazole (strong CYP3A4 inhibitor) increased upadacitinib exposure by 75% (StudyM13-401). Rifampin (strong CYP3A4 inducer) decreased upadacitinib exposure by 61% (Study M13-540). Therefore, upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors and is not recommended to be co-administered with strong CYP3A4 inducers." (FDA, 2019a)

This issue included two inputs from the clinical pharmacology discipline. It is important to note that the analysis of the impact on CYP3A4 was conducted independently by the clinical pharmacology reviewer, as noted during their interview: "That's based on our own data analysis". These two inputs were concrete analyses and also the results from clinical pharmacology studies and are listed in the table, below. Again, the inputs were commensurable in that they were of similar source, type, and findings.

Table 16: RIVNOQ Review Issue 4 Inputs

Input #	Discipline	Input Description
1	Clinical Pharmacology	Independent CYP3A4 Analysis
2	Clinical Pharmacology	Sponsor submitted Drug-Drug Interaction Studies

These two inputs, both from the clinical pharmacology discipline, for review issue 4 were processed in a single activity, which was the assessment by the clinical pharmacology discipline and an alignment discussion with the clinical discipline. While the assessment of the issue was led by clinical pharmacology, an emergent collaborative discussion, and the perspective of clinical was needed in order to arrive at the final labeling recommendation due to the need to determine clinical significance of the finding. In this instance and other similar instances, if the discipline only joined the integration process during a process activity, then the discipline was not reflected in the inputs. The clinical significance in this instance relates to the impact on the

effectiveness of the drug, as indicated in the final determination on this issue found in the summary review:

> "Coadministration with strong CYP3A4 inducers are not recommended because that may result in ineffective concentrations of upadacitinib" (FDA, 2019f)

The change in inputs was considered combinatorial in that clinical made the determination of clinical significance of the finding once that finding was presented to the team. This process step is described in the table, below.

Table 17: RINVOQ Review Issue 4 Process Step

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Finding of decreased exposure of UPA when co-administered with strong CYP3A4 inducers and increased exposure with strong CYP3A4 inhibitors discussed with clinical and recommended for labeling by the clin pharm reviewer. Clinical agreed. (1, 2)	No	Combinatorial

While there was a change in the inputs through the addition of clinical's determination of clinical significance, this change is considered low because the inputs remained mostly intact and conserved in the output, and this process of combining clinical's determination with the findings of the clinical pharmacology's assessment led to a concrete cross-disciplinary labeling recommendation (output) that the product should be prescribed to patients with caution when co-administered with CYP3A4 inhibitors and should not be used with strong CYP3A4 inducers. As the output included the inputs in a mostly unchanged form it is considered an instance of comprehensive but combinatorial integration, however, quite local in that this only had to do with the co-administration of the drug with CYP3A4 inhibitors and inducers. Additional

supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 4.D.

Based on these data, the integration found in this review issue can be modelled as follows in the figure, below. As with review issue 3, what is not reflected in this model is the additional clinical discipline perspective that was brought to bear in the process activity based on how inputs were characterized in this study.

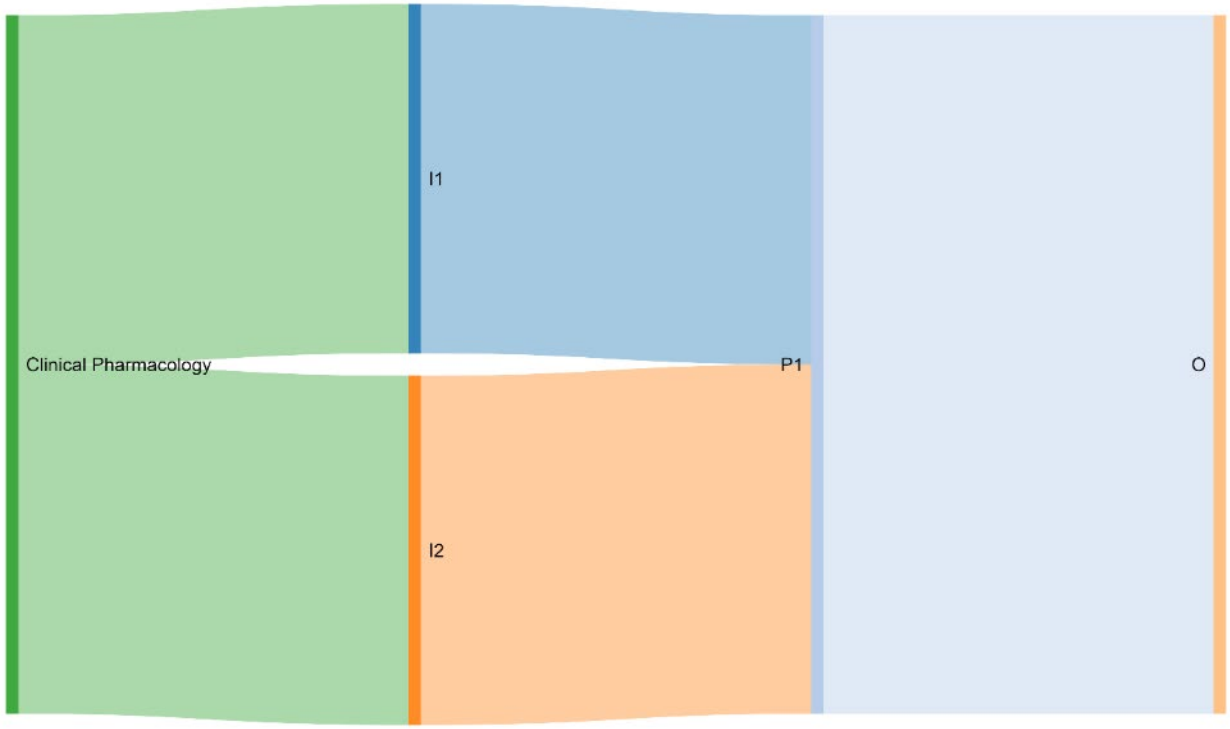


Figure 23: RINVOQ CYP3A4 Coadministration Review Issue Sankey Integration Model

Review Issue 5: JAK Safety

The fifth review issue found in the RINVOQ multidisciplinary case was related to the class safety of Janus Kinase (JAK) inhibitors. This issue was rather unique in that the initial identification of the issue was through the experience of the review team members with previous

products in the same class as indicated by the signatory reviewer and medical reviewer in their interviews:

> *Medical Reviewer*: “this drug is a JAK kinase inhibitor, and we saw a signal with the first in class, tofacitinib, that there was a malignancy signal and then later, possibly with another drug that was being developed, baricitinib, we saw that there was a deep vein thrombosis or a thromboembolic signal. So that's what we were really starting to focus on.”
>
> *Signatory Reviewer*: “One of the issues had been the design of studies and analysis of the safety data. This is, I think, the third JAK inhibitor with toxicities for the class. We had a very gnarly second JAK inhibitor, Baricitinib, that had a unique safety signal of venous thromboembolism for that.”

This issue involved two inputs, one concrete that involved the integrated safety analyses from clinical and statistics and one abstract that involved, as mentioned above, the clinical knowledge of known class safety signals for the JAK inhibitors. Commensurability of the inputs was low in this review issue in that the concrete data from the integrated safety analyses suggested no findings of safety risks, whereas the clinical discipline’s belief was that the class of JAK inhibitors would have these safety issues. These inputs are described in the table, below.

Table 18: RINVOQ Review Issue 5 Inputs

Input #	Discipline	Input Description
1	Clinical	Known class safety signals with JAK inhibitors but lack of finding of thromboembolic events
2	Clinical and Statistics	Integrated Safety Analyses

These two inputs were processed via two activities. The first activity was disintegrative as it intended to breakdown the findings from the integrated safety analyses and then validate the

negative findings against the expected safety events from the clinical discipline's experience. The validation of results would normally be a routine activity, but in this case the initial evidence did not warrant the additional interrogation of data and so the process was disintegrative in that the team was attempting to break down the safety data and analyses into separate antecedent inputs to search for the potential signal, as noted in this quote from the medical reviewer interview:

> "So, we basically identified it because there was none. There wasn't a signal in the data, but we were looking for it because of baricitinib."

The second activity was more integrative and included discussions with the sponsor of the drug product to align on the ultimate regulatory decision. It would take these discussions with the sponsor to ultimately arrive at the output. These two process steps reflect a high degree of change since even though the initial concrete input of negative findings of thromboembolic events led to a labeling recommendation of the events based on the abstract input of the clinical discipline and negotiations with the Sponsor. These process steps are described in the below table.

Table 19: RINVOQ Review Issue 5 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Validation of the safety analyses to confirm no findings of the class safety signals (1)	Yes	Disintegrative
2	Discussion with the Sponsor to align on class labeling for the product even though there was a negative finding for TE events (2)	No	Integrative

As mentioned above, these process activities led to the cross-disciplinary regulatory decision to include class safety labeling for thromboembolic events and other known JAK inhibitor class safety adverse events. As this output did not include the original safety analysis input, only the new disintegrative perspective that was formed and the potential expected signal

from the class (see below excerpt from the summary review), the comprehensiveness of the integration is considered low.

> "Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue and the upadacitinib product label will include a Boxed Warning regarding VTE." (FDA, 2019f)

This output is also considered to be localized as it was related only to the JAK inhibitor class safety. Additional supporting data, including excerpts from the review documents and quotes interviews can be found in the appendix 4.E.

Based on these data, the integration found in this review issue can be modelled as follows in the below figure. As discussed above, it should be noted that in the below model process activity 1 (P1) was disintegrative and would not normally be reflected as carrying the input through to the output. But, due to the way Sankey models are developed and the requirement for them to conserve all elements within the system, the model reflects P1 in this way.

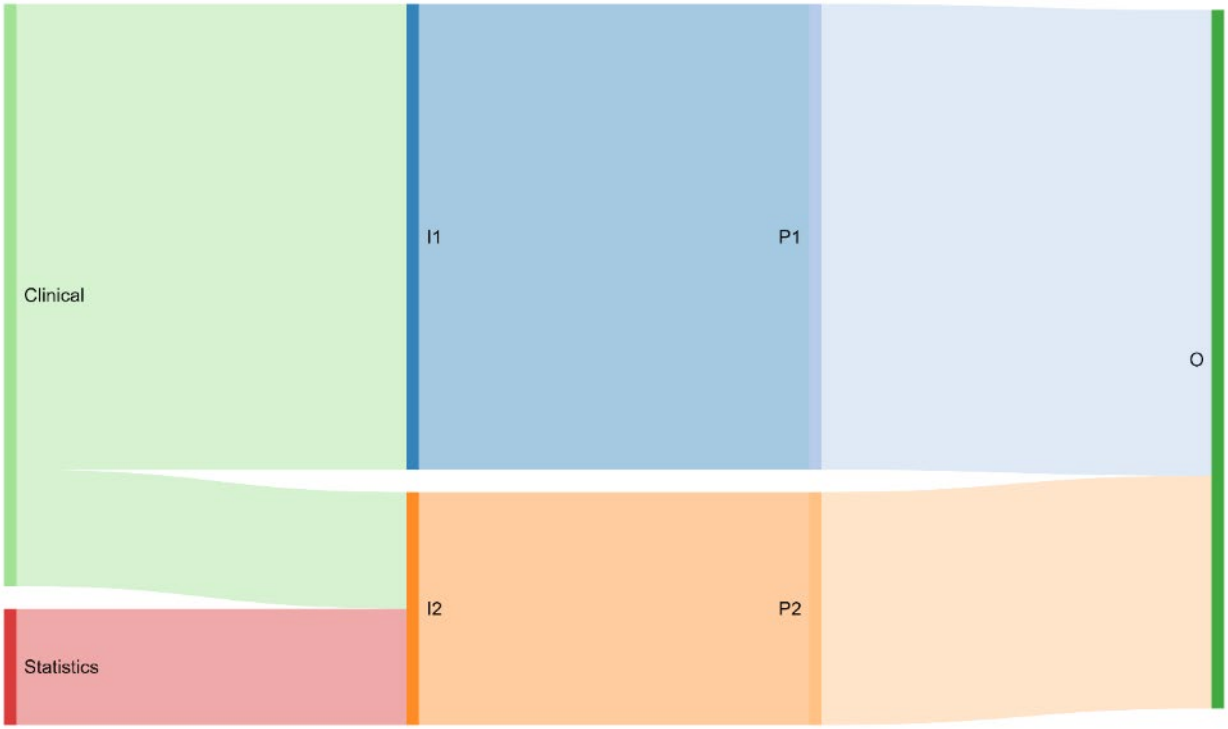


Figure 24: RINVOQ JAK Safety Review Issue Sankey Integration Model

Review Issue 6: Teratogenicity

The sixth and final review issue found in the RINVOQ multidisciplinary case was related to the identification of embryofetal toxicity, and the strength of the signal in comparison to other products in the class, as indicated in the following excerpt from the summary review:

> "the embryo-fetal toxicity finding with upadacitinib is more concerning compared to tofacitinib and baricitinib because of the relatively low exposure margins" (FDA, 2019f)

This issue involved three inputs from the pharmacology/toxicology discipline. While two of these inputs were concrete findings from nonclinical studies, the third was abstract and was a judgment by the reviewer that the signal was much more significant than that found in other JAK inhibitor programs. These inputs were rather commensurable, all coming from the

pharmacology/toxicology domain. The inputs from review issue 6 are further described in the table below.

Table 20: RINVOQ Review Issue 6 Inputs

Input #	Discipline	Input Description
1	Pharmacology/Toxicology	Teratogenicity signal in rabbit study
2	Pharmacology/Toxicology	Teratogenicity signal in rat study
3	Pharmacology/Toxicology	Signal was considered more significant than that found in other JAK inhibitor programs

These three inputs were processed in two activities that incorporated all inputs. The first was the discussion of the issue at multiple team meetings, which would be routine for such issues in a multidisciplinary review approach, as noted by the pharmacology/toxicology reviewer during their interview:

"we raised this pretty early on, I think, and discussed it at various meetings."

These discussions were integrative in that the team validated the significance of the finding and generated additional recommendations on how to proceed (i.e., consult the division of pediatric and maternal health) and the final recommendation on regulatory action. The consult to the division of pediatric and maternal health was considered combinatorial in that it led to an independent assessment from the consult team member and the clinical discipline that contributed to the output, as indicated by the following statement in the pharmacology/toxicology review:

> "An additional bullet statement regarding the potential for embryo-fetal toxicity with upadacitinib was added to the Warnings and Precautions based on a consultation with DPMH and discussions with the Clinical Team." (FDA, 2019c)

These process steps are described in the table below.

Table 21: RINVOQ Review Issue 6 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Discussed at several meetings, including early safety scoping meeting and mid-cycle meeting (1, 2, 3)	Yes	Integrative
2	Consulted with Division of Pediatric and Maternal Health, and Clinical (1, 2, 3)	No	Combinatorial

The discussions of the embryofetal toxicity signal led to a change of the inputs to the concrete recommendation for labeling (output) that a Warning and Precaution to use the product in pregnant and lactating women should be added. However, this output did include all inputs identified so is considered comprehensive and cross-disciplinary even though it is still localized to this specific safety issue, as indicated by the following statement in the pharmacology/toxicology review:

> "The review team agreed that the observed embryo-fetal toxicity data with upadacitinib represented a significant safety concern that potentially warranted inclusion in the Warnings and Precautions." (FDA, 2019c)

Additional supporting data, including excerpts from the review documents and quotes interviews can be found in the appendix 4.F.

Based on these data, the integration found in this review issue can be modelled as follows in the below figure. The interesting dynamic on display in this model is between process activity 1 and 2. While process activity 1 was integrative, and including additional discipline perspectives during the process activity, it appears similar to the combinator process activity 2 due to the way inputs were characterized in this study based on how they originated.

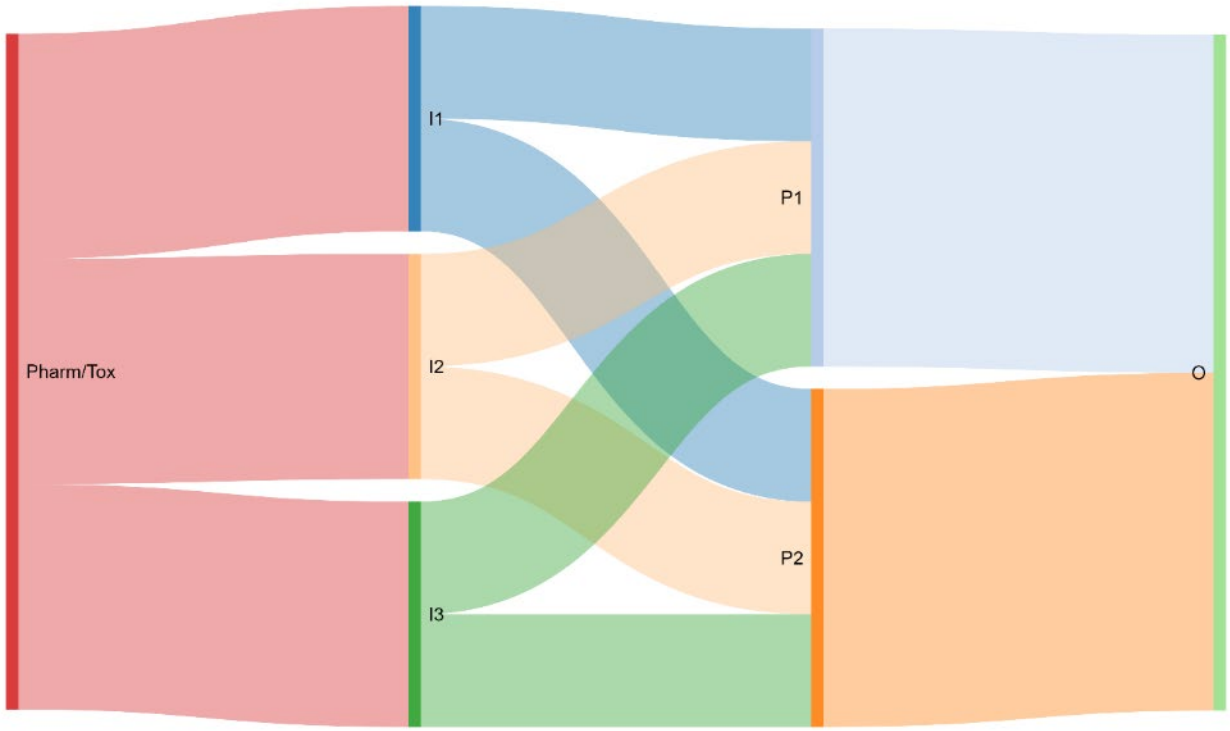


Figure 25: RINVOQ Teratogenicity Review Issue Sankey Integration Model

Description of overall integration in RINVOQ case

As described above and seen in the models of integration, the instances of integration surrounding the six identified cross-disciplinary review issues were mostly cross-disciplinary from the outset (i.e., at the inputs stage). Two review issues, review issue 4 and 6 began as unidisciplinary issues, but over the course of the process of integration became cross-disciplinary. These review issues had on average two to three disciplines involved and as many as six inputs contributing to the outputs. The average number of process steps or integrative activities was two. The majority (15 of 17) of the inputs were concrete. Outputs were evenly either concrete or abstract (3 and 3). The integrative nature of the process activities was mostly combinatorial (6 of 13) and integrative (4 of 13), with the remaining either being disintegrative (1) or not applicable since there was no change (2).

TAUVID Case

Description of interdisciplinary case

The interdisciplinary case for this comparative case study was NDA 212123 for TAUVID (flortaucipir F-18) for use with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibril tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD). The NDA was submitted by Avid Pharmaceuticals, Inc. on September 30, 2019 and approved on May 28, 2020, via a priority review timeline of 8 months. TAUVID (flortaucipir F-18) is a new molecular entity (NME), of which the drug substance is flortaucipir F-19, a benzimidazole-pyrimidine derivative small molecule labeled with fluorine 18 for imaging.

The NDA for TAUVID was reviewed in the Division of Medical Imaging and Radiation Medicine. Like with the NDA review of RINVOQ, because TAUVID was an NME, the signatory, for the application was from the division's parent office, the Office of Specialty Medicine. The review team for TAUVID was similarly made up of a regulatory project manager, a clinical reviewer and team leader, a statistical reviewer and team leader, a clinical pharmacology reviewer who was also acting as the clinical pharmacology team leader, a nonclinical pharmacology/toxicology reviewer and team leader, and a dedicated quality team with a drug substance reviewer and supervisor, a drug product reviewer and supervisor, and a process/microbiology/facility reviewer and supervisor. This application lacked the additional pharmacometrics and pharmacogenomics reviewers and team leaders, and biopharmaceutics reviewer and supervisor. These differences are mostly due to the nature of the development program, dosage and administration, and the information submitted in the application. For this application, as with the RINVOQ application, the clinical team leader served as the cross-

disciplinary team leader. Of this large review team, the following disciplines were represented in the interviews: signatory, clinical, statistics, clinical pharmacology, regulatory project manager, and nonclinical pharmacology/toxicology.

The TAUVID review team utilized a new approach to conducting its review of this application, known as the interdisciplinary assessment of marketing applications. This review approach is still new and little public documentation is available, however, it has been described by FDA staff as a more interdisciplinary, issue-focused approach to conducting the review of a new drug product application (Woodcock et al., 2020). This approach to the review is similar to and builds on the traditional multidisciplinary review of a new drug application in that it involves a review team of multiple disciplines working together, but in the interdisciplinary review approach, the disciplines work more collaboratively from the outset to identify review issues and resolve them as a team throughout the whole review process. As such, the review team works collaboratively to document their assessments in a single review document, known as the Integrated Review. The Integrated Review is to be completely drafted approximately one to two months prior to the action but is finalized just prior to action. A diagram of this new process is below.

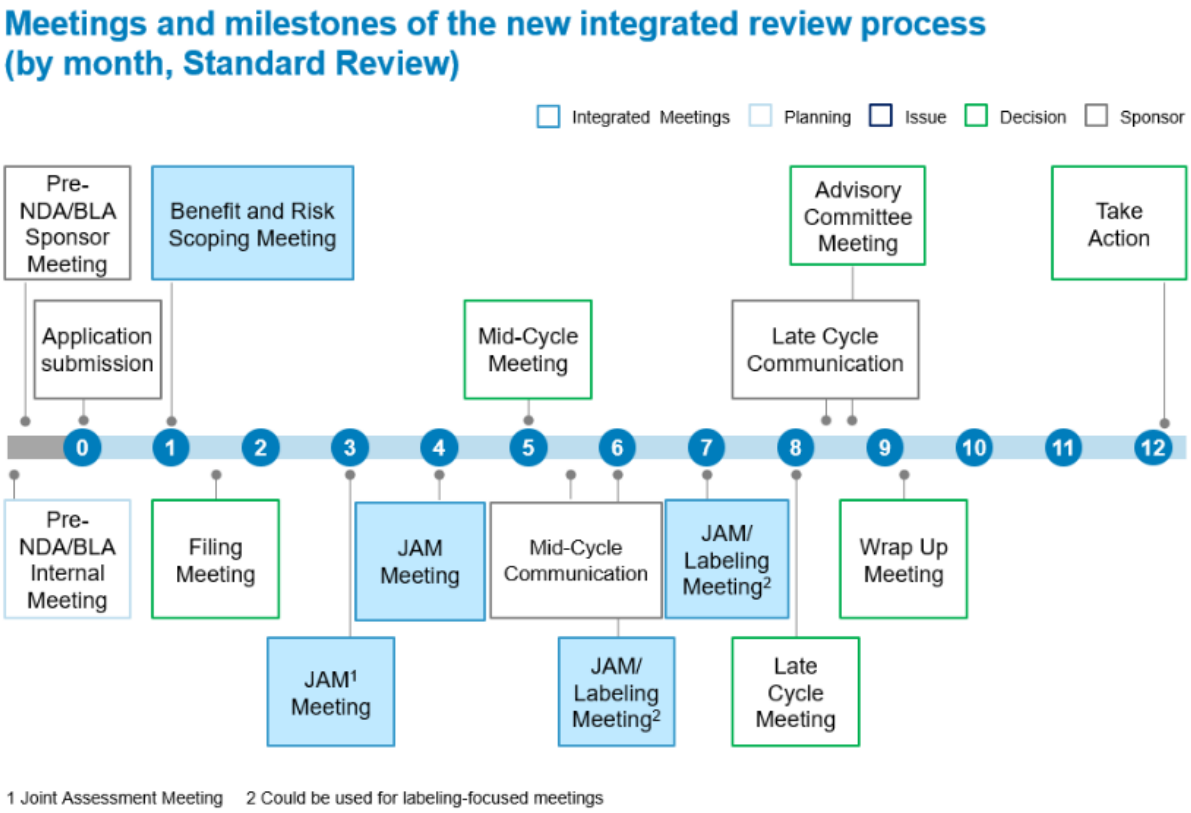


Figure 26: Integrated Review Process
(FDA, 2020b)

In this case, the Integrated Review was completed on May 27, 2020. The Integrated Review document used in the document analysis is listed in the table below.

Table 22: TAUVID Review Document

Document	Length in pages
Integrated Review	272

In the interdisciplinary approach, review teams follow the existing multidisciplinary process and in addition also conduct a benefit-risk scoping meeting prior to filing, and then for each review issue identified, conduct a joint assessment meeting, which is an issue focused meeting including all team members relevant to the issue. Noteworthy of these new process

activities, is that the signatory of the application is also included. Similar to the multidisciplinary review approach, recommendations for final decision are made by the review team members to the signatory at the wrap-up, but due to the early and more frequent involvement of the signatory during the interdisciplinary review process, there is less likely to be misalignment.

Description of cross-disciplinary review issues identified

In contrast to the RINVOQ application review documents, and as noted above, only one review document is generated by the review team. In addition, the integrated review is much more focused on documenting the review issues identified over the course of the review. As a result, the review issues were easily identified from the initial document analysis of the integrated review. The six review issues identified in the TUAVID review were described concisely in the introduction to the Interdisciplinary Assessment of the document and were listed as follows:

"Issues Relevant to Evaluation of Benefit

The team identified the following issues relevant to the evaluation of benefit (see Section 6.4):

- User Guide [for image interpretation] for Tauvid PET Image Display (see Section 6.4.1)
- Limitations of Efficacy Evidence for [redacted] (see Section 6.4.2)
- Lack of Substantial Evidence for [redacted] (see Section 6.4.3)

Issues Relevant to Evaluation of Risk and Risk Management

The team identified the following issues relevant to the evaluation of risk and risk management (Section 7.7):

- CTE Misdiagnosis (see Section 7.7.1)

- Effect of MAO Inhibitors on FTP Binding (see Section 7.7.2)
- QT Interval Prolongation (see Section 7.7.3)" (FDA, 2020a)

Within the Integrated Review alone, these six review issues were mentioned, and coded, extensively throughout the document, as illustrated in the following figure.

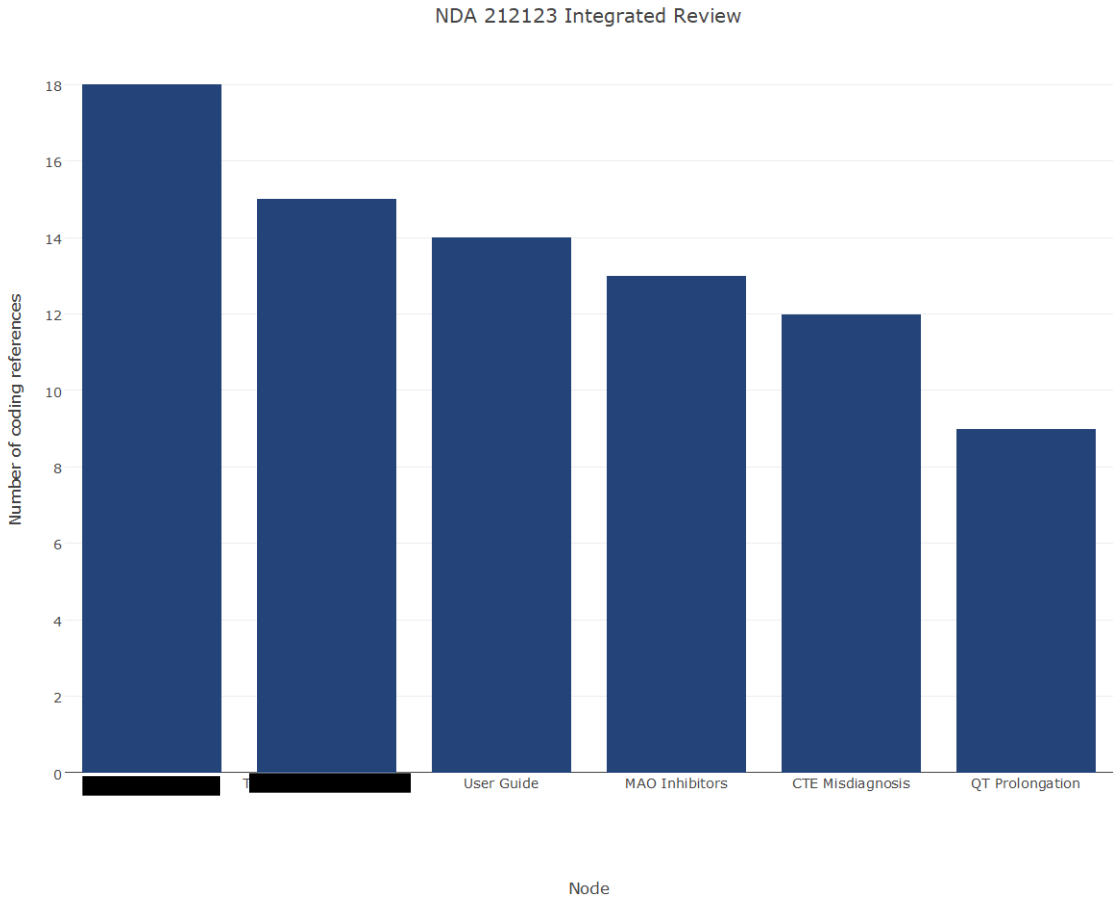


Figure 27: TAUVID Review Issue Mentions in the Integrated Review

These review issues were regularly mentioned in most interviews with the review team, further strengthening the apparent focus in the review of the review issues. This is illustrated in the following exploration of codes for the [redacted] issue across interviews.

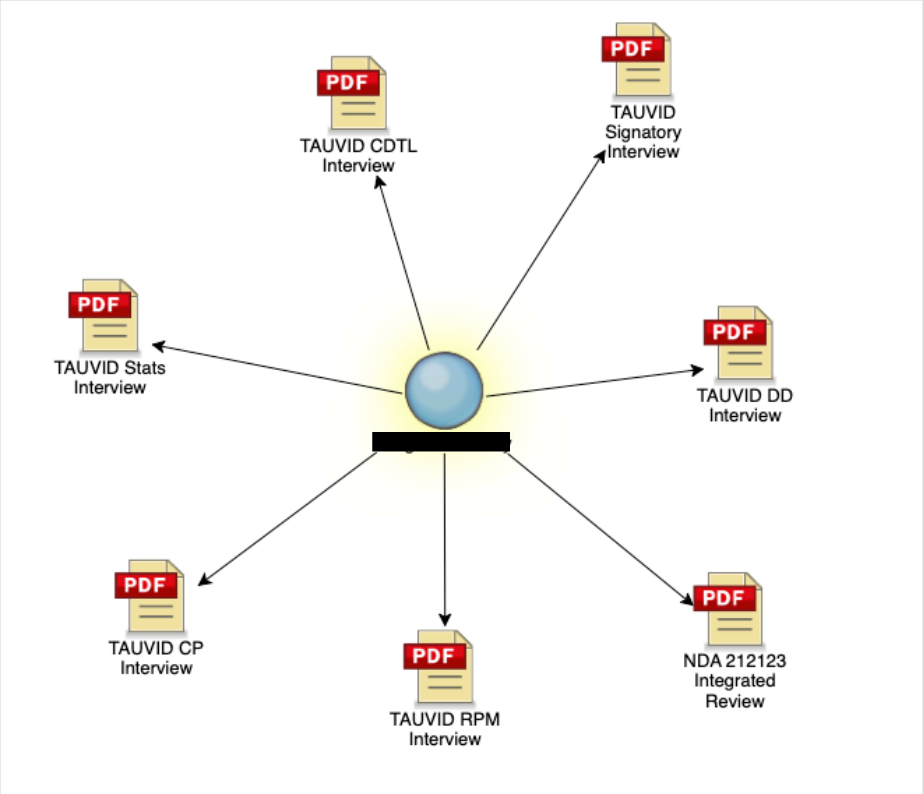


Figure 28: TAUVID [redacted] *Issue Across Objects*

Review Issue 1: MAO Inhibitors

The first review issue identified in the TAUVID interdisciplinary case was related to the effects of TAUVID off-target binding that was similar to other MAO inhibitors, and described as follows in the Integrated Review:

> "FTP binds to MAO-A, MAO-B, and tau-NFTs with low nanomolar affinities. This binding of FTP to MAO-A and MAO-B could potentially affect the interpretation of FTP PET images." (FDA, 2020a)

This issue involved four inputs and three disciplines. All inputs were concrete, including data and information from submitted literature and studies, except for one input which was abstract and related to the clinical pharmacologist's knowledge of the chemical structure of other compounds

that bind MAO, as indicated by the following quote from the interview of the clinical pharmacologist:

> "Well, from the very beginning we noticed that the structure, the chemical structure of [TAUVID] was slightly similar to some of the others of the compounds that bind to MAO inhibitors bind to monoamine oxidase enzymes and the structurally similar to some of those inhibitors. So, it was clear that there's a potential that the drug could inhibit."

These inputs were relatively commensurable, but there was some conflict, as reflected in the misalignment of potential significance between the abstract clinical pharmacology input and other more concrete inputs related to this issue. The inputs are described in the table below.

Table 23: TAUVID Review Issue 1 Inputs

Input #	Discipline	Input Description
1	Clinical Pharmacology	Chemical structure of TAU similarity to other compounds that bind MOA inhibitors
2	Clinical Pharmacology, Clinical, and Pharmacology/Toxicology	Literature on MAO inhibitor binding
3	Clinical Pharmacology and Clinical	Applicant submitted clinical study (unpublished but presented at a scientific meeting) with 50 patients to study MAO inhibitor effects on scans
4	Pharmacology/Toxicology	Secondary Pharmacology Studies

These inputs were processed via four activities that involved a varying degree of involvement from the inputs in each activity. Two of these process activities were purposive, or expected, including an early discussion at a benefit-risk scoping meeting and then a later mid-cycle meeting discussion. The other two activities were more emergent and occurred because of the need to discuss the issue with the Sponsor and within the team during collaborative writing of the Integrated Review. Both the early scoping and collaborative writing discussions were considered integrative. In the early scoping discussion, while one discipline, in this instance

clinical pharmacology, brought up the issue, the decision to further analyze the issue was one made by consensus. And the final collaborative writing appears to have driven further consensus on the review issue and the final recommendation is team-based and cannot be identified as being driven by any single review discipline in the integrated review. This may be a sign that real, meaningful integration is occurring along the way. The mid-cycle discussion was considered combinatorial as multiple disciplines summarized and presented their findings. The shift to more integrative nature of the collaboration post mid-cycle discussion was indicated in the pharmacology/toxicology reviewer interview, and can be seen in the following quote about the writing process:

> "Well, there was a lot of collaborative writing at later stages to try to document this both in like relevance in the clinical, clin/pharm, and nonclinical sections."

Lastly, the discussions with the sponsor were considered disintegrative in that the discussions were intended to break down each of the contributing pieces of evidence (i.e., literature, unpublished study, chemical structures) on this issue. In other words, the discussions were focused entirely on the specific evidence or inputs rather than the significance of the issue. These process steps are described in the table below.

Table 24: TAUVID Review Issue 1 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Early discussions with the review team, led by Clinical Pharmacology, to scope out the issue and agree on significance to the review (1, 2)	Yes	Integrative
2	Mid-cycle team discussions to review team members' conclusions on additionally submitted data and literature (3, 4)	Yes	Combinatorial

3	Discussions between the review team and the Sponsor on significance of the MAO inhibitor similarity (1, 2, 3, 4)	No	Disintegrative
4	Collaborative writing and discussions on how to label for this issue accurately without over alarming clinicians (1, 2, 3, 4)	No	Integrative

There was a high degree of change seen in the processing of the inputs to the output, in that the abstract perspective on how the chemical structure of TAU was transformed into a meaningful review issue. With this said, the reviewers were careful about the output of the integration and how this would be communicated, as indicated by the clinical pharmacology reviewer in their interview:

> "We didn't want to alarm people too much either because the issue is still being researched and still not clear so more studies need to be conducted."

This ultimately led to the concrete conclusion that there was a potential effect of MAO inhibitors and this was described in section 12 of the labeling (output). This output was cross-disciplinary and not overly comprehensive in that the final output in labeling did not fully include all inputs. Because this review issue was also considered local and did not impact the overall benefit-risk determination of the application. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 5.A.

Based on these data, the integration found in this review issue can be modelled as follows in the below figure. Noteworthy in the below diagram is the similar representation of process activity (P3) and process activity 4 (P4). While they appear similar due to their inclusion of all four inputs, P3 was disintegrative in that the Sponsor's perspective was divergent and the goal of the activity was to convert as opposed to incorporate that perspective. The flow from P3 to the

output would more appropriately be represented as fractured if not for the dynamics of Sankey diagrams.

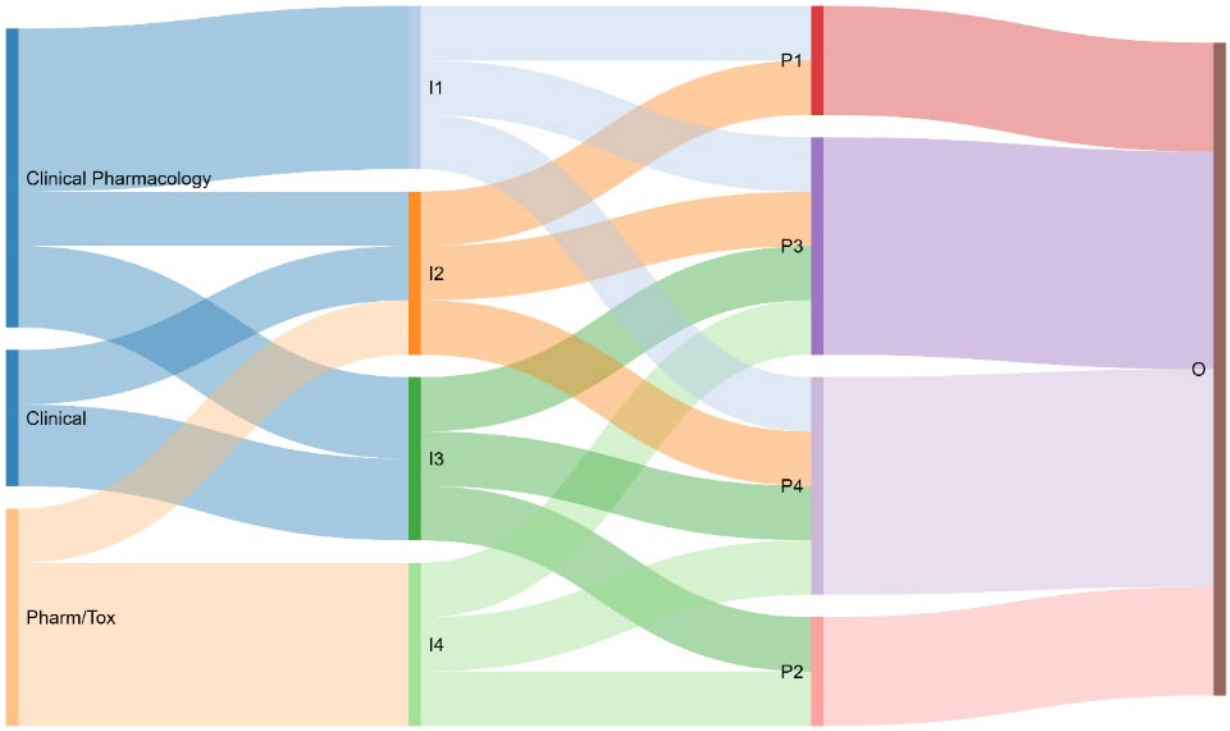


Figure 29: TAUVID MAO Inhibitors Review Issue Sankey Integration Model

Review Issue 2: User Guide

The second review issue in the TAUVID interdisciplinary case was related to the accuracy and usability of the sponsor-submitted user guide for the interpretation of medical imaging results following use of the drug. This issue was most simply described by the signatory during their interview in the following quote:

> "[The] issue, which was identified early on, was the user manual and the team leader who still reads nuclear scans, the user guide. Because they use different platforms for this, to be able to read them. There's different software out there that helps you read the digital image, but you have to put settings into it to be able to read it correctly. They had labeling

> that sort of explained how to do it, and he couldn't understand how to do it, and he's a very experienced nuclear medicine person. If he thought that he would have problems, he knew that was going to be a problem if it was going to get approved."

This review issue included three inputs from five disciplines, two of which were abstract and based on expert perspective or knowledge. One discipline team member was from another center, the Center for Devices and Radiologic Health (CDRH). One of the review issue's inputs was the proposed user guide itself, a concrete input. Commensurability was considered neither low nor high, with only some conflict seen between the regulatory requirements (Input 3) with the other inputs, in that the regulatory and policy input would have it (initially) that the review issue was outside the purview of the review team. The inputs are further described in the table below.

Table 25: TAUVID Review Issue 2 Inputs

Input #	Discipline	Input Description
1	Clinical	Proposed User Guide
2	Clinical, Division of Medication Errors Prevention, and CDRH	Expert perspective on usability
3	Regulatory and Policy	Regulatory requirements for User Guides as labeling

These inputs were processed over a series of three activities, only one of which was purposive or planned, which was the review of the proposed user guide by the clinician as this is standard practice. Two of the process activities were integrative. In one activity multiple experts had to share their experience and expert opinions regarding the usability of the user guides—this was then integrated into a shared team view that the user guides were deficient. In the second, multiple external stakeholders' perspectives were brought to bear. This process was nicely described in the Integrated Review, excerpt below:

> "In response, the Applicant contacted professional societies and also conducted a poll of image readers/imaging sites that participated in the Tauvid efficacy studies to gain insight

into which software platforms are commonly used for image review and analysis in a clinical setting. Based on the survey, the Applicant determined that the most commonly used image viewing software platforms in the US are MIM, GE, Siemens and Hermes. Subsequently, the Applicant created and submitted step-by-step user guides for the MIM and Siemens image viewing software platforms for review and comment on their adequacy." (FDA, 2020, p. 40)

These process steps are described in the table below.

Table 26: TAUVID Review Issue 2 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Identified very early by experienced clinician (a practicing nuclear radiologist) and shared with Sponsor (1, 2)	Yes	Integrative
2	Sponsor conducted multiple tests with experts via professional societies with revised user guides (2)	No	Integrative
3	Regulatory and policy issue with the use of a user guide vs official instructions for use required discussion with ORP and CDRH (1, 2, 3)	No	Disintegrative

Over the course of the process activities, there was a medium level of change because of the input from professional societies and the team, including colleagues from the Office of Regulatory Policy (ORP) and the CDRH. The integration ultimately led to a cross-center, cross-disciplinary and concrete revision to the product's labeling to reflect updated instructions for image interpretation (output). This output was mostly comprehensive but not completely in that it did not include or reflect the input related to the regulatory requirements. In the end, the regulatory policy determination was that labeling did not need to include the User Guide, however, it was referenced in labeling. This output is reflected in the Integrated Review:

> "The Applicant, in consultation with the Agency, added the following language in Section 2.4 (Image Display) of the PI: If additional guidance on image display is needed, refer to the TAUVID User Guide for PET Image Display available by request from the manufacturer." (FDA, 2020a, p. 40)

This issue did have an impact on the overall benefit-risk determination in that image interpretation is highly dependent on the user guide to avoid misinterpretation, but this issue was localized to the user guide alone. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 4.B.

Based on these data, the integration found in this review issue can be modelled as follows in the figure below. Process activity 3 (P3), as discussed above, was considered disintegrative in that the regulatory and policy disciplines sought to focus on the regulatory and legal bases for requiring or regulating a "user guide", which was considered beyond the otherwise regulatable Instructions for Use. In the Sankey diagram below, P3 appears to consume half of the process activity and contribute to half of the output. This is an interesting illustration in this model, but potentially misleading in that P3 was disintegrative and as such likely does not contribute significantly to the integrative output.

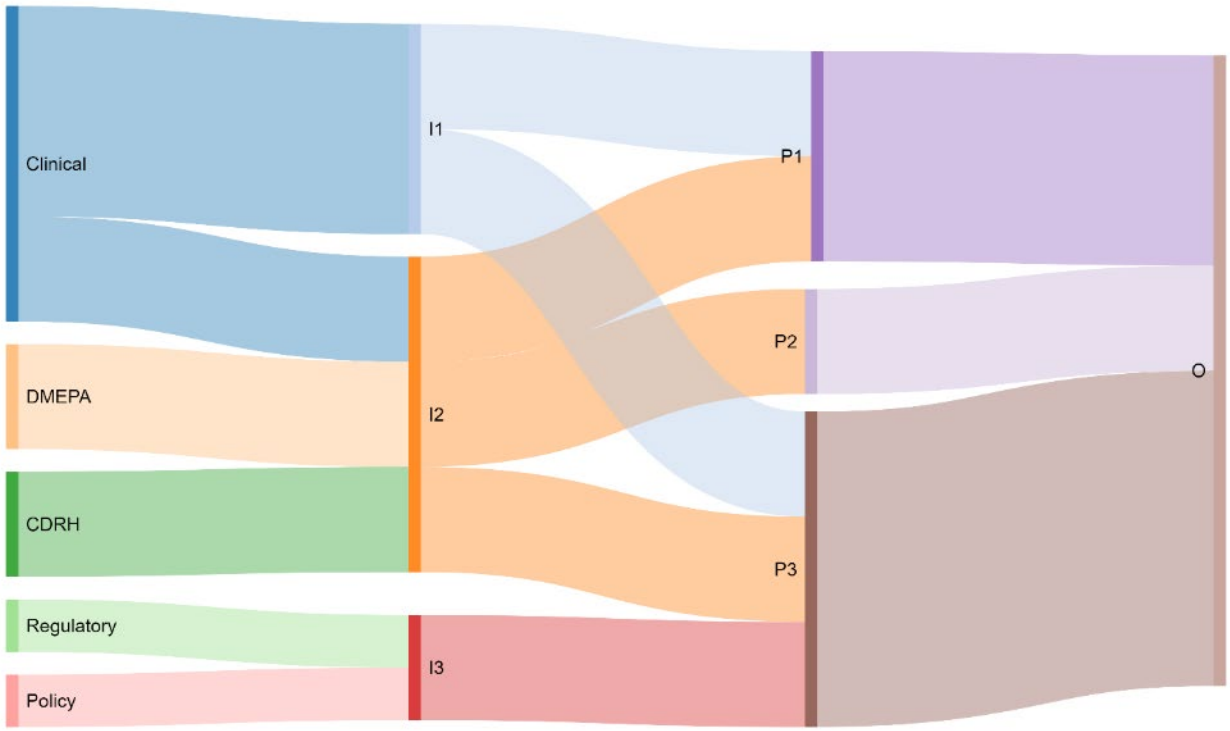


Figure 30: TAUVID User Guide Review Issue Sankey Integration Model

Review Issue 3: QT Prolongation

The third review issue identified in the TAUVID interdisciplinary case was related to QT interval prolongation. This issue was initially identified by the applicant in their application, as noted in the Integrated Review:

> "The Applicant reported small but statistically significant increases in QTcB and QTcF intervals around 2 hours following IV administration of FTP when compared to baseline predose measurements." (FDA, 2020a, p. 21)

This issue involved two inputs, one abstract and one concrete, and four disciplines. The fourth discipline is a self-described inter-discipline: "This issue was also reviewed by FDA's QT Interdisciplinary Review Team (QT-IRT)…" (FDA, 2020a, p. 22). Commensurability was high between the two inputs given that the input, while of an abstract or cognitive nature, was from a

discipline that is focused entirely on the subject matter of the concrete input. The inputs are described in the table below.

Table 27: TAUVID Review Issue 3 Inputs

Input #	Discipline	Input Description
1	Clinical Pharmacology, Statistics, and Clinical	QT Signal reported by Sponsor
2	Inter-discipline of QT Team	Expert input from the QT Interdisciplinary Review Team

These inputs were processed via two purposive activities, consultative review from the QT Interdisciplinary Team (QT-IRT) which was then combined with the inputs of the review team, and a more integrative discussion with the entire review team. The QT-IRT is routinely consulted when a QT signal is of interest and, as a safety issues, would be discussed at the benefit-risk scoping meeting. The discussion was considered highly integrative by the clinical pharmacology reviewer, as indicated in the following interview quote:

> "So, again I want to emphasize it was a, a nice integration between clin pharm team, QT-IRT and then discuss with the, the medical officer [medical reviewer], our medical team leader and the division director and everybody chimed in and looked at the evidence."

These process steps are described in the table below.

Table 28: TAUVID Review Issue 3 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	QT Interdisciplinary Review Team was consulted for input (1, 2)	Yes	Combinatorial
2	Discussed with clinical and clinical pharmacology reviewers and signatory of the review team (1, 2)	Yes	Integrative

There was very little change seen in the integration process. While the QT signal was found early because it was statistically significant, the output of the process was nothing more than confirmation that the signal existed, and no regulatory action was taken. The review team was not worried about the risk here, as indicated by the following comment made by the signatory during their interview:

> "[QT issue was pretty benign as well. There was something identified, but] Yeah, it was. …I didn't think much of it."

All inputs were incorporated making this a comprehensive instance of integration. It was considered local in scale. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 5.C.

Based on these data, the integration found in this review issue can be modelled as follows in the figure below. What is most interesting about the model below is the comparison of the disciplinary contributions to the input. As mentioned above, the QT interdisciplinary review team, is a novel discipline dedicated entirely to the study of QT prolongation safety issues (Input 1).

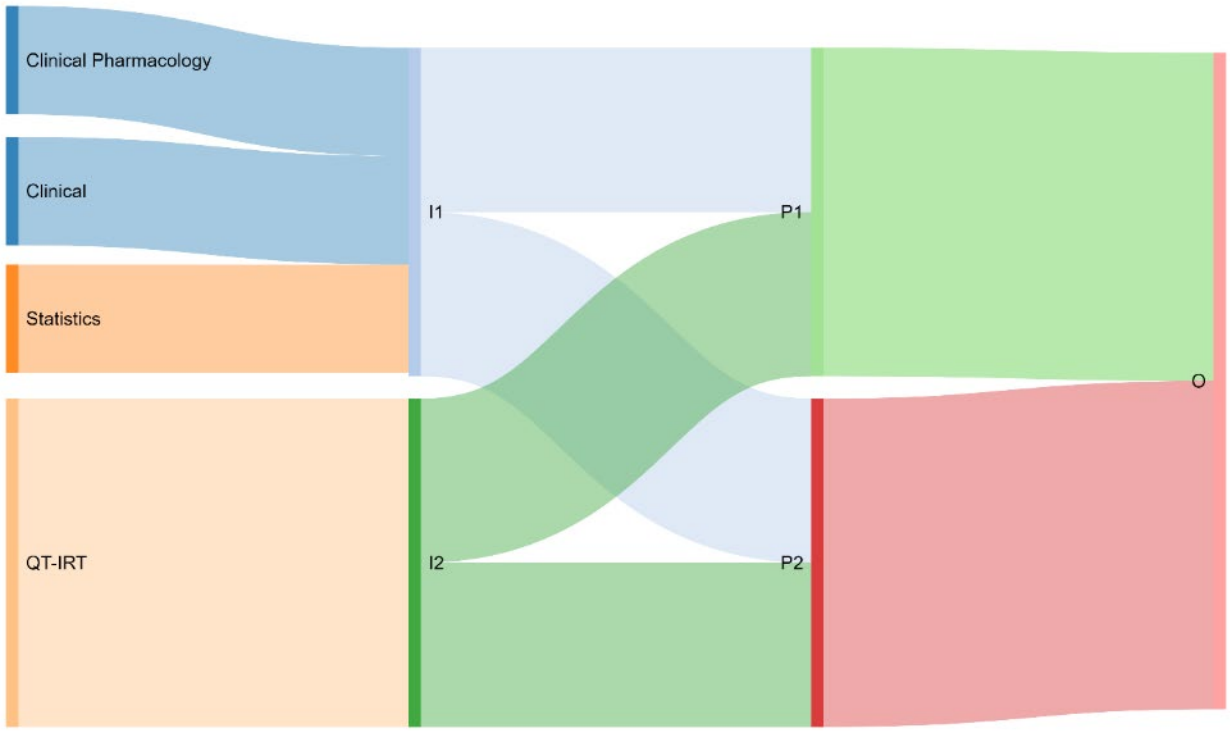


Figure 31: TAUVID QT Prolongation Review Issue Sankey Integration Model

Review Issue 4: CTE Misdiagnosis

The fourth review issue found in the TAUVID interdisciplinary case was related to the potential to misdiagnose chronic traumatic encephalopathy (CTE), and was mentioned early in the integrated review, in the benefit risk assessment: "There is a potential for inappropriate use of Tauvid in patients with CTE and other non-AD tauopathies" (FDA, 2020a, p. 8). This issue involved three inputs and two disciplines. Two of the inputs were concrete data sets and literature articles. The other input was abstract and involved the clinical reviewer's knowledge of how this product might be used given its ability to detect similar tau pathologies. These inputs were from similar sources and input types, so are considered commensurable. Descriptions of the inputs can be found in the table below.

Table 29: TAUVID Review Issue 4 Inputs

Input #	Discipline	Input Description
1	Clinical	Potential for off-label use
2	Pharmacology/Toxicology	Nonclinical Data
3	Clinical and Pharmacology/Toxicology	Published Literature (Falcon et al 2018, 2019; Marquie et al 2019; Mantyh et al 2020)

These three inputs were processed through an unplanned assessment by the review team in an emergent, integrative fashion that there was a lack of evidence to support the use of TAUVID for CTE diagnosis, so labeling would be needed to mitigate the risk of off-label use. This is reflective in the following excerpt from the Integrated Review:

> "Potential off-label use of Tauvid in chronic traumatic encephalopathy (CTE) and other tau-related neurodegenerative disorders is a concern because preliminary nonclinical and clinical investigations suggest differences in tau conformation and distribution may limit FTP binding in CTE."

The process step is described further in the below table.

Table 30: TAUVID Review Issue 4 Process Step

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Team assessed that due to lack of evidence for CTE diagnosis but the potential off-label use, the labeling needs to address this risk (1, 2, 3)	No	Integrative

The team's assessment led to the concrete, cross-disciplinary determination (output) that a limitation of use and a Warning and Precaution was needed in labeling to prevent off-label use of TAUVID for CTE. This output is further confirmed by the following statement during the signatory interview:

> "The CTE misdiagnosis was really something that was based on what had been published already in the literature. It turns out there's different isoforms of tau protein and this drug, the one that is generally present in CTE is somewhat different from, in terms of the type, than in Alzheimer's disease. Apparently, there was already evidence out there that this drug may not be good in trying to use it in patients that are thought to have that diagnosis. I don't recall that being as much of an issue, it came down more to a labeling issue."

This output fully incorporated all inputs and therefore was comprehensive in its integration, but of a local scale since the CTE claim was not a proposed indication for the product. Additional supporting data, including excerpts from the review documents and quotes interviews can be found in the appendix 5.D.

Based on these data, the integration found in this review issue can be modelled as follows in the figure, below.

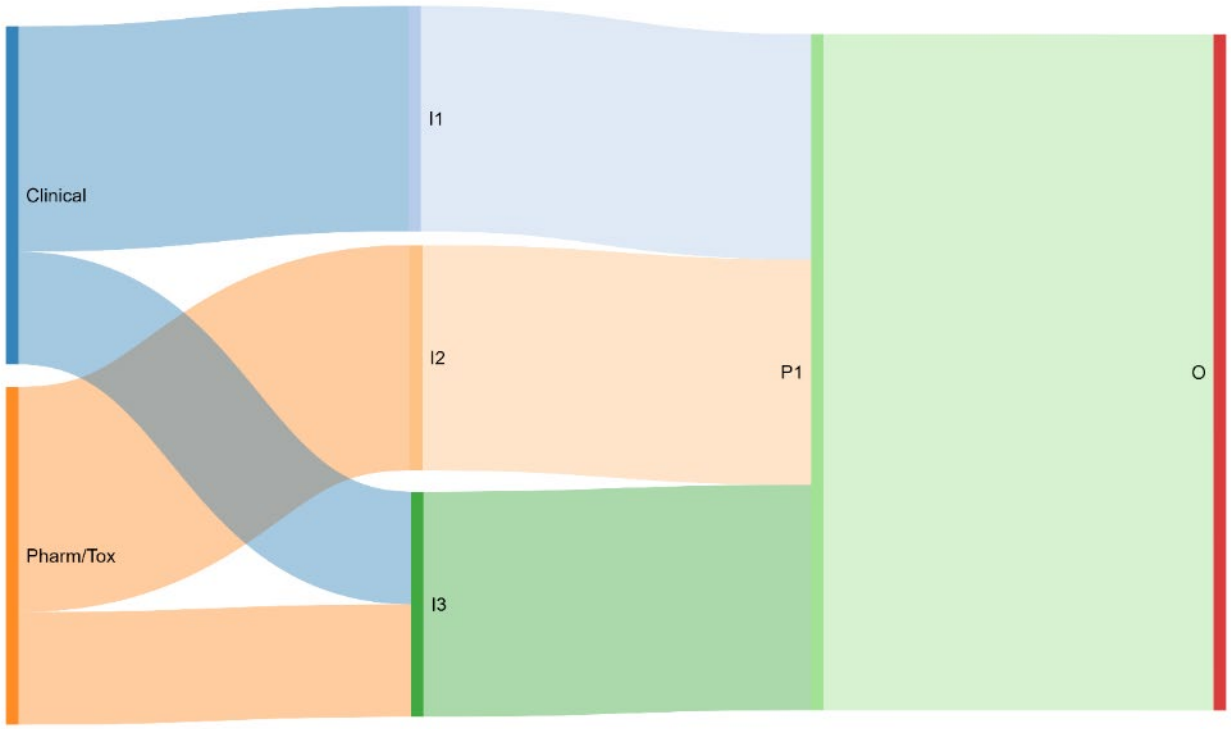


Figure 32: TAUVID CTE Misdiagnosis Review Issue Sankey Integration Model

Review Issue 5: [redacted]

The fifth review issue in the TAUVID interdisciplinary case was related to the detection of Tau pathologies and involved four inputs and three disciplines. This issue was rooted in [redacted]

[redacted]

Three of the inputs for this issue were concrete in nature and included clinical studies, case report forms, line listing data, literature, and the sponsor's proposed labeling. The abstract input

related to the clinical reviewer's knowledge of the disease pathology was best described by the signatory in their interview as follows:

"[redacted]."

There was some conflict in the inputs because the sponsor's proposal included broad labeling claims for Tau pathology detection and the evidence seen in studies and literature, so commensurability was low. The inputs are further described in the table, below.

Table 31: TAUVID Review Issue 5 Inputs

Input #	Discipline	Input Description
1	Clinical, CDRH, and Statistics	Two phase 3 neuropathologic correlation studies (A16 and FR01) including study reports, case report forms, and line item data
2	Clinical	Understanding of disease pathology, particularly earlier forms of disease
3	Clinical, CDRH, and Statistics	Published Literature (Hyman et al 2012)
4	Clinical, CDRH, and Statistics	Proposed labeling (Indication: to help establish a diagnosis of AD)

These inputs were processed in three purposive activities that would be routine or expected in the interdisciplinary review. The early scoping meeting and mid-cycle meeting discussions were considered integrative process activities in that multiple disciplines not only shared findings from their assessments but also focused their discussion on the significance of the issue(s) and impact on the potential regulatory action. The final output of these discussions reflects the integrated team position. The other two activities were combinatorial in that additional perspectives on the inputs were provided by colleagues in CDRH or by the Applicant and considered, as they routinely would be, but these were not integrated with the other members

of the team. This is indicative in the following comment made during the division director interview:

> "So, we negotiated with the company and they agreed to basically claims indication statement that was really consistent with the evidence that we had. And so, it was pretty much a routine kind of an approach."

These process steps are described in the table, below.

Table 32: TAUVID Review Issue 5 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Discussed at early scoping meeting and mid-cycle meeting with review team (1, 2, 4)	Yes	Integrative
2	CDRH was consulted to assess the devices used in the clinical studies (1, 2)	Yes	Combinatorial
3	Discussed with Sponsor during development and early in the review cycle (2, 3, 4)	Yes	Combinatorial

The integration process led the team to the cross-disciplinary conclusion that while tau neurofibrillary tangles (NFTs) associated with AD could be identified, [redacted] This decision was described in the Integrated Review as follows:

> "The team concluded that the results of the submitted phase 3 studies support the efficacy of TAUVID to estimate the density and distribution of aggregated Tau-NFTs in the indicated patient population (efficacy for tau pathology detection)." (FDA, 2020a, p. 39)

This abstract output was coupled with the concrete cross-disciplinary recommendation to revise labeling to reflect an Indication of detection of NFT beta-3 (B3) pathology (i.e., late stage AD pathology) and a Warning and Precaution was added to the labeling to warn clinicians about the

potential to misinterpret a negative finding. Concrete evidence was assessed by the team and the applicant's proposal for indication and labeling was changed to reflect [redacted], representing a high degree of change. These two outputs factored in all inputs and had a global impact on the review team's determination of the marketing application's overall benefit risk profile. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 5.E.

Based on these data, the integration found in this review issue can be modelled as follows in the figure, below. Two details stand out from the below model of integration. First, that Clinical contributed to all inputs, but that it appears these contributions were not equal (i.e., see differences in the flows to input 2 and inputs 1, 3, and 4). This likely reflects the degree of influence on the input and subsequent process activities that incorporated the inputs. Second, there is a substantial crossing of flows in both the disciplinary contributions to inputs and in the incorporation of inputs in the process activities, which may indicate a high degree of activity in the integration process for this review issue.

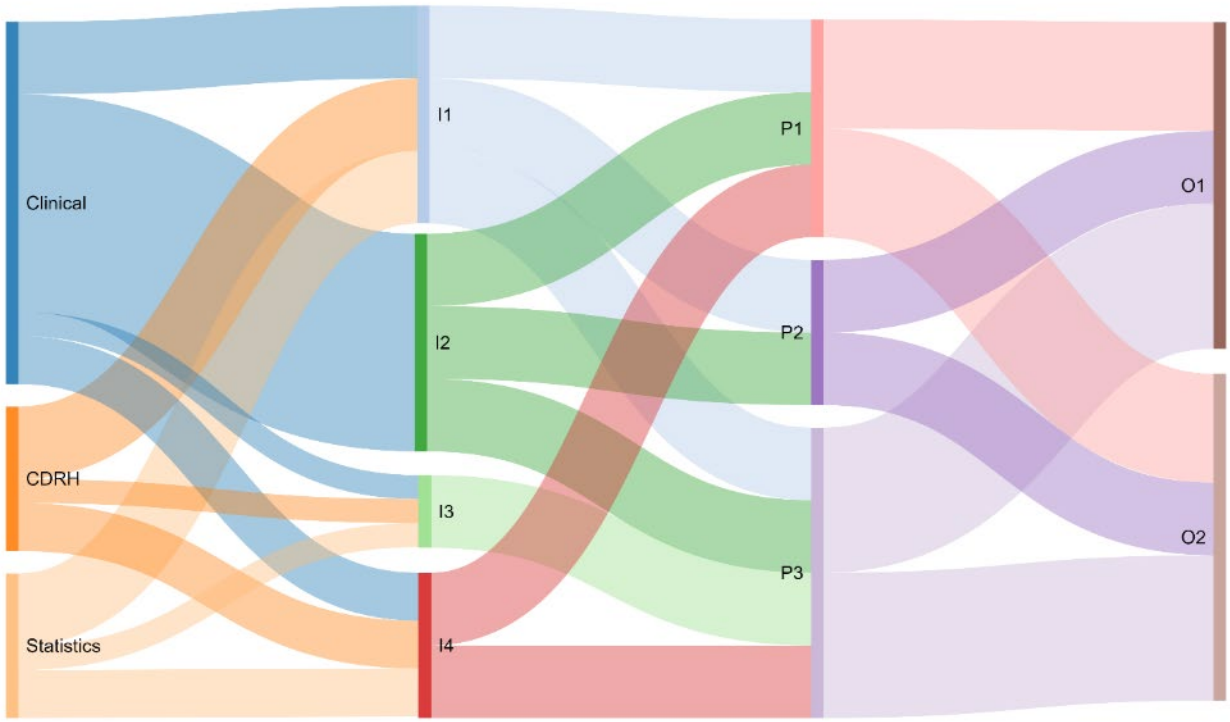


Figure 33: TAUVID [redacted] *Review Issue Sankey Integration Model*

Review Issue 6: [redacted]

The final review issue found in the TAUVID interdisciplinary case was the Sponsor's [redacted]. The division director aptly described this issue as follows in their interview:

> "the second component of the clinical development was going to be an assessment [redacted]. The study did not succeed".

This review issue included four inputs and four disciplines. Three of the inputs were concrete in nature and include clinical studies, data, analyses, and additional information submitted by the Sponsor during the review. There were pre-submission discussions with the Sponsor related to this issue which influenced the integration process by way of influencing early review team

perspectives. The Regulatory Project Manager (RPM) really stressed how early this issue was known to the team, and can be seen in the following quote from the RPM interview:

> "Because of the pre-NDA and the prior meetings, one of the biggest subjects that was constantly being brought up is how they had difficulty in getting their objective. Their objective was being able to [redacted]."

There was little conflict between the inputs and therefore considered highly commensurable. These inputs are further described in the table, below.

Table 33: TAUVID Review Issue 6 Inputs

Input #	Discipline	Input Description
1	Clinical, CDRH, and Statistics	Two phase 3 studies (A05C and PX01), including study reports, case report forms, and line item data
2	Statistics	Sensitivity Analyses
3	Regulatory, Clinical, and Statistics	Pre-submission meeting discussions
4	Clinical and Statistics	Additional data and information requested by the review team

These inputs were processed in three purposive or expected activities ranging from disintegrative, to combinatorial, to integrative. For the combinatorial process activity, the combination occurs by the addition of the consult to CDRH (also seen in Review Issue 5) to assess devices used in the studies and their subsequent findings to the rest of the team's assessment. For the disintegrative activity, based on interviews, the applicant attempted to differentiate between their interpretation of the efficacy findings from the studies and that of the review team, representing a disintegrative change. Such negotiations are anticipated to occur when there is a difference of opinion between the FDA and the Sponsor. This is illustrated in quote from the signatory interview, below.

> "[the Applicant] [redacted]
>
> [redacted]

[redacted]

Similar to process step 1 of review issue 5, the team held multiple integrative discussions to align their views on the path forward on this issue. These discussions involved primarily clinical and statistics. Further information on the process steps can be found in the table below.

Table 34: TAUVID Review Issue 5 Process Steps

Process Step #	Process Description (Inputs involved)	Purposive	Integrative Nature
1	Multiple review team discussions primarily between clinical and statistics, led by clinical (1, 2, 3)	Yes	Integrative
2	CDRH was consulted to assess the devices used in the clinical studies (1)	Yes	Combinatorial
3	Review team held negotiations with the Applicant [redacted] (1, 3, 4)	Yes	Disintegrative

The resultant output of the integration process for review issue 6 was twofold with the abstract recommendation from the review team that an [redacted] This was explicitly stated in the Integrated Review in the conclusions section of the benefit risk assessment:

“[redacted]” (FDA, 2020a, p. 9).

There was a low degree of change in the integration process of the inputs for review issue 6, with the output being somewhat expected and reflected all inputs, making the integration

comprehensive. This was also an issue of global scale due to the impact on the overall benefit-risk determination. Additional supporting data, including excerpts from the review documents and quotes from interviews can be found in the appendix 5.F.

Based on these data, the integration found in this review issue can be modelled as follows in the below figure. While this model is similar to the model of review issue 5, it is worth mentioning that process activity 3 (P3) was disintegrative and if the Sankey diagram could reflect the lack of conservation of inputs' contributions to this process activity and subsequent output then the model might look much more different for review issue 6.

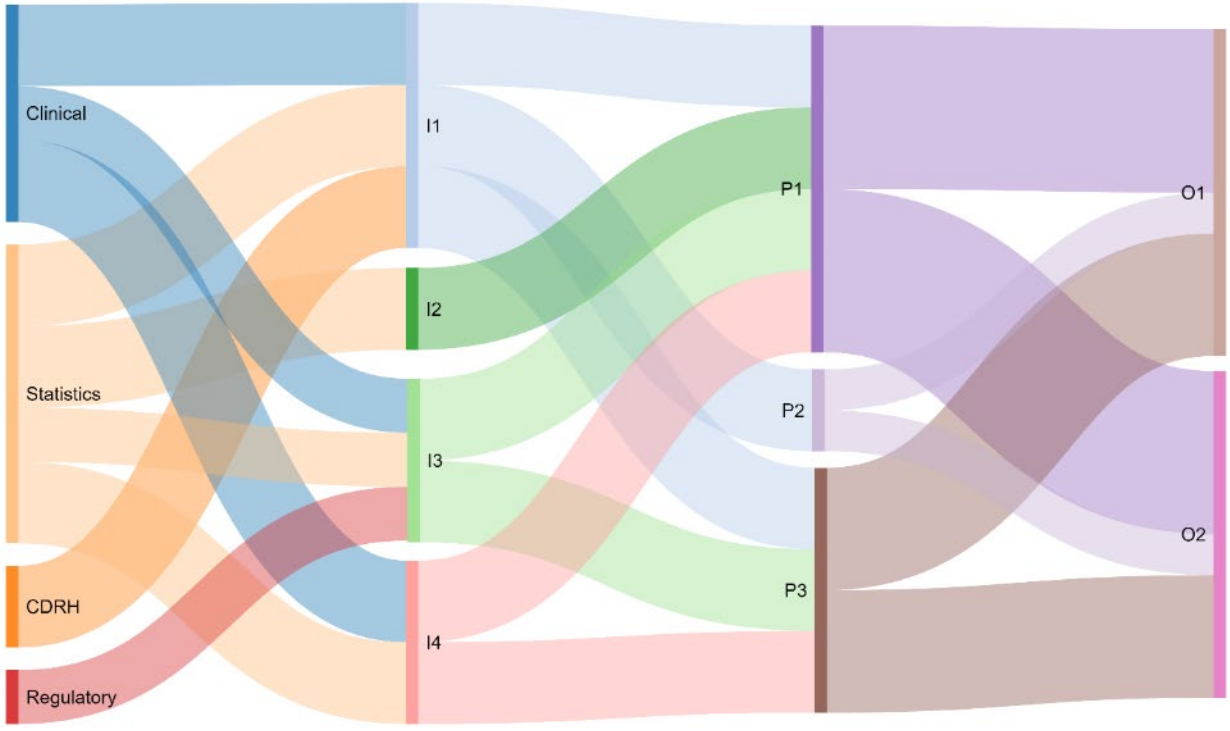


Figure 34: TAUVID [redacted] Review Issue Sankey Integration Model

Description of overall integration in TAUVID case

As described above and seen in the models of integration, the instances of integration surrounding the six identified cross-disciplinary review issues were cross-disciplinary from the

outset (i.e., at the inputs stage). Review issues from the TAUVID case had on average three to four disciplines involved and as many as four inputs contributing to the outputs. The average number of process steps or integrative activities was three. The majority (14 of 20) of the inputs were concrete. Outputs were mostly concrete (6 of 8). The integrative nature of the process activities was mostly integrative (8 of 16) and combinatorial (5 of 16), with the remaining being disintegrative (3).

Differences between Cases and Integration

Key differences between cases

Cross-disciplinary integration in FDA new drug product review teams occurs in response to the review issues or problems that the teams must tackle during their reviews. Therefore, the integration seen is directly related to the uniqueness of each review issue (micro level), the team that tackles it (macro level), and the context of the application in which the issue is found (meso level). As such these micro, macro, and meso level factors and the differences between and among them are important to consider.

At the meso or application level, both applications were for new molecular entities. These were new products that had not been reviewed by the FDA before and therefore would require a comprehensive degree of research and development to understand the full safety and effectiveness aspects of each product to support an initial market registration. This is important because the comprehensiveness of the research and development program translates to the comprehensiveness of the data package submitted to the FDA new drug product review team. These applications did differ substantially in the therapeutic areas of interest, one being for rheumatoid arthritis and the other for imaging in Alzheimer's disease, and in terms of product attributes (i.e., a monoclonal antibody and the other a small molecule delivered in a micro-dose).

In addition, the data package submitted was quite difference in that the RINVOQ product included five well-controlled and adequately powered trials. The TAUVID application included several studies, but none were randomized controlled trials due to the nature of the product and disease. In addition, the TAUVID application included, during the review, several reports from additional published and unpublished studies.

At the macro or team level, both applications were managed and signed off by a review team that was overseen by an OND office director due to the applications each being submitted for an NME. However, because the RINVOQ review utilized the traditional multidisciplinary approach to marketing application reviews the office director may not have been involved until late in the review; whereas with the TAUVID interdisciplinary review the office director would have been involved early and often, beginning with scoping meetings with the review team. At the next level of leadership for the team, both teams were managed by a cross-disciplinary team leader from the clinical discipline. The cross-disciplinary team leader (CDTL) is responsible for integrating the various disciplines viewpoints and final recommendation into a comprehensive benefit-risk determination and recommendation to the signatory for regulatory action. In the case of the interdisciplinary review the CDTL is also responsible for guiding the team through the collaborative writing process. In the multidisciplinary review, the CDTL may be involved in the discipline-specific review document writing but only routinely for the clinical discipline (or the discipline they represent).

Both teams were similar in make up with clinical, pharmacology/toxicology, clinical pharmacology, statistics, and quality disciplines participating. But, the RINVOQ application had a much larger team involved from the clinical pharmacology and quality perspective, with multiple sub-disciplines being integrated within these two disciplines, such as pharmacometrics,

pharmacogenomics, biopharmaceutics, and microbiology. However, on the TAUVID application, additional experts outside of the routine new drugs disciplines were required to assess review issues, such as regulatory policy experts and colleagues from the Center for Devices and Radiologic Health. In the TAUVID review, it is also noteworthy that the Regulatory Project Manager played a more important role in the writing sections of the integrated review.

In addition, there are several planned or purposive process activities in the interdisciplinary review case that likely had an impact on integration. For example, in the TAUVID interdisciplinary case, a benefit risk scoping meeting took place. This meeting occurs early in the review and includes all members of the review team and the signatory, with the focus being on identifying and confirming any review issues that need to be reviewed collaboratively by the review team. As seen in the TAUVID case, multiple review issues included inputs that originated from these discussions, including more abstract inputs.

At the micro or review issues level, the review issues were dissimilar between cases as would be expected, with the exception that the issues were all related to either the potential benefits or risks and the benefit-risk assessment associated with use of the new drug product. Review issues are emergent and highly dependent on the deficiencies seen in the development program that informed the marketing application. In the RINVOQ multidisciplinary case, the review issues were specific to manufacturing or formulation changes and safety or toxicity signals. The TAUVID interdisciplinary case illustrated a few similar safety signal issues but also introduced more complex efficacy issues and issues related to treating physician’s and radiologist’s use of labeling for the safe and effective use of the product.

Key differences in Integration

The next section walks through the key differences in the integration seen in the RINVOQ and TAUVID review cases using the O'Rourke *et al* cross-disciplinary integration framework, or IPO model, as a tool for making analytical comparisons.

Inputs

The RINVOQ multidisciplinary case included a total of 17 inputs across six review issues with a mean and median number of inputs per review issue of three and three, respectively. Inputs per RINVOQ review issue were unidisciplinary 33% (2/6) of the time. For the 67% of review issues that began cross-disciplinary, the mean and median number of disciplines contributing to inputs was four and two, respectively. All review issues, including those that began as unidisciplinary became cross-disciplinary through process. The vast majority of RINVOQ review issues included concrete inputs 88% (15/17). In those instances of integration that included an abstract input, it was a lone input.

The TAUVID interdisciplinary case included a total of 20 inputs across six review issues, with a mean and median number of inputs per review issue of three and four, respectively. Inputs were cross-disciplinary 100% of the time in the TAUVID case, with the mean and median number of disciplines contributing to inputs being four and four, respectively. 70% (14/20) of the TAUVID inputs were concrete and all instances of integration (i.e., review issues) included an abstract input. As noted above, the addition of the benefit risk scoping meeting in the interdisciplinary review approach may offer additional opportunities for disciplines of the review team to offer their subject matter expertise (an abstract input) to the discussion of review issues.

As can be seen in the table below, the TAUVID interdisciplinary case involved a larger number of inputs than the RINVOQ multidisciplinary case, but the mean and median number of

inputs per issue was similar. There is a significant increase in the number of abstract inputs in the TAUVID interdisciplinary case. This may reflect a more interdisciplinary process where experts are communicating earlier and with more abstract contributions to the integration. In addition, the median number of disciplines that contributed to inputs in the instances of integration for the TAUVID interdisciplinary case was substantially higher, double, that of the RINVOQ multidisciplinary case. This may reflect that more discipline expertise is being brought to bear for review issues through more deliberate collaboration (i.e., review team discussions, collaborative writing). That the RINVOQ multidisciplinary case included more than one instance of integration around a review issue where the issue began as unidisciplinary is also an interesting difference and this may finding reflect a key temporal difference in review process between the two cases, where earlier interdisciplinary interactions in the interdisciplinary review case avoid late review cycle collaboration and integration.

Table 35: Comparison of Inputs

Variable	RINVOQ	TAUVID
Number of Inputs	17	20
Number of Inputs per Issue	Mean: 3 Median: 3	Mean: 3 Median: 4
Number of Abstract Inputs	2 (12%)	6 (30%)
Number of Concrete Inputs	15 (88%)	14 (70%)
Number of Disciplines Contributing	Mean: 4 Median: 2	Mean: 4 Median: 4
Degree of Discipline Involvement by Input Contributions	Clin Pharm (9) Clinical (4) Pharm/Tox (4) Statistics (3) Biopharm (3) Chemistry (1)	Clinical (14) Statistics (8) CDRH (5) Clin Pharm (4) Pharm/Tox (4) Regulatory (2) DMEPA (1) Policy (1) QT IRT (1)

Process

The RINVOQ multidisciplinary case included a total of 13 process activities across its six review issues or instances of integration. The mean and median number of process activities per review issue was two and two, respectively. In the RIVNOQ case, the abstract inputs were involved in all review issue process activities. In addition, in the RINVOQ case the inputs were shared across multiple process activities in 50% (3/6) of the review issues or instances of integration, with 54% (7/13) of the total process activities including multiple inputs. Eight of the process activities included cross-disciplinary inputs. The majority (5/6) of review issues in the RINVOQ case contained purposive or deliberate and planned process activities, with 61% (8/13) of the process activities being purposive. Of these process activities, a small majority were combinatorial (6/13).

The TAUVID interdisciplinary case included a total of 16 process activities across its 6 review issues or instances of integration. Of these 16 process activities, the mean and median number of process activities per review issue was 3 and 3, respectively. In the TAUVID case, the abstract inputs were involved in all process steps only 66% (4/6) of the time. Inputs were shared across multiple process activities in the majority (4/6) of review issues or instances of integration, with 14 of the 16 process activities including multiple inputs. All 16 process activities included cross-disciplinary inputs. The majority (5/6) of review issues in the TAUVID case contained purposive or planned and deliberate process activities, with 69% (11/16) of the process activities being purposive. The majority (8/16) of the process activities were integrative in the TAUVID case.

As can be seen in the table below, the TAUVID interdisciplinary case involved a greater number of process activities in total and per review issue. There is a dramatic increase in the

number of process activities that involved multiple inputs and multiple disciplines, which again hints at the increase in collaboration in the interdisciplinary review approach of the integrated review. This also suggests a greater degree of interdisciplinarity in the integration process. There was also a much larger – double, in fact – number of integrative process activities in the TAUVID interdisciplinary case than in the RINVOQ multidisciplinary case.

Table 36: Comparison of Outputs

Variable	RINVOQ	TAUVID
Number of Process Activities	13	16
Number of Process Activities per Review Issue	Mean: 2 Median: 2	Mean: 3 Median: 3
Multi-input Process Activities	7 (54%)	14 (88%)
Cross-disciplinary Process Activities	8 (62%)	16 (100%)
Purposive Process Activities	8 (62%)	11 (69%)
Combinatorial Process Activities	6 (46%)	5 (31%)
Integrative Process Activities	4 (31%)	8 (50%)
Disintegrative Process Activities	1 (8%)	3 (19%)
Process Activities with no change	2*	0

* Represents 13% of the process activities and were not assessable for integrative nature

Outputs

In the RINVOQ multidisciplinary case, six outputs—three abstract and three concrete—were observed. And, each review issues or instance of integration terminated in a single output. In the TAUVID interdisciplinary case, eight outputs were observed—six concrete and two abstract. And, in two separate instances of integration, or review issues, in the TAUVID case there were 2 outputs, which was an interesting difference between the TAUVID case and the RINVOQ case. This may suggest that in the TAUVID case, the review team was more efficient and could create additional outputs. However, this is also more likely to represent the nature of the decisions that were made and the necessary companion regulatory actions.

Integration Parameters

At the instance or review issue level, as mentioned earlier, several parameters exist in the O'Rourke *et al* framework for cross-disciplinary integration that allow the integration's context

to be assessed. In the RINVOQ case, inputs in four of the cases were highly commensurable compared to three of the cases in the TAUVID case. In the RINVOQ case, the vast majority (5/6) of review issues were local in scale compared to only half of the issues (3/6) in the TAUVID case. The majority of review issues in both cases experienced integration that was comprehensive.

Table 37: Comparison of Integration Parameters

	Commensurability	**Scale**	**Comprehensiveness**
RINVOQ Review Issue 1	High	Global	High
RINVOQ Review Issue 2	High	Local	High
RINVOQ Review Issue 3	NA	Local	High
RINVOQ Review Issue 4	High	Local	High
RINVOQ Review Issue 5	Low	Local	High
RINVOQ Review Issue 6	High	Local	High
TAUVID Review Issue 1	Medium	Local	Low
TAUVID Review Issue 2	Medium	Medium	Medium
TAUVID Review Issue 3	High	Local	High
TAUVID Review Issue 4	High	Local	High
TAUVID Review Issue 5	Low	Global	High
TAUVID Review Issue 6	High	Global	High

Findings

As noted above, there were key differences between the integration seen in the cross-disciplinary review issues from the RINVOQ and TAUVID case studies, but more importantly,

there was integration seen in both cases. The similarities related to the integration, except for one review issue in the RINVOQ case (RINVOQ review issue 3), all instances of integration experienced some form of integration in all process activities suggesting that both cases are collaborative and seek integration. This finding is also supported by a similar percentage of process/changes that were found to be purposive or planned. Lastly, that review issues across both cases were mostly found to be comprehensive suggests the integration is occurring effectively. While these two cases may not be generalizable to all multidisciplinary and interdisciplinary FDA new drug product reviews, this finding of widespread integration in process activities suggests that integration is an expected activity in all new drug reviews and not a unique feature of either case or approach.

While integration appears common to both cases, the degree of cross-disciplinary integration and the nature of integration (i.e., combinatorial, integrative) appears more integrative in the TAUVID interdisciplinary case. This is reflected in the greater number of disciplines observed to contribute to each review issue and the greater number of cross-disciplinary and integrative process activities in the TAUVID case. This can be seen visually in the Sankey diagrams of the review issues where clearly there are more crossing of flows in a greater number of the diagrams, with three instances in the RINVOQ case and five instances in the TAUVID case. This is even more interesting considering the larger number of review team members participating in the RINVOQ review compared to the TAUVID review. It is noteworthy that with a smaller team, there was greater cross-disciplinary integration observable in the TAUVID case.

In addition, a few key findings related to differences in the parameters of integration were noted. First, there was a slight increase in conflict seen in the TAUVID review issues as seen in

less commensurability. Secondly, there was also a slight increase in the global nature of the review issues and the integration, suggesting the review issues were more impactful on the overall new drug product application review in the TAUVID case. These two parameters, however, are expected to shed light on the context of the integration more than the integration itself. In other words, these two parameters of commensurability and scale reflect the nature of the review issues more than the specific integration. Nevertheless, these two parameters are helpful to understanding the integration and some differences between these two cases.

With regards to context, there are several key differences between the applications or cases that may have impacted the integration and should be noted. The RINVOQ application was submitted by a large and highly experienced pharmaceutical company, AbbVie, Inc, with gross earnings of $33.3 billion in 2019 (*ABBV | AbbVie Inc. Annual Income Statement | MarketWatch*, n.d.). Whereas, Avid Pharmaceutical, Inc. reported gross earnings of $59.7 million in fiscal year 2020 (*CDMO | Avid Bioservices Inc. Profile | MarketWatch*, n.d.). This is an order of magnitude in difference. It might be expected that the experience of the Sponsor can have a large impact on the quality of both the drug development program and the corresponding application that is submitted to the FDA.

It may have also been the case that the Sponsor of the RINVOQ application, through their experience worked out most of the challenging issues that could have impacted benefits and risks during development and as such those issues did not emerge over the course of the FDA's review. Even the review issue associated with the doses of 30 mg and 15 mg appear to have been well worked out by the Sponsor and in fact the Sponsor did not even propose the 30 mg in their labeling. As one RINVOQ team member remarked, "this was a very clean application".

Another key difference between the cases was in the new drug products reviewed. While both products are generally expected to have a minimal risk profile due to their nature (i.e., a monoclonal antibody and a micro-dosed, radio labeled small molecule), the chemistry and manufacturing sections of the marketing applications are quite different. Monoclonal antibodies, like RINVOQ, are biologically synthesized in living cells whereas small molecules, like TAUVID, are chemically synthesized. This mostly translates to the complexity of the quality review issues seen, such as the formulation changes in the RINVOQ case, but could also impact safety as noted in this review with the additional need to assess minor but unexpected safety signals for such a micro-dose product, such as the QT signal for TAUVID, or known class safety signals for RINVOQ given the proposed chronic administration of the product. Given that the integration was evaluated in these cases by assessing the emergent review issues, much of the interpretation of integration from this comparative case study may be dependent on some of these specifics of the product or application that drove the review issues. This makes it challenging to fully extrapolate these findings to all multidisciplinary and interdisciplinary reviews as the review issues will be quite unique and may vary by nature of application, Sponsor, or product. Additional cases may need to be evaluated using this model to establish replicability and validity for more rigorous evaluations.

It is also worth mentioning the importance of differences in review process, see figure 26, and in the writing of the review document. As discussed earlier, in the interdisciplinary review there were earlier and more frequent planned review team meetings and involvement from the signatory or decision-maker for the application. These new meetings were seen in the data and appeared to contribute to additional inputs and to the integrative of process activities. In addition, as figure 35 below illustrates, the shift to a more collaborative document is likely to promote

greater integration due to the requirement to write collaboratively and speak with a single, issue focused voice. In previous forms of reviews, such as the traditional review or the Unireview, disciplines still focused on their separate documents or sections of a review document.

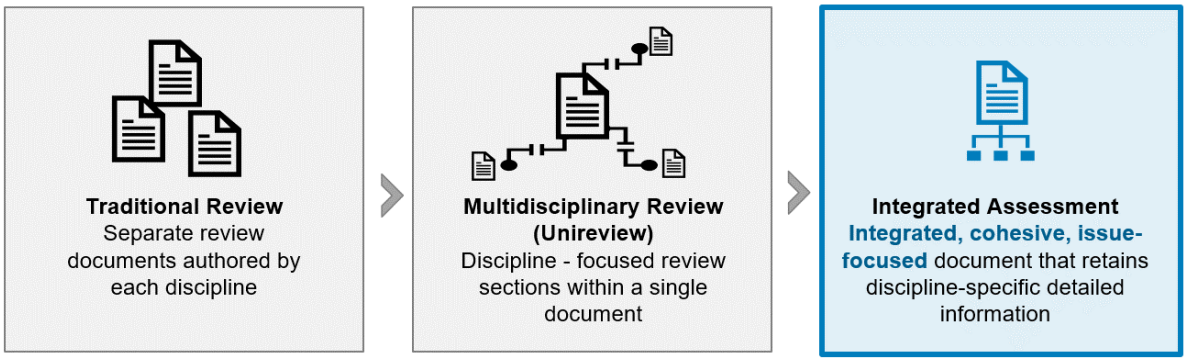


Figure 35: Shift in Review Documentation
(FDA, 2020b)

The final interesting finding worth noting is related to the greater clarity of integration found in the documentation for integrated review for the TAUVID review compared to the multiple reviews for the RINVOQ case and the ease of navigating the documentation. A much larger quantity of information was analyzed in the RINVOQ case (736 pages) compared to the TAVUID case (272 pages). In addition, it was more difficult to identify the review issues in the RINVOQ case until the summary review was analyzed. In contrast, the TAUVID integrated review had a heightened focus on review issues in its documentation and even called them out in the executive summary and regularly referred to them in the interdisciplinary assessment section of the review document. As a result, more reliance on interviews in the RINVOQ case was needed to supplement the review documents and help home in on the key review issues.

However, while it was easy to identify the review issues in the TAUVID documentation it may make identifying conflict between disciplines in the documentation more challenging. For example, even though there was bit more conflict/scientific disagreement in review issues seen in the TAUVID case, this lower commensurability was not necessarily seen in the documentation. It

was found through interviews with team members. It is not clear if this is case specific or related to the approach to the review (i.e., multidisciplinary, or interdisciplinary) or related to other factors. It is possible that the earlier and increased focus on collaboration shifted the conflicts to earlier in the review process activities and as such at the time of documentation these issues were resolved. If that is the case, FDA may need to consider increased awareness of the importance of contemporaneous documentation of review issues earlier in the review cycle, particularly when there is conflict within the review team.

To conclude, these findings support the assertion that collaborative cross-disciplinary integration is present in both the RINVOQ multidisciplinary case and the TAUVID interdisciplinary case, as illustrated by the presence of integrative process activities, multidisciplinary inputs. Furthermore, the observed collaboration and integration was more integrative and cross-disciplinary in the process activities in the TAUVID interdisciplinary case. This can be visually observed by placing the most integrative and cross-disciplinary review issue from the RINVOQ case side-by-side with an input and output-matched TAUVID review issue below. The process for the TAUVID review issue is visibly more active, with more flows and more crosses, reflecting greater cross-disciplinary collaboration in the process activities.

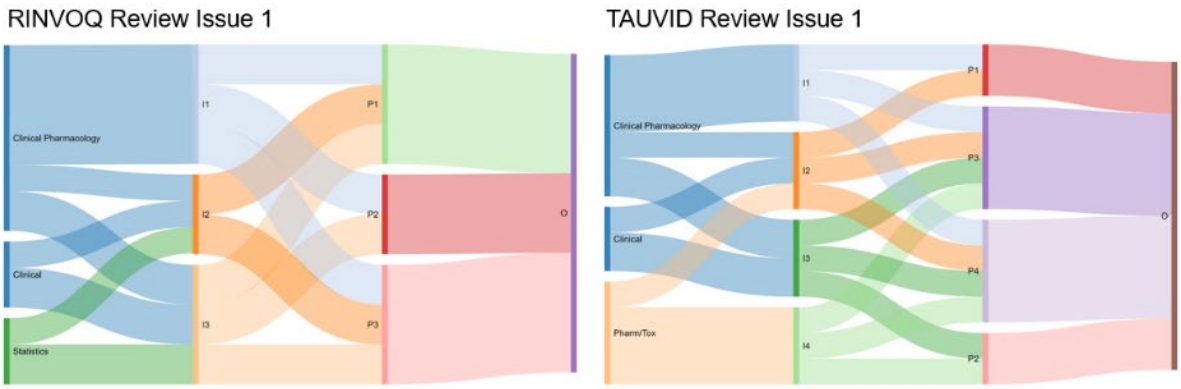


Figure 36: Side-by-Side Integration Comparison

With the finding that collaborative cross-disciplinary integration was found in both the multidisciplinary and interdisciplinary FDA new drug product review cases in this study, but that it is more collaborative in the interdisciplinary review, FDA should feel confident that its new approach is operating as intended and headed in the desired direction. FDA might consider evaluating integration with this IPO framework in additional multidisciplinary and interdisciplinary reviews to understand validity of these findings and guide its further implementation. For the Science of Team Science practitioners, the IPO framework and approach used in this study should be used to further characterize the integration seen in other collaborative cross-disciplinary ventures to promote both generalizability and additional sensitivity to evaluating integration. In time, building a repository of instances of integration evaluated using this approach could inform future research.

Chapter 5

Introduction

Cross-disciplinary integration is a key feature of interdisciplinary research and the collaborative form is often a desired outcome of Team Science (Bammer, 2013; Klein, 2012; O'Rourke et al., 2013). In 2019, the FDA sought to increase integration in its new drug product marketing application reviews with the implementation of the new interdisciplinary assessment process and integrated review document (Woodcock et al., 2020). The FDA's intention was to support integration more collaboratively and early on to avoid the "last minute", often individually led integration of discipline reviews common in the traditional multidisciplinary approach.

However, FDA lacked an approach to evaluate integration and would be unable to evaluate the implementation of its new approach. The Science-of-Team-Science (SciTS) has similarly sought to evaluate integration in Team Science, but many of those efforts have often used too contextually specific approaches or sought to mostly evaluate the outputs of cross-disciplinary research and its antecedents. And so, a more objective, flexible, and process-focused method for evaluating integration was developed based off of O'Rourke et al.'s cross-disciplinary integration framework and applied in this research study (O'Rourke et al., 2016).

This study deployed a phenomenological descriptive comparative case study approach to identify and characterize the nature of the collaborative integration occurring in FDA review teams for two new drug product application using two different forms of cross-disciplinary research. As Julie Thompson Klein articulated in her 2014 discussion of interdisciplinarity, this integration increases across the continuum of cross-disciplinary research from unidisciplinary to transdisciplinary and is characterized heuristically by different forms of integration (Thompson

Klein, 2014). For this reason, integration in a multidisciplinary and interdisciplinary case is expected but should be different.

The O'Rourke *et al.* framework and associated model (i.e., Inputs > Process > Outputs) for integration was adapted for the FDA context to both characterize integration found in key review issues in the two cases and facilitate analytical comparisons. Contextual adaptation came through the coupling of the IPO model with the FDA's benefit-risk framework for determining that a new drug product was approvable. The two research questions for this study were:

1. What are examples of integration in a "multidisciplinary review" and an "integrated review" of an FDA new drug product?
2. What are the specific differences in integration between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?

These research questions were explored via a document analysis and semi-structured interviews. Following a validation of data collection using member checking with participants, data was organized using the cross-disciplinary integration framework, to enable granular comparative analyses, and then modelled as both logical models and Sankey models. This approach to analyzing integration was found to be effective and practical. As noted above, integration was expected in both cases since the approaches that the two teams utilized were cross-disciplinary. This was indeed confirmed, and the study also found that the approach to evaluating integration was sensitive enough to enable comparisons of the integration between both the instances of integration with each case and between the two cases overall. And it was found that the interdisciplinary review, at least in this case, and in comparison to the multidisciplinary review in this case, was more integrative.

Considering these findings, FDA can feel confident that its traditional multidisciplinary and the new interdisciplinary approaches to conducting team-based marketing application reviews are both integrative and that the new approach is leading to the desired outcome of increased integration. In addition, FDA and Team Science may have now have an objective method for evaluating collaborative cross-disciplinary integration. It will be important to continue to apply this evaluation method to additional FDA and non-FDA teams to continue to refine and validate it. The sections that follow review the findings from the study, discuss implications for practice, both in the field of SciTS and in FDA where great value is expected, and finally discuss implications for future research.

Summary of Findings

As mentioned above, this study successfully identified and characterized multiple instances of integration in two cases of new drug product application reviews, the RINVOQ multidisciplinary review and the TAUVID interdisciplinary review. This finding confirms that integration is indeed occurring in FDA new drug product reviews. In addition, the approach to characterizing the collaborative cross-disciplinary integration using the adapted O'Rourke et al. cross-disciplinary integration framework enabled enable objective, analytical comparisons between the two cases.

That integration occured in both cases of FDA new drug product application review approaches is noteworthy because it confirms that FDA review teams are effectively integrating. Second, that the nature of the integration was collaborative and cross-disciplinary is also important in that it demonstrates FDA is truly engaged in Team Science.

In the RINVOQ case, integration was found in six review issues and observed as mostly cross-disciplinary from the beginning of the process. There were two instances of integration that originated from a single discipline, but over the course of the integration became cross-disciplinary through the collaborative involvement of other disciplines in process activities. Most process activities for RINVOQ were characterized as combinatorial, which would align with a multidisciplinary form of collaboration (Thompson Klein, 2014), an expected finding.

In the TAUVID case, integration was cross-disciplinary in all six identified review issues and comprehensively cross-disciplinary (i.e., from beginning to end). The TAUVID integration process activities were found to be mostly integrative, which aligns with an interdisciplinary form of collaboration, another expected finding.

Both of these findings confirm that per the framework from O'Rourke et al. for collaborative cross-disciplinary integration and the continuum of integration heuristic from Julie Thompson Klein, that FDA new drug product review teams using either a multidisciplinary or interdisciplinary approach operate in collaborative cross-disciplinary ways to effectively integrate their insights and perspectives related to review issues that impact the benefit-risk determination (O'Rourke et al., 2016; Thompson Klein, 2014).

Numerous comparisons of the two cases were enabled by use of the cross-disciplinary integration framework and Sankey modelling approach. There was a relatively similar number of inputs in the multidisciplinary and interdisciplinary cases (17 and 20, respectively) across all review issues. One difference in inputs between the two cases was that of the input types, abstract and concrete, with three times as many inputs being abstract in the TAUVID interdisciplinary case. Given the operational definitions used in this study for concrete and abstract, this would suggest a greater cognitive dimension to the interdisciplinary case, which

would require greater communication and collaboration in processing (Bergmann., 2012; Frodeman et al., 2017). While the number of process activities overall and per issue was only slightly more in the TAUVID case, the process activities were otherwise quite different. In the TUAVID case, process activities involved multiple disciplines and multiple inputs twice as often as in the RINVOQ case. These two differences resulted in starkly different integration "flows" when modelled in Sankey diagrams, as seen in the figure below, which illustrates a comparison of integration in two other review issues from the two cases.

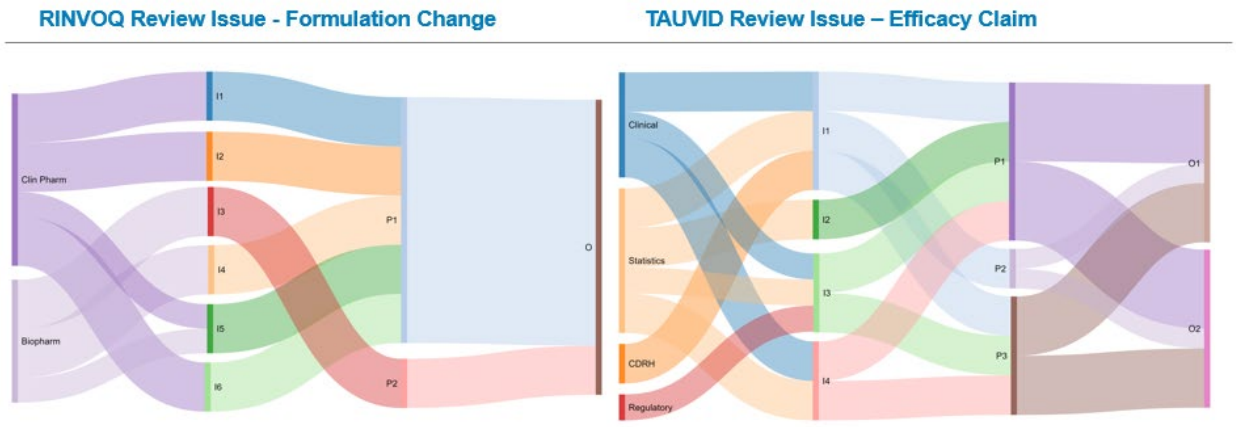


Figure 37:Side-by-Side Integration Comparison

In addition to the quite "visible" differences in process activities, differences in the outputs of the integration in the two cases were also found. These differences related to the increased occurrence of multiple outputs for review issues. One instance is illustrated in the figure above. And outputs tended to be more concrete in the TAUVID case, with six of the eight outputs in TAUVID being concrete and only three of the six outputs in the RINVOQ case being concrete. Given the nature of FDA recommendations and actions, these outputs might be more driven by the direction of the FDA action (e.g., an approval or a recommendation not to approve)

rather than some finding related to integration. However, it might be the case that simply the integration is more efficient in the interdisciplinary case and so more concrete outputs and multiple outputs are created. Finally, there were some interesting findings related to the integration parameters (i.e., commensurability, scale, and comprehensiveness). There were slight increases in the number of global review issues and the conflict seen in the TAUVID case. As noted in Chapter 4, this reflects the context of the integration (i.e., the review issues), but might connect to other observed differences in the integration.

As noted in Chapter 2, much of the literature on cross-disciplinary research and integration focuses heavily on the individual approach to cross-disciplinary integration or in the evaluation of either integrative capacity or integration in its outputs. The findings from this study contribute to the ongoing research in these spaces by providing a more objective way to model and subsequently evaluate the integration that occurs over the course of collaborative cross-disciplinary research in teams.

Recommendations for Research

This study identifies several important recommendations for future research in cross-disciplinary research, collaborative cross-disciplinary research (i.e., team science), and FDA team science in particular. At the most fundamental level, the approaches to collaborative cross-disciplinary research and even specific process activities that contribute to integration can now be modelled. This modelling of integration in collaborative cross-disciplinary research should continue in different teams to further characterize and refine the use of this modelling approach. In addition, understanding the influence of time on the collaborative cross-disciplinary integration process, or simply how the integration unfolds over time, could also lead to several

impactful new findings. Lastly, exploring improvements to the collaborative approaches or processes of Team Science in conjunction with the objective approach to evaluating integration utilized in this study could lead to a much greater understanding of differences between integrative teams that truly make a difference in outcomes.

As mentioned, the FDA took a page from the team science playbook and chose to further promote integration in its team-based reviews for new drug product marketing applications. FDA believed that greater integration of its scientific and technical staff would be needed to assess the benefits and risks of the growing complexity of new drug products and diseases it is responsible for regulating. In its pursuit of greater integration, the FDA identified new collaborative activities for its teams to follow during marketing application reviews, such as a team-based benefit-risk scoping of the application early with senior leadership involvement, interdisciplinary joint assessment meetings, and a collaborative template for the team's final work product. As seen in this study these pre-determined collaborative activities and template led to greater cross-disciplinary interactions and more integrative outcomes, as if by design. This "Team Science by Design" approach to promoting integration should be further explored by SciTS researchers to see if simple built-in collaboration for Team Science endeavors can similarly drive collaborative outcomes.

An interesting observation from this study was that of the variable of time. Because this study focused on the collaborative process that led to integration, it was able capture data and information that spanned a longer than normal observed period of cross-disciplinary integration. In this study, the integration process unfolded for some review issues or instances of integration from the beginning of the team's time together (i.e., at the benefit-risk scoping meeting) and terminated only at the recommendation for the final labeling of the product, which occurs at the

end of the review process. In other review issues, the integration may have only unfolded from early on and terminated around the mid-way point of the review process, or some other variation.

In previous SciTS research, instances of integration evaluated were typically contained either in a final work product or from a conversation/discussion that unfolded over a much shorter period (Frodeman et al., 2017; Laursen, 2018; MacLeod & Nagatsu, 2016; O'Rourke & Crowley, 2013). That this study, and its methods, was able to capture integration unfolding over such a longer period of time would be worth further exploration since the variable of time was not thoroughly evaluated or considered in the design of this study. A future study would require a greater degree of documentation of the process or perhaps a more ethnographic approach. Future studies should consider the impact of time on the integration process and track it to see how it might affect the integration. For example, did earlier onset of integration in the process result in some unique outcome or phenomenon? Or would the amount of time that elapsed from the start of the integration process to the end of it have any impact on outcomes? At the very least, SciTS researchers should consider the importance of time and tracking collaboration over the course of Team Science activities to enable future studies on the effect of this variable on collaboration or the integration process.

As seen in this study, the new interdisciplinary review process and documentation template in the integrated assessment that the FDA has begun implementing for its new drug product marketing application reviews has somewhat increased the collaborative cross-disciplinary integration and FDA is still early in the implementation process. As FDA continues to implement the new integrated assessment it should be expected that FDA's integration in these reviews would improve. However, this would be worthwhile to study. In this study, it appears both the new process activities and the template, which drove the team to write collaboratively,

contributed to the integration. It would also be interesting to explore these two key features (i.e., the process and template) of the interdisciplinary assessment separately to determine the impact of each.

Revisiting the O'Rourke et al. cross-disciplinary integration framework, this study has confirmed that in at least the context of FDA Team Science that the IPO framework for thinking about integration can be applied in a universal way as was hypothesized (Laursen & O'rourke, 2019; O'Rourke et al., 2016). The universality is derived from the contextualization of the model, which was mostly in the building of familiarity with the subject matter area rather than any fundamental change to the IPO framework. In addition, the pragmatic methodology deployed in this study to both analyze the teams' work products and speak to team members enabled the description of each integrative cross-disciplinary issue and the objective comparison of the integration across issues in quantitative and qualitative means. Future studies of integration would be wise to include a similar pragmatic approach prospectively to enable objectivity and rigor in the evaluation. This could serve as a nice complement to more traditional qualitative approaches for describing integration.

Even so, the use of the IPO framework and the approach to using it analytically in this study would benefit from continued use in additional contexts to validate the universal claim. Replication of its sensitivity to integration, sufficient to distinguish between different forms of integration, would be a worthwhile investigation. The application of Sankey diagrams, an approach borrowed from Laursen, to evaluate interdisciplinary reasoning has proven quite useful in visually modelling the dynamics of collaborative cross-disciplinary integration (Laursen, 2018). But SciTS researchers should continue to explore this approach to modelling integration and collaborative cross-disciplinary research to address any shortcomings. For example, the

Sankey diagram's strict principle for the conservation of elements within system may not fully lend itself to cross-disciplinary research, where inputs may leave or enter the system at different times based on the dynamics of the collaboration, especially over time. This aspect of the model might need to be improved.

Lastly, it is worth noting the uniqueness of the disciplines and disciplinary interactions within the FDA. While there is a great diversity of disciplines at FDA involved in the new drug product marketing application review (e.g., clinical, statistical, chemistry, regulatory, pharmacology, etc), these disciplines, when engaged in the assessment of benefits and risks of a new drug product, may become more similar than they are different. This phenomenon may have even led to the creation of new inter-disciplines at the FDA, such as clinical pharmacology, clinical research science, regulatory science, and so on. This phenomenon alone warrants further research to study the sameness or distance between these internal FDA disciplines and compare them to external, more academically derived, disciplines. This disciplinary re-focusing over time may also be contributing to the team science outcomes at FDA, such as those observed in this study. Therefore, further research on the impact of this phenomenon is critical to fully understanding collaborative cross-disciplinary integration at the FDA.

Implications for Practice

This research has several implications for the practice of SciTS and for FDA Team Science. The utility, sensitivity, and universality of the collaborative cross-disciplinary integration framework and associated modelling approaches is a useful tool in the SciTS toolbox. The findings from these two cases also add meaningful new data to the evidence base of SciTS related to the impacts of communication and collaboration on integrative capacity and

integration. And, for FDA Team Science, the ability to better characterize and evaluate integration in its team science ensures it can measure the progress and impact of its new team effectiveness programs and improvements, create improved records or documentation of these increasingly team-based activities, and proceed confidently towards full implementation of the integrated assessment of marketing applications.

Implications for the Science-of-Team-Science

SciTS is continuously seeking to further understand the circumstances that lead to the effectiveness of collaborative research or team science and manage those circumstances to promote improved outcomes for teams (National Research Council, 2015). This study has addressed both by confirming the theoretical basis of integration described in the O'Rourke *et al* philosophical framework for cross-disciplinary integration and the practical application of the framework via an analytical framework and modelling approach. In addition, in scientific endeavors the providence of new evidence is almost as important as the evidence itself. With the increasing use of teams for scientific research to achieve interdisciplinary and transdisciplinary solutions to complex problems it is important to be able to describe the collaborative process that led to the integrative outputs of the collaborative research.

In the case of FDA Team Science, and new drug product marketing application reviews specifically, stakeholders are increasingly interested in the providence of FDA's decisions and on the individual perspectives of scientists on the FDA review teams (Herder et al., 2020; MacGregor et al., 2020). As FDA shifts to more collaboratively based documentation some of the documentation of this providence may be lost. The use of the integration framework and model to characterize the processes that led to decisions related to key review issues could be

used to augment the collaboratively written integrated review to make up for any decrease in written review documentation and help stakeholders both within the FDA and those external to better understand the review team's thinking and decision-making process. In fact, during this study several participants remarked during the member checking (validation) of the integration models that this research study's approach led to a remarkable grasp of the application and its issues in a short period of time.

The integration framework and models also enabled a robust comparative analysis of the integration for key review issues or "problems" encountered by the teams thanks to the operationalization of variables and parameters within each instance of integration. Operationalization in this sense means the use of pre-defined contextualization of quantitative and qualitative features of the expected inputs, process, and outputs of the team science activity. Equipped with this operationalized analytical framework, the integration can be logged and then analyzed across multiple instances of integration in an objective way. For those interested in either understanding integration generally across cases and contexts, or more specifically within select types of collaborative research endeavors, the use of this pragmatic integration modelling approach and the analytical framework is a major step forward in objectivity and replicability.

In addition, visualizing the integration or integration process is also helpful and sought after in SciTS to help understand interdisciplinarity and cross-disciplinary research (Klein, 2012; Laursen & O'rourke, 2019). By cataloguing the variables and parameters of integration in this study using the cross-disciplinary integration framework and IPO model, data becomes readily available for further manipulation and can be then subsequently modelled in other forms that are amenable to the logic of an IPO model. For example, the Sankey flow diagrams, initially used by Laursen to study collaborative interdisciplinary reasoning, were an effective tool for visualizing

collaborative cross-disciplinary integration. These Sankey diagrams were only possible due to the use of the framework and IPO model and the richness and structure of the data collected in this study that the framework enabled (Laursen, 2018). Given the origins of the Sankey diagram in industrial ecology this is also a rather remarkable example of translation and disciplinary boundary spanning in its own right (Schmidt, 2008).

These implications for SciTS are enabled by the universality of the cross-disciplinary integration framework and IPO model discussed earlier. Researchers interested in interdisciplinarity and collaborative research have long sought to understand and assess integration. Previous models have proved insightful but seemed to lack the ability to be used in a more diverse set of contexts without great adaptation, which limits practical utility. This was perhaps due to the heavy influence of the Principle of Variance from a leading thinker on integration, Julie Thompson Klein, that drove early evaluations of integration far too into the concrete details of the circumstances of each case of integration that was sought to be understood (Klein, 2012; Laursen & O'rourke, 2019). With the more abstract O'Rourke *et al* framework and IPO model able to accommodate the overall process of integration and adapt to new contexts through the specification of parameters and variables at the input and output level, there does appear to be a more universal approach to thinking about integration emerging.

It is important to mention that while the parameters and variables of the cross-disciplinary integration framework and IPO model enable a certain universality there is no loss of sensitivity. With a focus on the overall process, inclusive of inputs and outputs, the model was quite effective at teasing out small differences in the integration between separate instances of integration within teams and among differing teams working on similar problems, as confirmed by this study. With that said, the approach may lack some sensitivity when used only on the

outputs of a collaborative research endeavor (e.g., an article or a study finding) and as such calls for either prospective data collection or a phenomenological approach. This study found incredible value and necessity in speaking with the team members of each case to fill in details related to key inputs and process activities. Future research using this framework and modelling approach should be sure to collect and analyze data directly on the inputs and process activities whenever possible.

Beyond integration and studying this feature of science teams, this study also has several broader implications for the practice of SciTS. As a reminder, this study took advantage of the fact that the FDA has begun implementing a new interdisciplinary process and collaborative documentation template for its marketing application review. As such, it was able to evaluate the impact of these interventions designed to increase collaboration and communication on the team's ability to achieve its goals—one of which was scientific integration.

In the traditional multidisciplinary review, review teams would by standard operating procedure routinely engage in team meetings to discuss major review decisions, such as whether the application was suitable for filing or ultimately approvable. Absent a shared mental model or collaboration principles, the individual members of the teams would come together at these team meetings and make recommendations, based on their discipline's perspective, to a single decision-maker. However, the new interdisciplinary review introduced a more collaborative approach to these interactions by anchoring review decisions and issue identification around the benefit-risk framework (FDA, 2018b; Woodcock et al., 2020). This was done by building new activities into standard operating procedures for the team, specifically new benefit-risk oriented team meetings (e.g., benefit risk scoping meeting, joint assessment meetings) with more deliberate and purposeful collaboration that focused on the benefit and risk issues as opposed to

individual disciplinary recommendations. In addition, decision-makers or signatory authorities were involved earlier and more frequently in these team meetings to ensure team alignment and the benefit of their experience. While this study only examined one case from a traditional multidisciplinary review and an interdisciplinary review respectively, these new meetings were cited by participants from the interdisciplinary case multiple times as the origin of inputs for issues, for the integrative resolution as a team of issues, and for increasing the sense of collaboration and communication of the team.

Furthermore, the new interdisciplinary review introduced a new template for collaboratively documenting the assessment of the new drug product marketing application. A stark shift from the traditional multidisciplinary review which amounted to individual disciplinary review documents (i.e., reviews) and a summary review. This "Team Science by Design" approach to guiding the team to collaborate with an end in mind for its documentation further increased the collaboration and communication on the team because the teams now needed to align on the outline for their collaborative writing and collaborate effectively to ensure all team members' perspectives were incorporated in the final document. Team Science and SciTS practitioners should consider how to build in similarly appropriate activities, procedures, or templates/tools to guide teams to more collaborative and integrative outcomes.

Implications for FDA Team Science

As discussed previously, FDA is currently engaged in a modernization of the new drugs regulatory program and as part of this modernization in 2019 began implementing a new interdisciplinary approach to the assessment of new drug product marketing applications (Bugin et al., 2020; FDA, 2019h; Woodcock et al., 2020). Implementation Science and Program Theory

both call for a thorough evaluation of new programs and initiatives to ensure the design and expected outcomes are achieving the desired impact (Damschroder et al., 2009; Funnell & Rogers, 2011). As the FDA continues to implement the interdisciplinary process and integrated review template for its integrated assessment of marketing applications it will need to rely on the cross-disciplinary integration framework and IPO model to objectively evaluate integration, an expected outcome, in the completed new drug product reviews.

Evaluating integration in more cases and over time in review teams implementing the new interdisciplinary assessment of marketing applications will be an important measure of implementation and could internally guide change management initiatives to help teams successfully adopt the new process and template. As discussed in a public workshop on October 30, 2020, review teams are experiencing some challenges with implementing the new interdisciplinary approach and collaborative template for documentation (FDA, 2020b). FDA may need to deploy new training or provide coaches to teams to assist them with implementation. This training and coaches can leverage these objective measurements of integration to inform and track the effect of these initiatives to improve integration or collaboration.

With integrated assessments and integration being a key strategic objective and expected outcome of the new drugs regulatory program modernization and its initiatives, respectively, the evaluation of integration is also critical to measuring the success of this organization development program (Bugin et al., 2020; FDA, 2019h; Funnell & Rogers, 2011). With a now tested and proven approach to measure integration, the FDA will be able to detect changes in integration and therefore evaluate this aspect of the theory of change of the modernization (Funnell & Rogers, 2011). This necessity to evaluate integration is even further strengthened by

the finding in this study that integration is already occurring in FDA traditional reviews. If there are tradeoffs to seeking "more integration", such as the loss of individual reviews, then FDA must track and qualify the change in integration to weigh what is gained.

Furthermore, conflict or scientific disagreement is neither unexpected in FDA new drug product reviews nor in collaborative cross-disciplinary research more broadly. "The very nature of scientific work requires a certain degree of conflict" (Fiore et al., 2015, p. 277). And SciTS research points to a moderate level of task-conflict, or differences in opinion, viewpoint, and/or ideas, as having several advantages for teams. A recent analysis of FDA reviews completed between 2011 and 2015—well before the integrated assessment of marketing applications was implemented—suggests that FDA teams are no different with nearly a quarter (24.1%) of approvals having at least one scientific disagreement found in their documentation (MacGregor et al., 2020). As FDA seeks more collaborative cross-disciplinary means for its review activities and approaches to documentation, these task-conflicts will still occur and may even increase due to increased collaboration. But the conflicts would be expected to be better managed, perhaps even earlier, during the review.

A downside of increased integration and earlier conflict resolution from the new integrated assessment might lead to less explicit documentation of disagreements since the final documentation would reflect the final more integrative output and be less obvious of earlier disagreement. Given that this study found that integration is best understood using data and information related to the inputs and process activities in addition to the outputs, and to avoid the potential lack of information related to scientific disagreements resolved early in the review process, the FDA is strongly advised to consider implementing a means similar to that employed in this study to capture the information associated with the "rise and fall" of review issues in

either its workflows or templates. This would not only boost the FDA's ability to understand the integration occurring in its review issues but also create a more accurate and thorough record of the review issue for posterity. Therefore, it is highly recommended that FDA adopt and standardize the use of the integration framework and IPO model in the integrated assessment and other interdisciplinary initiatives at the FDA for both evaluation and routine documentation.

Conclusion

This study of collaborative cross-disciplinary integration in either a case of FDA's multidisciplinary or interdisciplinary assessment of a new drug product marketing application has validated the use of an approach to thinking about and studying cross-disciplinary integration from the O'Rourke et al. framework and associated IPO model in a new context. It has identified multiple well-characterized instances of integration in both a multidisciplinary case and interdisciplinary case of FDA cross-disciplinary team science. And, it has found that the process and collaborative documentation of the interdisciplinary assessment for marketing applications has led to more integration in this interdisciplinary case. Future SciTS and FDA Team Science research can benefit from using this framework and modelling approach for evaluating integration and benefit-risk review issues. And, practitioners of team science, SciTS, organization development, implementation science, and program evaluation can take advantage of a new tool in their toolboxes.

In the future, exploring additional contexts for the application of the philosophical cross-disciplinary integration framework and expansion on this method will greatly add to both the origins in the philosophy of science but also lead to the application of this knowledge more practically. Applying learned scientific knowledge in the more practical sense to the goals and

objectives of real-world problems has the potential to return greater impacts on society and future science. For future expansions, it will be important to identify a contextually relevant framework, such as the benefit-risk framework in this study, to couple with the cross-disciplinary integration framework. This was the key to practical adaptation seen in this study. Seeking out these additional contextual applications will further confirm potential universality and generalizability and add to a growing playbook for practical uses in the future. Furthermore, using similar methods to collect and inventory qualitative data per the analytical IPO framework should be deployed in future cases to enable more empirical evaluations of this sort, add to a growing evidence base of cross-disciplinary integration, and potentially identify noteworthy themes across contexts.

In addition to expanding on the original framework and methods, it is worth further exploring the study of the Science-of-Team-Science in the space of drug development and regulatory science, as was done in this study. This space is rich with cross-disciplinary and collaborative cross-disciplinary endeavors. And its proximity to public health impact makes it of key import. In addition, this space, while full of exciting, emerging science and innovation, has not traditionally seen this level of scholarship and external invitation to the exploration and improvement of its internal processes for conducting regulatory science. Typically, this sort of work would be done internally or only in partnership with consultant organizations. Beyond the FDA environment, there is a near mirror image of the collaborative cross-disciplinary research on drug development occurring in industry that could similarly benefit from the research methods in this study.

Future utilization of the cross-disciplinary integration framework and IPO model from this study in more everyday documentation of internal FDA activities could open the door to a

new age of understanding for those external to the FDA and for the FDA itself lead to greater enhancements of its internal processes. As was noted, many external researchers seek to better understand the rationale for FDA decision-making. And, while documentation has been extensive in the past, it has never quite focused on the processes of internal FDA staff. And, never quite on the transformation of information into decisions or knowledge such as was seen in this study. The IPO framework, coupled with the benefit risk framework, as used in this study has the potential to revolutionize how the FDA communicates the bases for its decisions and details related to benefit-risk review issues.

Lastly, the field of organization development, change management, implementation science, and program evaluation will benefit greatly from the methods used in this study and the associated case studies. The FDA has embarked on a major organizational transformation via its New Drugs Regulatory Program Modernization. That it has thoughtfully crafted program objectives, outcomes, and anticipated impacts, communicated those to staff, designed interventions around them, and set to evaluate these sets a great example for future organization development efforts and translational scientists. This example can serve as a case study for these additional fields for years to come.

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Appendices

Appendix 1: Recruitment Email

Example

Dear NDA 212123 Tauvid Review Team,

I hope all is well with you during these unusual and difficult times. I fully recognize and appreciate that this is a challenging time and that you may be busy managing with this new normal under the COVID-19 pandemic and its impacts on your work. But, I hope you will afford me a few minutes of your time to consider this request to help me and the CDER better understand a key feature of our reviews.

You may already know me but for those who do not, I'm Kevin Bugin, director of special programs from the Office of New Drugs. As part of my doctoral research at the George Washington University, and in support of the center's interests to improve the review of new drugs, I am conducting a study of cross-disciplinary integration in FDA review documents. I am particularly interested in comparisons between multidisciplinary reviews (i.e., individual discipline reviews that are integrated into a summary review) and the new interdisciplinary reviews (i.e., the collaboratively written Integrated Assessment). The key research questions of this case study are: (1) What are examples of integration in FDA new drug product reviews? (2) What are the specific differences between integration in a multidisciplinary review and an interdisciplinary review?

You have been identified as a potential participant for this study due to your role as a reviewer/TL or a signatory for the completed integrated review of NDA 212123 for Tauvid (fluoroestrdiol F18) that was approved on May 28, 2020. I'd like to invite you to

share your perspective on the integration that occurred in this integrated review related to key review issues that impacted the benefit-risk assessment by joining a one-time 30-minute interview. The interviews will occur in July per your availability. Due to the ongoing COVID-19 situation, the interview will be conducted virtually (i.e., phone and/or video conference) for everyone's safety.

Disclaimer: It is possible that your participation in this study will not remain anonymous. This is because publicly available reviews are the subject of this study and your information may already be public as a result of routine public disclosure practices of FDA. However, your specific participation (i.e., the information you share during the interview and focus group) will be kept strictly confidential and any attributions to you will be protected. The only person that will be aware of your participation is myself. Please also note that this study has been reviewed and exempted by the IRBs of GWU and FDA—your participation in this study has been determined to be of minimal psychological risk. You do not have to take part in this research. You can agree to take part and later change your mind. If you choose not to take part or choose to stop taking part at any time, there will be no penalty to you or loss of benefits to which you are otherwise entitled. And as an employee of the FDA, if you decide not to take part in this study, your choice will have no effect on your employment status. For a complete description of benefits or risks, please refer to the Detailed Consent Form which you will be provided should you agree to participate.

This research is supported by Dr. Peter Stein (copied) and CDER/OND. It is being conducted in collaboration with the George Washington University via the principal investigator, a Science of Team Science researcher from GW and President of the International Network for

the Science of Team Science, Dr. Gaetano Lotrecchiano, (glotrecc@gwu.edu; 202-994-9855). Please visit the International Network for the Science of Team Science for more information on the Science of Team Science.

Please let me know if you have any questions and/or would be willing to participate in study and I will follow-up with more information. Thank you!

Appendix 2: Informed Consent

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

U.S. FOOD & DRUG ADMINISTRATION

Study Assigned Consent Version #/Date: **GW OHR Document Revision Date: 04Jan2019**

Informed Consent for Participation in a Research Study

Title of Research Study: *Modelling Cross-Disciplinary Integration in FDA Multidisciplinary and Integrated Reviews: A phenomenological descriptive comparative case study*
Investigators: Gaetano Lotrecchiano, EdD, PhD; Kevin Bugin, MS, PhD (ABD) RAC

Key Information:

You are being asked to take part in a research study about integration in new drug product reviews conducted by FDA. This page will give you key information to help you decide whether or not you want to participate in this study. More detailed information can be found on the next pages. Ask the research team questions during the consent process, and use the contact information on this form to ask questions later.

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THIS STUDY?

By doing this study, we hope to learn more about the integration process in new drug reviews. You will participate in a semi-structured interview and a focus group. Your participation in this research from initial contact to close-out will last about 3 months.

WHAT ARE THE REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

The most important benefit of participating in this study is contributing to the generation of knowledge on the process by which integration occurs within FDA new drug product reviews and providing useful information that can validate an approach to evaluating integration in collaborative cross-disciplinary team science. For a complete Description of benefits please refer to the Detailed Consent.

WHAT ARE THE REASONS YOU MIGHT NOT CHOOSE TO VOLUNTEER FOR THIS STUDY?

It is possible that your participation in this study will not remain anonymous. This is because publicly available reviews will be the subject of this case study and as a result your participation as a team member of that publicly available review could be ascertained. Your specific participation (i.e., interview and focus group participation) would be kept confidential. For a complete Description of risks please refer to the Detailed Consent.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

You do not have to take part in this research. It is your choice whether or not you want to take part. You can agree to take part and later change your mind. If you choose not to take part or choose to stop taking part at any time, there will be no penalty to you or loss of benefits to which you are otherwise entitled.

As an employee, if you decide not to take part in this study, your choice will have no effect on your employment status.

WHAT IF YOU HAVE QUESTIONS OR CONCERNS?

The person in charge of this study is Gaetano Lotrecchiano, Ed, Phd {Principal Investigator (PI)}. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is: glotrecc@gwu.edu; 202-994-9855.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to them at 202-994-2715 or via email at ohrirb@gwu.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team or if you wish to talk to someone independent of the research team.
- You have questions about your rights as a research subject.

other team members to inform a schematic model or diagram of the integration that occurred during your review. You will then be invited to join a focus group with your team members to review the schematic model and validate its ability represent the integration that occurred during your review

What happens if I agree to be in research, but later change my mind?

Your employment status will not be affected in any way should you choose not to take part or to withdraw at any time. You may refuse to participate, or you may discontinue your participation at any time without penalty or loss of benefits to which you would otherwise be entitled. If you decide to leave the research, please contact the research team so that they can document your withdrawal of consent.

Is there any way being in this study could be bad for me?

Most of the data collection for this study will come from publicly available documents that may already contain your personal identifying information. Therefore, there is some risk associated with sharing information during interviews being linked back to you because of your known participation in the publicly available review. In extreme cases, this could lead to altered peer or leadership perceptions of your role or performance as part of the review team. However, this risk is expected to be minimal through the anonymized collection of interview feedback and masking of any review team names and roles with pseudonyms or unique subject identifiers. And, your specific feedback in interviews or focus groups will be kept confidential and reported only in an unidentified, aggregate format.

The risks and discomforts associated with participation in this study are not expected to be greater than those ordinarily encountered in daily life or during the performance or routine physical or psychological examinations or tests.

What happens if I believe I am harmed as a result of my participation in this study because I took part in this study?

You should promptly notify the research team in the event of any harm as a result of being in the study. You will not receive any financial payments from GWU or FDA for any harm. You do not waive any liability rights for personal injury by signing this form.

Will being in this study help me in any way?

You will not receive any benefits from participating in this research.

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include a better understanding of how you and your team members collaborate during the review of marketing applications. In addition, findings from this research will inform future training, resources, and development programs that may be accessible to you and your colleagues in the future.

What happens to my information collected for the research?

To the extent allowed by law, we limit your personal information to people who have to review it. We cannot promise complete secrecy. The IRB and other representatives of this organization may inspect and copy your information. Others include the Food and Drug Administration IRB.

Detailed Consent Form:

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you completed either a multidisciplinary review (i.e., Unireview) or an Integrated Review of a new drug marketing application in the past 12 months that is available at drugs@fda.

Who can I talk to if I have questions?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at kevin.bugin@fda.hhs.gov; 240-401-6673.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to them at 202-994-2715 or via email at ohrirb@gwu.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team or if you wish to talk to someone independent of the research team.
- You have questions about your rights as a research subject.

Why is this research being done?

A greater understanding of the underlying integration process in FDA marketing application reviews, particularly the new integrated review is needed to help develop practical guidelines to promote the effectiveness of its integrated assessments, to evaluate the success of the new drugs regulatory program, and inform future supporting resources or training that aim to promote integration. In addition, by creating a model of the integration in FDA reviews, both new and old, the FDA could better explain the integration process and confirm that changes in documentation achieve an increased degree of integration and reduce redundancy in the new integrated review. Finally, integration in cross-disciplinary scientific collaborations is a desired outcome and the knowledge gained in this study could help promote integration in a broad range of team science endeavors. In addition to your participation in an interview and focus group, a qualitative document analysis of your completed review will be conducted to analyze the integration achieved in the final review using an inputs-process-outputs model for integration.

How long will I be in the study?

We expect that you will be in this research study for 3 months.

How many people will take part in this research study?

We expect about 10 people will take part in the entire study.

What happens if I agree to be in this research?

You will be contacted to participate once your completed review is identified and selected for the case study. You are receiving this informed consent as part of that process. Following your consent to participate you will be invited to participate in a 60-minute interview. During this interview you will be provided with additional information about the study, including its goals and intended research questions. Then you will be asked 3 questions related to the integration process that occurred during the identified review for which you were a team member. Following the interview, your feedback will be reviewed along with the feedback of

Signature Block

By signing below, you agree that the above information has been explained to you and you have had the opportunity to ask questions. You understand that you may ask questions about any aspect of this research during the course of the study and in the future. Your signature documents your permission to take part in this research.

_____

Printed name of subject

_____ _____

Signature of subject Date

Appendix 3: Interview Slide Deck

FDA's assessment of new drug products is a critical activity that requires team-based integration and transparency

"Setting standards for approval and assessing innovative new drugs requires large and well-coordinated teams of highly trained professionals with many different types of expertise… A central component of our proposed changes involves stronger integration of our talented staff so they can better work together – within and across offices, a concept we refer to as "**integrated assessment.**" Previously, CDER reviewers would seek consults from specialists in other scientific disciplines (as issues were identified in the course of review). For greater collaboration, a cross-disciplinary team will be assigned to work on a new drug application at the outset."

Dr. Janet Woodcock
CDER Center Director
2018

In 2019, the FDA began rolling out a new interdisciplinary approach to the assessment of marketing applications, with the key feature being integrated, collaborative review documents

As FDA makes these shifts to more integrated approaches, some external stakeholders are concerned with transparency and a loss of knowledge

VIEWPOINT

HEALTH CARE POLICY AND LAW JAMA Internal Medicine Published online March 2, 2020

Integrated Drug Reviews at the US Food and Drug Administration—Legal Concerns and Knowledge Lost

In summary, the FDA's long-standing practice of generating and publishing individual scientific reviews has been a great service to public health, largely because of the detail contained in these reviews. Despite the importance of individual scientific reviews, the FDA is phasing them out. Although implementing the use of integrated reviews will take time, there is no indication that the agency plans to revisit its decision. If the FDA's aim is to circumvent its legal obligation to prepare and publicly disclose individual scientific reviews, congressional action or litigation may be needed. For the FDA to earn and maintain public trust, its decision-making processes should be transparent and prioritize the public release of detailed, comprehensive, and unredacted information. The agency can best meet its goal of improving public and clinician understanding of its review process by creating better summaries of its individual scientific reviews, not by replacing them.

US FDA's Integrated Review Document Would Dramatically Downsize Public Information Interdisciplinary Replaces Multidisciplinary

Silverman, B. (2019). US FDA ' s Integrated Review Document Would Dramatically Downsize Public Information Interdisciplinary Replaces Multidisciplinary. *Pink Sheet*, 6–9.

While Integration is a desired outcome in FDA's new integrated assessment approaches, how integration occurs is unknown

Describing the integration process will allow FDA and external stakeholders to:

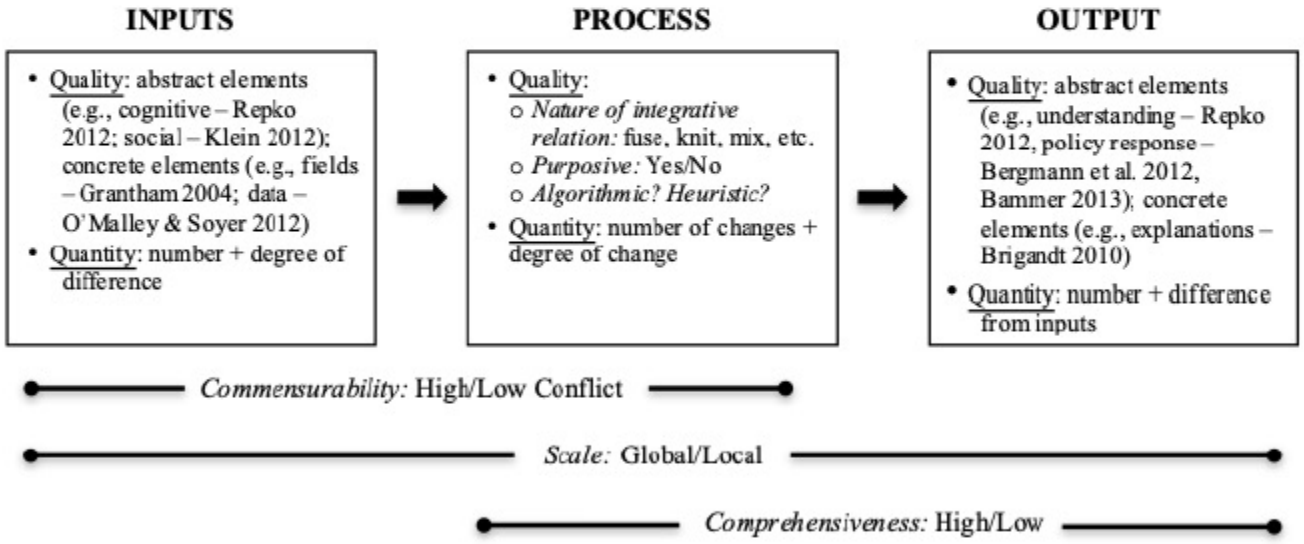
- better **understand the process** that leads to a final regulatory decision on a new drug product
- **promote knowledge management** within the FDA **and transparency** in FDA decision-making
- **develop practical guidelines and trainings** for FDA teams to promote the effectiveness of its team-based assessments of new drug products.
- **evaluate the success of improvement initiatives** under the New Drugs Regulatory Program Modernization that aim to promote more integrated assessments

This research study seeks to identify:

- **Examples of integration** in a "multidisciplinary review" and an "integrated review" of an FDA new drug product
- **Specific differences in integration** between a "multidisciplinary review" and an "integrated review" of an FDA new drug product?

Central *and novel* to this study is the use of the O'Rourke philosophical theoretical framework

This IPO framework allows the instances of integration in the FDA's team-based assessments of new drug products to be modelled. With this models, the FDA can better understand integration in its reviews



O'Rourke, M., Crowley, S., & Gonnerman, C. (2016). On the nature of cross-disciplinary integration: A philosophical framework. *Studies in History and Philosophy of Science Part C :Studies in History and Philosophy of Biological and Biomedical Sciences*, *56*, 62–70. https://doi.org/10.1016/j.shpsc.2015.10.003

Introduction for interviewee

Please tell me about yourself, your background, and your role in this review?

Questions – Issues of Interest

Review Issues (Outputs)

- Can you tell me about the key application-specific review issue(s) that you and your team found in your review of this application that impacted the benefits, risks, or benefit-risk assessment?

  Examples noted in the Integrated Review Document included:

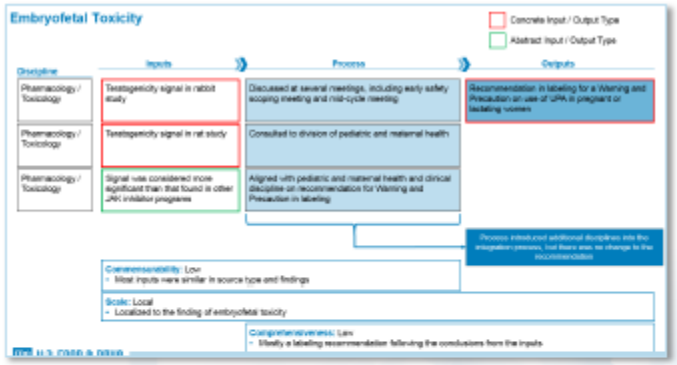
  - User Guide for Tauvid PET Image Display
  - [redacted]
  - [redacted]
  - CTE Misdiagnosis
  - Effect of MAO Inhibitors on FTP Binding
  - QT Interval Prolongation

Questions for each Issue

Issue Identification (Inputs)	• How did you or your team come to identify the review issue? • What information, data, analyses, or discussions did you leverage to work through the review issue?
Review Process (Integration)	• What strategies did you use to resolve review issue and what was the impact of the review issue on the benefit-risk determination ? • How did you work through the review issue in an integrated way? • How would you describe the incorporation of your inputs and contributions into the final documentation of the review issue in the

Wrapping up

- The information you have shared today will help inform the creation of models of the integration that occurred around the issue(s) we discussed (i.e., the what and how integration occurred)
- I will circle back to you in the near future with models of the integration around the issue(s) you identified for validation—this will likely occur via email with others from your review team
- Questions?



U.S. FOOD & DRUG ADMINISTRATION

Appendix 4: RINVOQ Review Issue Inventory

4.A. Review Issue 1

Review Issue: 30 v 15 mg Dose Selection

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Exposure-Response Analysis	1	Clinical Pharmacology	Concrete	1, 2, 3	Analysis/Assessment of Safety at 15 and 30 mg	Yes	Combinatorial	15 mg Dose found to have favorable Benefit-Risk and Approved by FDA, but 30 mg Dose was found to have an unfavorable Benefit-Risk profile and was not approved by the FDA	Cross-disciplinary	Abstract
Integrated Safety Analyses	2	Clinical, Clinical Pharmacology, & Statistics	Concrete	1, 3	Analysis/Assessment of Benefit at 15 and 30 mg	Yes	Combinatorial			
Results from five Phase 3 Studies	3	Clinical, Clinical Pharmacology, & Statistics	Concrete	1, 2, 3	Comparative Analysis of Adverse Events between 15 and 30 mg	Yes	Combinatorial			
Number of Inputs: **3** Degree of Difference in Inputs: **Low;** given the shared data sources, these inputs are quite similar				Number of Changes in Inputs: **3; no change in safety analyses, but results from Phase 3 studies would require additional assessment for comparative analysis acros s the 2 doses** Degree of Change in Inputs: **Low**				Number of Outputs: **1** Difference from Inputs: **Med; required combnining findings of safety, benefit, and E-R analyses into a benefit-risk determination for both doses; also these determinations are made all the way up through the Cross-disciplinary Team Leader and Signatory Reviewer**		

Commensurability:	Low; analyses (inputs) were relatively similar although rooted in different disciplines
Scale:	Global; relevant to the entire application
Comprehensiveness:	High; the output (i.e., BR determination) provides a more comprehensive assessment of the issue between the 30 and 15 mg doses and reflects all inputs

Input 1 Data:

- CP Transcript: “reviewer has done the provided exposure response analysis.”
- CP Review: “Overall, results from Phase 3 studies and exposure-response analysis support the proposed 15 mg QD dosing regimen as it provides the optimal benefit-risk balance in patients with moderately to severely active RA”
- CP Review: “The applicant’s exposure response analysis for safety is consistent with the observed safety data.”

Input 2 Data:

- CP Review: “the safety profile of upadacitinib has demonstrated a dose-dependent increase in the number of reported adverse events.”
- Med Review: “Analysis of the overall safety database demonstrated that UPA-treated subjects experienced a greater proportion of AEs and SAEs compared to PBO-treated subjects. “
- Med Review: “Analysis of the phase 3 UPA 15 mg and 30 mg analysis set (Studies M13-542, M13-545, M13-549, M15-555) showed a higher proportion of serious infections in the UPA 30 mg treatment arm compared to the UPA 15 mg treatment arm”
- Stats Review: “Based on the integrated safety analyses during the placebo-controlled or MTX-controlled period,”

Input 3 Data:

- CP Review: “Overall, results from Phase 3 studies “
- Med Review: “Similar to the results observed in Study M13-542, the results of this study demonstrate a clinically meaningful benefit from treatment with UPA 15 and 30 mg but do not support a dose-dependent increase of clinical efficacy with the higher dose of UPA in this patient population. Consequently, the overall benefit-risk assessment for UPA 30 mg will need to be determined in the context of the overall safety evaluation.”

Process 1 Data:

- Med Review: “it is worth noting that the safety analyses included comparisons of AEs between the UPA 15 mg and 30 mg doses but only the UPA 15 mg dose is being sought for approval by the Applicant. “

Process 2 Data:

- Summ Review: “There was lack of numerical trends towards greater mean change from baseline in F ACIT-F at Week 12 for patients treated with the higher dose of UP A for studies M13-542 and M13-545”

Process 3 Data:

- Summ Review: “While both doses of upadacitinib are effective, comparisons between the two dosing regimens did not suggest a consistent trend in favor of a particular dose. Given these results, the Applicant is only requesting approval of the upadacitinib 15 mg QD dose.”
- Sig Interview: “which really comes down to the safety assessment and whether there's any dose related toxicities, and then the efficacy assessment as well, to sort of balance out and determine which dose is appropriate”

Output 1 Data:

- Summ Review: " The benefit-risk profile of the upadacitinib 15mg dose is more favorable than the 30mg dose. The small incremental benefit of the 30mg dose does not outweigh the dose-related safety findings with the 30mg dose of upadacitinib."

4.B. Review Issue 2

Review Issue: Immediate Release to Extended Release Formulation and Clinical Trial Material to To Be Marketed Material Bridging

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Bioequivalence Study	1	Clinical Pharmacology	Concrete	1, 2, 4, 5, 6	Results presentation to the Team	Yes	Combinatorial	Immediate Release and Extended Release Formulations & Clinical Trial Material and To-Be-Marketed Material were found to be bioequivalent	Cross-disciplinary	Abstract
Repeated Bioequivalence Study	2	Clinical	Concrete	3	Discussion of clinical significance with	No	Integrative			
Release Profiles	3	Biopharmaceutical	Concrete							
In Vitro Dissolution Study	4	Biopharmaceutical	Concrete							
Bioavailability Study	5	Biopharmaceutical & Clinical	Concrete							
PBPK Analysis	6	Pharmacology	Concrete							
Number of Inputs: **6** Degree of Difference in Inputs: **Low**					Number of Changes in Inputs: **2; only a change for the population based PK analyses across all the Phase 3 studies** Degree of Change in Inputs: **Low; combinatorial for the PBPK analyses**			Number of Outputs: **1** Difference from Inputs: **Low**		

Commensurability:	High; most inputs were similar in source type and findings
Scale:	Local; localized to the bridging of formulations
Comprehensiveness:	High; mostly reflects a sum of the findings from the inputs

Input 1:

- CP Transcript: “BE, the sponsor submitted their own data set”
- Chem Review: “in vitro dissolution comparison and an in vivo BE study”

Input 2:

- CP Transcript: “critical … to repeat the data analysis”

Input 3:

- BP Transcript: “release profiles. Like if they can show the release profiles “

Input 4:

- Chem Review: “in vitro dissolution comparison and an in vivo BE study”

Input 5:

- Chem Review: “the Applicant has performed a bioavailability study under fasting conditions according to a randomized, 2-period crossover design in 40 healthy subjects comparing the Phase 3 formulation to the Commercial formulation”
- CP Review: “Upadacitinib PK was compared between using IR formulation and ER formulation in a dedicated, randomized, open-label, two period, two-sequence, crossover, relative bioavailability study (Study M14-680)”

Input 6:

- CP Review: “PBPK analysis has adequately bridged the clinical DDI effect of strong CYP3A4 modulator (inducer or inhibitor) observed with upadacitinib IR formulation to the ER formulation.”

Process 1:

- CP Transcript: “I normally discuss with the team leader first to finalize the slides, and then we presented with the whole review team”

Process 2:

- BP Transcript: “communications were between both clinical and clinical pharmacology teams in trying to make sure that the plus or minus 10% is okay in terms of establishing the boundaries”
- Chem Review: “The Biopharmaceutics Reviewer consulted the Clinical Reviewer for establishing the acceptable boundaries for efficacy and safety.”

Output 1:

- BP Transcript: “The applicant did submit the release, but I think the release profile is common for any kind of change, be it level one, level two, level three [inaudible 00:15:10] and for level three, in addition to the release profile, we need the B study. So once we integrate all this part, we'll say, okay, bridging”
- CP Review: “PBPK analysis has adequately bridged the clinical DDI effect of strong CYP3A4 modulator (inducer or inhibitor) observed with upadacitinib IR formulation to the ER formulation.”
- CP Review: “Bioequivalence was established between the to-be-marketed ER tablets and the ER tablets used in Phase 3 studies”
- CP Review: “Cmax, AUCO-t, and AUCO-inf are well within 80-125% limit, indicating the to-be-marketed tablet is bioequivalent to the clinical study tablet”
- Summ Review: “The biopharmaceutics team has determined based on the submitted information that bridging of the two formulations has been adequately established and the two formulations are similar to each other.”
- Summ Review: “The clinical pharmacology team has determined, and we agree, that the to-be-marketed formulation is bioequivalent to the clinical study tablet”

4.C. Review Issue 3

Review Issue: Impurities

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Identified impurities	1	Pharm/Tox & Chemistry	Concrete	1	Nonclinical Safety Assessment conducted on the range of impurities	Yes	NA	No safety concerns	Cross-disciplinary	Abstract
				1	Computational Toxicology Consult was issued to evaluate the impurities	No	NA			
				1	Chemistry Collaboration to review impurities	Yes	Integrative			
Number of Inputs: **1** Degree of Difference in Inputs: **NA**					Number of Changes in Inputs: **1** Degree of Change in Inputs: **Low**			Number of Outputs: **1** Difference from Inputs: **Low**		

Commensurability:	NA; single input
Scale:	Local; focused on single concept (impurities in drug product)
Comprehensiveness:	High; mostly reflects a sum of the findings from the inputs

Input 1:

- PT Transcript: “I guess the other complexity to this one was there was, compared to some applications, kind of a lot to sift through regarding impurities.”
- PT Transcript: “yeah, so the impurities are often one thing that really can't be completely resolved until the NDA is in house because it's a combination of data sources on the quality side and the nonclinical side”

Process 1:

- PT Review: “safety assessment was conducted on a range of observed and potential impurities and degradants”

Process 2:

- PT Transcript: “also our internal computational toxicology experts, they offer a consult service so I'm quite certain we consulted them as well”

Process 3:

- PT Transcript: “requires collaboration with the CMC review team “

Output 1:

- PT Review: “There are no safety concerns related to UPA impurities for the proposed dose, duration, and patient population”
- Summ Review: “Pharmacology/Toxicology team evaluated 35 impurities [redacted] and concluded these did not present any safety concern”

4.D. Review Issue 4

Review Issue: CYP3A4 Coadministration

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Independent CYP3A4 Analysis	1	Clinical Pharmacology	Concrete	1, 2	Finding of decreased exposure of UPA when coadministered with strong CYP3A4 inducers and increased exposure with strong CYP3A4 inhibitors discussed with clinical and recommended for labeling by the clin pharm reviewer. Clinical agreed.	No	Combinatorial	Labeling recommendation that UPA should be used with caution with CYP3A4 inhibitors and should not be used with strong CYP3A4 inducers	Cross-disciplinary	Concrete
Sponsor submitted Drug Drug Interaction Studies	2	Clinical Pharmacology	Concrete							
Number of Inputs: **2** Degree of Difference in Inputs: **Low**					Number of Changes in Inputs: **1; findings from independent analysis translated to a recommendation to clinical discipline for labeling related to CYP3A4 inhibitors and inducers** Degree of Change in Inputs: **Low**			Number of Outputs: **1** Difference from Inputs: **Low**		

Commensurability:	High; most inputs were similar in source type and findings
Scale:	Local; localized to CYP3A4 interactions
Comprehensiveness:	High; mostly reflects a sum of the findings from the inputs

Input 1:

- CP Transcript: “That's based on our own data analysis.”

Input 2:

- CP Transcript: “so yeah, in the DDI study, they also have in one DDI study”

Process 1:

- CP Interview: "normally discuss with the team leader first to finalize the slides, and then we presented with the whole review team"

Output 1:

- CP Review: “Therefore, we recommend that upadacitinib should not be co-administered with strong CYP3A4 inducers.”
- Summ Review: “Coadministration with strong CYP3A4 inducers are not recommended because that may result in ineffective concentrations of upadacitinib.”

4.E. Review Issue 5

Review Issue: JAK Class Safety

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Known class safety signals with JAK inhibitors but lack of finding of thromboembolic events	1	Clinical	Abstract	1, 2	Required validation of the safety analyses to confirm no finding of the class safety signals	Yes	Disintegrative	Class safety labeling recommendation for TE and other known JAK class safety AEs	Cross-disciplinary	Concrete
Integrated Safety Analyses	2	Clinical & Statistics	Concrete	1	Required discussion with the Sponsor to align on class labeling for the product even though there was a negative finding for TE events	No	Integrative			
Number of Inputs: **2** Degree of Difference in Inputs: **Med;** the data showed now signal, but the experienced reviewer was looking for this signal					Number of Changes in Inputs: **2; safety analyses had to be re-worked to explore the initial negative finding of TE events to confirm there was no signal, then the class labeling requirement had to be discussed with the Sponsor** Degree of Change in Inputs: **High; even though the study results and both the Sponsor and FDA findings were negative, the product received class safety labeling related to TE events**			Number of Outputs: **1** Difference from Inputs: **Low**		

Commensurability:	Low; FDA review team was expecting certain signals due to known class safety issues, but data was negative
Scale:	Local; this issue was isolated to safety
Comprehensiveness:	Low; output mostly the result of negotiations with the Sponsor

Input 1 and Input 2:

- Summ Review: “JAK inhibitors are potent immunosuppressants and there are a number of well-known safety issues associated with use of this class of medications,”
- Summ Review: “Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue.”
- Sig Transcript: “One of the issues had been the design of studies and analysis of the safety data. This is, I think, the third JAK inhibitor [inaudible 00:03:43] toxicities for the class. We had a very gnarly second JAK inhibitor, Baricitinib, that had a unique safety signal of venous thromboembolism for that.”
- Med Transcript: “o this drug is a JAK kinase inhibitor, and we saw a signal with the first in class, tofacitinib, that there was a malignancy signal and then later, possibly with another drug that was being developed, baricitinib, we saw that there was a deep vein thrombosis or a thromboembolic signal. So that's what we were really starting to focus on. “
- Med Transcript: “We know what to expect. But it was basically the thromboembolism and malignancy that we were looking at.”
- Med Transcript: “So we basically identified it because there was none. There wasn't a signal in the data, but we were looking for it”

Process 1:

- Med Transcript: “So we basically identified it because there was none. There wasn't a signal in the data, but we were looking for it because of baricitinib. Since it did occur at both doses, not necessarily dose-dependent, we still wanted to analyze that information. So we had stats help us look at the different levels that we could parse out to see about the thromboemboli.”

Process 2:

- Med Transcript: “Did AbbVie give pushback on that? A lot. Yeah, [inaudible 00:09:07]. But I think they're understanding. I'm not in pharma, but I'm pretty sure what their strategy is is get it out in the market and then just market it. It's all marketing.”

Output 1:

- Summ Review: “Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue and the upadacitinib product label will include a Boxed Warning regarding VTE.”

4.F. Review Issue 6

Review Issue: Embryofetal Toxicity

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Teratogenicity signal in rabbits study	1	Pharmacology/ Toxicology	Concrete	1, 2, 3	Discussed at several meetings, including early safety scoping meeting and mid-cycle meeting	Yes	Integrative	Recommendation in labelling for a Warning and Precaution on use of UPA in pregnant or lactating women	Cross-disciplinary	Concrete
Teratogenicity signal in rats study	2	Pharmacology/ Toxicology	Concrete	1, 2, 3	Consulted to division of pediatric and maternal health and Clinical	No	Combinatorial			
Signal was consider more significant than that found in other JAK inhibitor programs	3	Pharmacology/ Toxicology	Abstract							
Number of Inputs: 3 Degree of Difference in Inputs: **Low**					Number of Changes in Inputs: **1** Degree of Change in Inputs: **Low**			Number of Outputs: **1** Difference from Inputs: **Low**		

Commensurability:	High; most inputs were similar in source type and findings
Scale:	Local; localized to the finding of embryofetal toxicity
Comprehensiveness:	High; the labeling recommendation included all the conclusions from the inputs

Input 1:

- Sig Transcript: “I think it was identified because it was a nonclinical study that identified the risk. I can't recall. I think they might've recommended a contraindication, and this would've been different than the other JAK inhibitors. “
- PT Transcript: “we get full GLP study reports for all these pivotal studies on the nonclinical side and those reports include all the raw data. So yes, while the reports have a summary, but we're not parroting the sponsor's summary. This is why nonclinical review is so intensive at times because we're reviewing the data ourselves “
- Med Review: “The nonclinical review team identified a teratogenicity signal in rats and rabbits at clinically relevant exposures that represent a potential serious risk for human fetal toxicity. “
- PT Review: “In embryofetal development studies, upadacitinib was teratogenic with skeletal malformations observed in rats and rabbits; other findings and decreased fetal body weights and increased postimplantation loss in rabbits.”
- Summ Review: “Animal studies with upadacitinib showed teratogenicity findings (skeletal malformations and death), but these findings were more concerning compared to other JAK inhibitors because teratogenicity was noted at lower exposure margins considered clinically relevant exposures.”

Input 2:

- PT Transcript: “we get full GLP study reports for all these pivotal studies on the nonclinical side and those reports include all the raw data. So yes, while the reports have a summary, but we're not parroting the sponsor's summary. This is why nonclinical review is so intensive at times because we're reviewing the data ourselves “
- Med Review: “The nonclinical review team identified a teratogenicity signal in rats and rabbits at clinically relevant exposures that represent a potential serious risk for human fetal toxicity. “
- PT Review: “In embryofetal development studies, upadacitinib was teratogenic with skeletal malformations observed in rats and rabbits; other findings and decreased fetal body weights and increased postimplantation loss in rabbits.”
- Summ Review: “Animal studies with upadacitinib showed teratogenicity findings (skeletal malformations and death), but these findings were more concerning compared to other JAK inhibitors because teratogenicity was noted at lower exposure margins considered clinically relevant exposures.”

Input 3:

- PT Transcript: “One was the reproductive risks based on the nonclinical data. We felt the data was substantially worse than the previous class members and so we wanted the fetal risk to be included in the warnings and precautions section of the label, which would be a difference between this and its competitors in the class. “
- Med Review: “ The nonclinical reviewer, Brett Jones, PhD, considered the embryo-fetal toxicity data with UPA as comparatively more concerning than that observed with previously approved JAK inhibitor products, namely tofacitinib and baricitinib, based on the observed lower exposure margins to proposed clinical dose levels.”
- Summ Review: “The embryo-fetal toxicity finding with upadacitinib is more concerning compared to tofacitinib and baricitinib because of the relatively low exposure margins.”

Process 1:

- PT Transcript: “So we raised this pretty early on, I think, and discussed it at various meetings.”
- Med Review: “concerns were discussed at the March 4, 2019 Safety Mid-Cycle Meeting and the review team agreed that safety signal potentially warranted inclusion in the Warnings and Precautions section of the label, particularly in light of the large number of women of childbearing potential in the RA patient population.”
- PT Review: “Mid-Cycle Meeting on March 4, 2019, the nonclinical safety concerns regarding the observed teratogenicity of upadacitinib at exposures similar to the proposed clinical dose levels in both rats and rabbits were presented and subsequently discussed with the clinical review team and other associated review team members. The review team agreed that the observed embryo-fetal toxicity data with upadacitinib represented a significant safety concern that potentially warranted inclusion in the Warnings and Precautions “

Process 2:

- PT Review: “An additional bullet statement regarding the potential for embryo-fetal toxicity with upadacitinib was added to the Warnings and Precautions based on a consultation with DPMH and discussions with the Clinical Team.”

Output 1:

- Sig Transcript: “I think it was identified because it was a nonclinical study that identified the risk. I can't recall. I think they might've recommended a contraindication, and this would've been different than the other JAK inhibitors.”
- PT Transcript: “One was the reproductive risks based on the nonclinical data. We felt the data was substantially worse than the previous class members and so we wanted the fetal risk to be included in the warnings and precautions section of the label, which would be a difference between this and its competitors in the class.”
- Med Review: “given the embryo-fetal toxicity observed in animals at the to-be-marketed dose, the Agency recommends labeling for UPA should include a Warning and Precaution statement regarding potential teratogenicity.”
- PT Review: “Mid-Cycle Meeting on March 4, 2019, the nonclinical safety concerns regarding the observed teratogenicity of upadacitinib at exposures similar to the proposed clinical dose levels in both rats and rabbits were presented and subsequently discussed with the clinical review team and other associated review team members. The review team agreed that the observed embryo-fetal toxicity data with upadacitinib represented a significant safety concern that potentially warranted inclusion in the Warnings and Precautions “

Appendix 5: TAUVID Review Issue Inventory

5.A. Review Issue 1

MAO Inhibitors

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporates Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Chemical Structure of TAU similarity to other compounds that bind MAO inhibitors	1	Clinical Pharmacology	Abstract	1, 2	Early discussions with the review team, led by Clinical Pharmacology, to scope out the issue and agree on significance to review	Yes	Integative	(Potential) Effect of MAO inhibitors was described in the labeling (Section 12)	Cross-disciplinary	Concrete
Literature on MAO inhibitor binding	2	Clinical Pharmacology, Clinical, and Pharm/Tox	Concrete	3, 4	Mid-cycle team discussions to review team's conclusions on additionally submitted data and literature.	Yes	Combinatorial			
Applicant submitted clinical study (unpublished but presented at a meeting) with 50 patients to study MAO inhibitor effects on scans	3	Clinical Pharmacology and Clinical	Concrete	1, 2, 3, 4	Discussions with the Sponsor on significance of the MAO inhibitor similarity	No	Disintegrative			
Secondary Pharmacology Studies	4	Pharm/Tox	Concrete	1, 2, 3, 4	Collaborative writing and discussions on how to label for this issue accurately without overalarming clinicians	No	Integrative			
Number of Inputs: 4 Degree of Difference in Inputs: Medium - Mostly basic science with one clinical study					Number of Changes in Inputs: 4 - expert opinion on chemical structure changed into a research question for the team. Input from Applicant (i.e., clinical study submission) turned into a validating piece of evidence to support labeling Degree of Change in Inputs: Medium - transformation of an abstract perspective on chemical structure to meaningful review issue			Number of Outputs: 1 Difference from Inputs: Low - While this was labeled, it maintained the moniker of "Potential" and only included in Section 12, which is a descritptive section of labeling, meaning its still not a signficant issue.		

Commensurability:	Medium - some conflict between the chemical structure extrapolation and rest of the concrete evidence that did not demonstrate off-target binding on MAO
Scale:	Local - this did not impact overall Benefit-Risk Determination
Comprehensiveness:	Low - final output is relatively brief and not entirely comprehensive to all inputs (i.e., it is a brief description of the potential off-target effects of TAU-MAO binding

Input 1:

- CP Transcript: “Well, from the very beginning we noticed that the structure, the chemical structure of [TAUVID] was slightly similar to some of the others of the compounds that bind to MAO inhibitors bind to monoamine oxidase enzymes and the structurally similar to some of those inhibitors. So it was clear that there's a potential that there's a drug could inhibit.”
- PTS Transcript: “clinical pharmacology raises substantial issue about the effect of MAO”

Input 2:

- CP Transcript: “ there was one paper that reported the binding for MAO the subtypes in these enzymes. One is MAO A and another one is MAO B and there were comparative reports in the literature, whether it really binds to MAO A or not”
- RPM Transcript: “I believe it was the MAO inhibitor issue, that there was something known from literature, it didn't necessarily come up in the studies, but it was known in literature, and that triggered a lot of investigation by the review team into the impact”

Input 3:

- CP Transcript: “And then the company came back to us with a, the results of a clinical study that was being conducted currently, and the results they said that are not published.”

Input 4:

- PT Transcript: “I contributed some amount to the MAO inhibitors for TAUVID, flortaucipir binding because they actually, the sponsor, Avid, submitted a lot of secondary pharmacology data to evaluate the effect of MAO inhibitors”
- Integrated Review: “TAUVID PET signal was slightly reduced by rasagiline, a MAO-B inhibitor, in vivo in low tau, high MAO-B areas of the brain such as the nucleus accumbens, putamen, and caudate.”

Process 1:

- PT Transcript: “we had these like a scoping meeting and then a kind of introduction to the integrative review and how to use the review tracker. And it might've been the scoping meeting, or it could have even been during the filing meeting where I discussed with the clinical pharmacology team new data that was included within the NDA to evaluate off-target binding. And then we kind of initiated some discussions on that and then those discussions wound up, so then I had reviewed a lot of those studies to include in my, we do a mid-cycle and includes several slides to discuss, summarize all the data for the NDA, from the nonclinical perspective.”

Process 2:

- PT Transcript: “so then I had reviewed a lot of those studies to include in my, we do a mid-cycle and includes several slides to discuss, summarize all the data for the NDA, from the nonclinical perspective.”
- RPM Transcript: “If I recall, there wasn't a lot of data on it, and so there was discussions primarily with the clin pharm group as to how that could be addressed in labeling more than anything else. It wasn't necessarily a huge concern.”

Process 3:

- PT Transcript: “what it boiled down to was what in vivo, in humans, what really would be the end result of that? Would it be of significant concern that it would affect the interpretation of a scan? And there was some contention between the agency and the sponsor as to how to capture that in the labeling”

Process 4:

- PT Transcript: “Well, there was a lot of collaborative writing at later stages to try to document this both in like relevance clinical Clin/Pharm and nonclinical sections”
- Integrated Review: “These findings suggest that flortaucipir binds with low affinity to MAO-A and very weakly to MAO-B in postmortem normal human tissue and that MAO-B would not contribute much to FTP uptake in PET imaging.”

Output 1:

- CP Transcript: “We didn't want to alarm people too much either because the issue is still being researched and still not clear so more studies need to be conducted”
- Integrated Review: “Therefore, it appears that there is little potential for MAO binding to affect Tauvid PET image interpretation. The language in the proposed label Image Interpretation (2.4) and Warnings and Precautions (5.1) sections states that “only uptake in neocortex should contribute to the interpretation of a positive Tauvid scan” would be adequate to mitigate any putative effect of MAO inhibitors on scan interpretation.”
- Integrated Review: “The team concluded to include the off-target binding potential of FTP to MAO-A and MAO-B in Section 12 of the prescribing information.”

5.B. Review Issue 2

User Guide

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	incorported Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Proposed User Guide	1	Clinical	Concrete	1, 2	Identified very early by experienced clinician (a practicing nuclear radiologist) and shared with Sponsor.	Yes	Integrative	Prescribing Information revised to reflect updated instructions for image interpretation.	Cross-disciplinary	Concrete
Expert Perspective on Usabilty	2	Clinical, Division of Medication Errors Prevention, and CDRH	Abstract	2	Sponsor conducted multiple tests with experts via professional societies with revised user guides.	No	Integrative			
Regulatory Requirements for User Guide as Labeling	3	Regulatory and Policy	Abstract	1, 2, 3	Regulatory and policy issue with the use of a user guide vs official instructions of use required discussion with ORP and CDRH colleagues.	No	Disintegrative			
Number of Inputs: 3 Degree of Difference in Inputs: Medium - regulatory considerations were different from the expert opinion on usage of the instructions					Number of Changes in Inputs: 3 Degree of Change in Inputs: Medium - input from professional socieities and team led to revisions to the user guides but not a major transformation			Number of Outputs: 1 Difference from Inputs: Medium - clearly changed via input from experts but essentially the same object		

Commensurability:	Medium - with only some conflict with the regulatory requirements for the instructions
Scale:	Medium - had the potential to impact the benefit-risk determination given the likelihood to misinterpret
Comprehensiveness:	Medium - confined to the instructions for use and expert opinion, regulatory opinion not reflected in the output

Input 1:

- DD Transcript: “I think that the issue of a user guide that was an issue that came up during the review that we had not anticipated. “

Input 2:

- DD Transcript: “The question of the image guide was actually something that did require discussion with the colleagues from CDRH. We also had to have policy people involved and the issue is whether this should be considered labeling and so there was a fair amount of discussion about how to incorporate this into the labeling.”
- Sig Transcript: “The other issue, which was identified early on was the user manual and the team leader who still reads nuclear scans, the user guide. Because they use different platforms for this, to be able to read them. There's different software out there that helps you read the digital image, but you have to put settings into it to be able to read it correctly. “
- Integrated Review: “For the assessment of image interpretation, the team, including experts from the Center for Devices and Radiological Health (CDRH), viewed a set of images from the pivotal studies provided by the Applicant as reviewer aids, reviewed and tested the instructions in the proposed prescribing information (PI) to image readers for Tauvid image interpretation.”
- Integrated Review: “The team, including members from CDRH and DMEPA, assessed that Tauvid readers will need more detailed instructions for image display to supplement the high-level instructions provided in the Tauvid PI.”

Input 3:

- DD Transcript: “The question of the image guide was actually something that did require discussion with the colleagues from CDRH. We also had to have policy people involved and the issue is whether this should be considered labeling and so there was a fair amount of discussion about how to incorporate this into the labeling.”
- RPM Transcript: “regulatory policy definition that had to be discussed with ORP, and so that to me was the interesting review issue, “
- Sig Transcript: “You're also writing a user guide for a device, in essence, and so it raised some legal issues, and we brought them [OND Policy] in towards the end once we saw a clear path of how to proceed with being able to address this issue”

Process 1:

- Sig Transcript: “So that was identified early on in the first couple weeks, I'd say. So that issue was brought to the company's attention quite early on. “

Process 2:

- Integrated Review: “In response, the Applicant contacted professional societies and also conducted a poll of image readers/imaging sites that participated in the Tauvid efficacy studies to gain insight into which software platforms are commonly used for image review and analysis in a clinical setting. Based on the survey, the Applicant determined that the most commonly used image viewing software platforms in the US are MIM, GE, Siemens and Hermes. Subsequently, the Applicant created and submitted step-by-step user guides for the MIM and Siemens image viewing software platforms for review and comment on their adequacy. “

Process 3:

- RPM Transcript: “RPM Transcript: “regulatory policy definition that had to be discussed with ORP, and so that to me was the interesting review issue, “

Output 1:

- Sig Transcript: “They had labeling that sort of explained how to do it, and he couldn't understand how to do it, and he's a very experienced nuclear medicine person.”
- Integrated Review: “the Applicant, in consultation with the Agency, added the following language in Section 2.4 (Image Display) of the PI: If additional guidance on image display is needed, refer to the TAUVID User Guide for PET Image Display available by request from the manufacturer.”

5.C. Review Issue 3

QT Prolongation

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporated Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
QT signal reported by applicant	1	Clinical Pharmacology, Statistics, and Clinical	Concrete	1, 2	QT Interdisciplinary Review Team was consulted for input	Yes	Combinatorial	Following input from QT-IRT and discussions with Clinical, the signal, while statistically significant was deemed of no clinical significance	Cross-disciplinary	Abstract
Expert input from the QT Interdisciplinary Review Team	2	Interdiscipline of QT Team	Abstract	1, 2	Discussed with clinical and clinical pharmacology reviewers and signatory of the review team	Yes	Integrative			
Number of Inputs: 1 Degree of Difference in Inputs: NA					Number of Changes in Inputs: 2 Degree of Change in Inputs: Low			Number of Outputs: 1 Difference from Inputs: Low		

Commensurability:	High
Scale:	Local - confined to risk/safety
Comprehensiveness:	High - all inputs incorporated

Input 1:

- Integrated Review: “The Applicant reported small but statistically significant increases in QTcB and QTcF intervals around 2 hours following IV administration of FTP when compared to baseline predose measurements.”

Input 2:

- CP Transcript: “so QT, as you know whenever we see a QT signal, this was first identified early in the... Our review meetings and then a consult we'll send to the QT IRT team”
- Integrated Review: “This issue was also reviewed by QT Interdisciplinary Review Team (QT-IRT) and they concluded that no additional regulatory action was indicated.”

Process 1:

- CP Transcript: “And essentially I did my own analysis as well, and QT IR team. They did their analysis as well. And for the most part even though the assessments were independent,”
- Integrated Review: “We do not propose QT-related labeling language for the small increases in QTcF observed in the safety database”

Process 2:

- CP Transcript: “So again I want to emphasize it was a, a nice integration between clin pharm team, QT IRT and then discuss with the, the medical officer medical review, our medical team leader and the division director and everybody chimed in and looked at the evidence. And I think I agreed with clin pharm that it's something that we don't need to be concerned”

Output 1:

- Integrated Review: “The team concluded that this observation is not clinically important.”

5.D. Review Issue 4

CTE Misdiagnosis

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporated Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Potential for off-label use	1	Clinical	Abstract	1, 2, 3	Team assessed that due to lack of evidence for CTE diagnosis but the potential off-label use, the labeling needs to address this risk	No	Integrative	Limitations of Use and Warning and Precautions was added to the labeling to prevent off-label use of the product for Chronic Traumatic Encephalopathy (CTE)	Cross-disciplinary	Concrete
Nonclinical Data	2	Pharm/Tox	Concrete							
Published Literature (Falcon et al 2018, 2019; Marquie et al 2019; Mantyh et al 2020)	3	Clinical and Pharm/Tox	Concrete							
Number of Inputs: 3 Degree of Difference in Inputs: Medium - data inuts varied between pharm/tox and clinical, and the potential for off-label use was based on expert perspective					Number of Changes in Inputs: 1 Degree of Change in Inputs: Low - Inputs were mostly confirmed by correlation in the findings from the literature and nonclinical studies, and literature			Number of Outputs: 1 Difference from Inputs: Low		

Commensurability:	High
Scale:	Local - had this been an application for use in CTE, this would have been a global issue, but as it stands this was just an off-label issue that required enhanced labeling to mitigate
Comprehensiveness:	High - pulled in all inputs for the final labeling recommendation

Input 1:

- Integrated Review: “Potential off-label use of Tauvid in chronic traumatic encephalopathy (CTE) and other tau-related neurodegenerative disorders is a concern because preliminary nonclinical and clinical investigations suggest differences in tau conformation and distribution may limit FTP binding in CTE.”
- Integrated Review: “There is a potential for inappropriate use of Tauvid in patients with CTE and other non-AD tauopathies.”

Input 2:

- PT Transcript: “CT misdiagnosis, I mean, that's clear from both published studies and some of the nonclinical data.”
- DD Transcript: “Concussions and so on. And so it was clear based on preclinical data that the binding of this drug was not going to be, it was going to be specific only to the Alzheimer type of neurofibrillary tangles.”

Input 3:

- PT Transcript: “CT misdiagnosis, I mean, that's clear from both published studies and some of the nonclinical data.”
- Sig Transcript: “CTE misdiagnosis was really something that was based on what had been published already in the literature.”
- Integrated Review: “the tau aggregates in CTE contain all six isoforms with the presence of both the 3R and 4R repeats of the microtubule binding domain that is similar to AD but no other tauopathies, electron cryomicroscopy studies show the tau filament conformation in CTE differs from the tau filaments in NFTs of AD (Falcon et al. 2018; Falcon et al. 2019).”
- Integrated Review: “Marquie et al. explored the correlation between FTP binding patterns in pathologically confirmed CTE tissue using phosphor screen and high-resolution autoradiography and quantitative tau measurements obtained through immunohistochemistry, Western blotting, and tau seeding activity in the same samples (Marquie et al. 2019).”
- Integrated Review: “Another study (Mantyh et al. 2020) compared in vivo FTP activity with phosphorylated tau immunohistochemical analysis of postmortem brain tissue (Mantyh et al. 2020).”

Process 1:

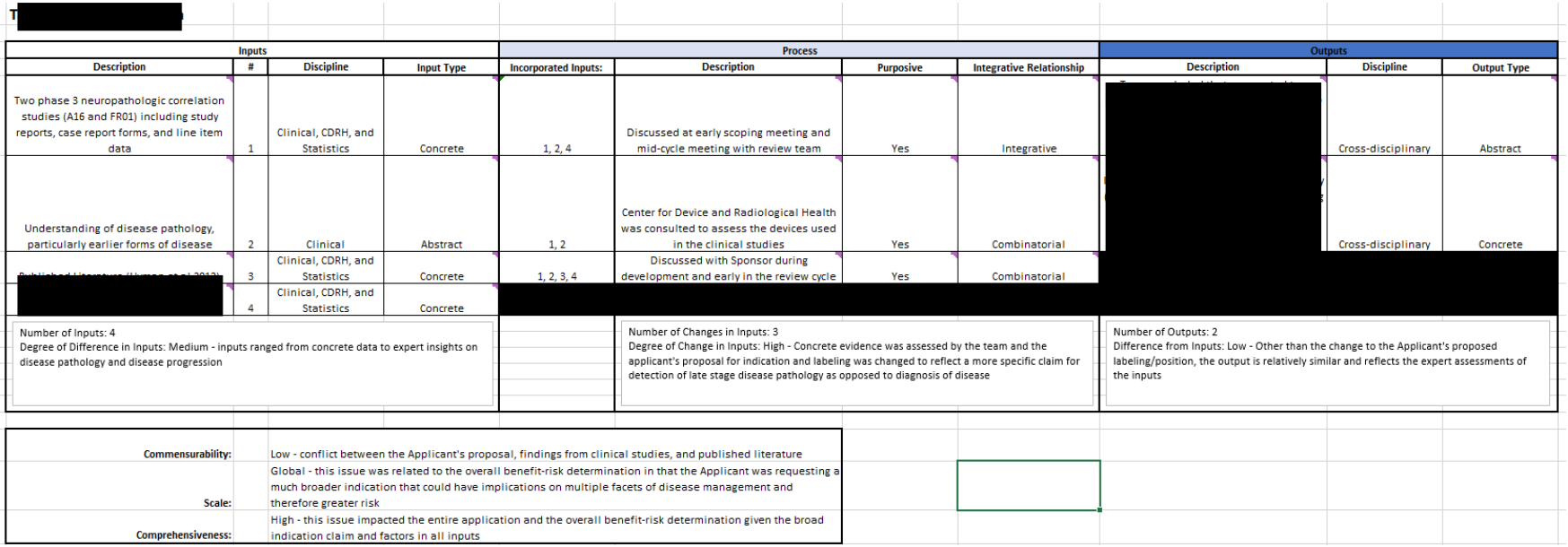
- Integrated Review: “To mitigate risk, the Applicant agreed to accept addition of a Limitations to Use in prescribing information (PI)”

- Integrated Review: “Potential off-label use of Tauvid in chronic traumatic encephalopathy (CTE) and other tau-related neurodegenerative disorders is a concern because preliminary nonclinical and clinical investigations suggest differences in tau conformation and distribution may limit FTP binding in CTE.”

Output 1:

- Integrated Review: “To mitigate risk, the Applicant agreed to accept addition of a Limitations to Use in prescribing information (PI). This limitation emphasizes that Tauvid is not indicated for evaluation of patients for chronic traumatic encephalopathy (CTE) and cross-references an added Warning and Precaution under the heading “Risk of Chronic Traumatic Encephalopathy Misdiagnosis.””

5.E. Review Issue 5



Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporated Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Two phase 3 neuropathologic correlation studies (A16 and FR01) including study reports, case report forms, and line item data	1	Clinical, CDRH, and Statistics	Concrete	1, 2, 4	Discussed at early scoping meeting and mid-cycle meeting with review team	Yes	Integrative	[redacted]	Cross-disciplinary	Abstract
Understanding of disease pathology, particularly earlier forms of disease	2	Clinical	Abstract	1, 2	Center for Device and Radiological Health was consulted to assess the devices used in the clinical studies	Yes	Combinatorial		Cross-disciplinary	Concrete
[redacted]	3	Clinical, CDRH, and Statistics	Concrete	1, 2, 3, 4	Discussed with Sponsor during development and early in the review cycle	Yes	Combinatorial			
[redacted]	4	Clinical, CDRH, and Statistics	Concrete	[redacted]						
Number of Inputs: 4 Degree of Difference in Inputs: Medium - inputs ranged from concrete data to expert insights on disease pathology and disease progression				Number of Changes in Inputs: 3 Degree of Change in Inputs: High - Concrete evidence was assessed by the team and the applicant's proposal for indication and labeling was changed to reflect a more specific claim for detection of late stage disease pathology as opposed to diagnosis of disease				Number of Outputs: 2 Difference from Inputs: Low - Other than the change to the Applicant's proposed labeling/position, the output is relatively similar and reflects the expert assessments of the inputs		

Commensurability:	Low - conflict between the Applicant's proposal, findings from clinical studies, and published literature
Scale:	Global - this issue was related to the overall benefit-risk determination in that the Applicant was requesting a much broader indication that could have implications on multiple facets of disease management and therefore greater risk
Comprehensiveness:	High - this issue impacted the entire application and the overall benefit-risk determination given the broad indication claim and factors in all inputs

Input 1:

- DD Transcript: “One was sort of a study that looked at the accuracy of the reading, PET imaging, with a truth standard consisting of autopsy diagnosis and so that was a standard portion that succeeded.”
- [redacted]
- Integrated Review: “To assess the utility of Tauvid to estimate the density and distribution of aggregated tau NFTs in patients with cognitive impairment being evaluated for AD, the Applicant conducted two neuropathologic correlation studies—the A16 autopsy study and the FR01 reader study.”

Input 2:

- [redacted]

Input 3:

- Integrated Review: “To illustrate this issue, consider the publication cited by the Applicant for support of the AD neuropathological criteria used in Study A16 (Hyman et al. 2012)."

Input 4:

- DD Transcript: “The other issue, maybe that it also is important that the sponsor [redacted]. “

- Integrated Review: [redacted]

Process 1:

- RPM Transcript: “Because of the pre-NDA and the prior meetings, one of the biggest subjects that was constantly being brought up is how they had difficulty in getting their objective. “

Process 2:

- Integrated Review: “For the assessment of image interpretation, the team, including experts from the Center for Devices and Radiological Health (CDRH), viewed a set of images from the pivotal studies provided by the Applicant as reviewer aids, reviewed and tested the instructions in the proposed prescribing information (PI) to image readers for Tauvid image interpretation.”

Process 3:

- [redacted]

Output 1:

- Integrated Review: “The team concluded that the results of the submitted phase 3 studies support the efficacy of Tauvid to estimate the density and distribution of aggregated tau-NFTs in the indicated patient population (efficacy for tau pathology detection).”

Output 2:

- DD Transcript: “[redacted].”
- Integrated Review: “To address this issue, the PI was revised in Section 5 WARNINGS AND PRECAUTIONS to alert the prescribing clinicians of the limitation of a Negative Tauvid scan read by including the following: 5.1 Risk of Misdiagnosis in Patients Evaluated for Alzheimer’s disease TAUVID does not target β-amyloid, one of two required components of the neuropathological diagnosis of AD.”

5.F. Review Issue 6

[redacted]

Inputs				Process				Outputs		
Description	#	Discipline	Input Type	Incorporated Inputs:	Description	Purposive	Integrative Relationship	Description	Discipline	Output Type
Two phase 3 studies (A05C and PX01), including study reports, case report forms, and line item data	1	Clinical, CDRH, and Statistics	Concrete	1, 2, 3	Multiple review team discussions primarily between clinical and statistics, led by clinical	Yes	Integrative	[redacted]	Cross-disciplinary	Abstract
Sensitivity analyses	2	Statistics	Concrete	1	Center for Device and Radiological Health was consulted to assess the devices used in the clinical studies	Yes	Combinatorial	[redacted]	Cross-disciplinary	Concrete
Pre-Submission Meetings	3	Regulatory, Clinical, and Statistics	Abstract	1, 3, 4	[redacted]	Yes	Disintegrative	[redacted]		
Additional data and information requested by the review team	4	Clinical and Statistics	Concrete	[redacted]						
Number of Inputs: 4 Degree of Difference in Inputs: Low - Mostly data driven inputs with exception of early applicant interactions in pre-submission meetings				Number of Changes in Inputs: 3 Degree of Change in Inputs: Low - concrete evidence was assessed and lack of evidence for claim was found, one abstract finding for an additional study				Number of Outputs: 2 Difference from Inputs: Low		

Commensurability:	High - not much conflict between these inputs, however the pre-submission meeting interactions were not as definitive or concrete as the other inputs
Scale:	Global - this issue had the ability to impact the overall benefit-risk determination due to the potential to misinform clinicians, practitioners, or caregivers
Comprehensiveness:	High - this issue impacted the entire application and the overall benefit-risk determination given the broad indication claim and factors in all inputs

Input 1:

- CDTL Transcript: "Well, the module five, the [inaudible 00:11:51] data submissions. I mean, at least from my perspective, the most viable affect is a submission in order or the … line item data, the key support forms that get informed that line item data, and then the [inaudible 00:12:18] study reports that sort of represent the applicants on and out and write up of that data."
- DD Transcript: "And then the second component of the clinical development was going to be an assessment [redacted]"

Input 2:

- Stats Transcript: "you will not see any exploratory analysis that the stat team did regarding prognostic indication."
- Stats Transcript: "The stat team interacts with clinical team a whole lot, and we shared our analysis with them and go from there. So we identified this issue much earlier in the review cycle and shared, we identified but it took some time to learn all those exploratory analysis and to convince ourselves first and then clinical team that this was the serious issue. "

Input 3:

- [redacted]

[redacted]

Input 4:

- RPM Transcript: “So a lot of data were missing, that they found out, and that sort of helped them gel or solidify what this issue really was. Because a lot of what was discussed in the pre-NDA meetings didn't come through when they actually came in for the NDA. There were things that were just- did not get presented when they were asked. So a lot of it was internal meetings, data analysis, and gathering more information that was just not there when they submitted the NDA.”

Process 1:

- RPM Transcript: “I think they just couldn't [redacted]
- RPM Transcript: “ it wasn't quite until mid-cycle that they started to put pen to paper on how they actually all agreed about some particular issue. Right, and then that's sort of when all the other jam meetings and mid-cycle meetings, that's sort of when it started to be more pressure, "get this on paper,””
- Sig Transcript: “it was a close interaction between the statisticians and the clinical staff that helped sort through all the deficiencies, and that's why it got resolved it is.”
- Stats Transcript: “The clin and stat meetings took place lot of time. There were many clin stat meetings. And through those meetings we decided eventually [redacted]

Process 2:

- [redacted]

Process 3:

- DD Transcript: “So we negotiated with the company and they agreed to basically claims indication statement this were really consistent with the evidence that we had. And so it was pretty much a routine kind of an approach.”
- Sig Transcript: “[the Applicant] were trying to take individuals who would be characterized as having a very positive scan, sort of the extreme of the pathology and follow them for a year and a half and measure cognitive function and be able to prognostically say whether the individuals who fell into this group based on their reads, you can project their cognitive decline. That was the issue with the controversy about prognosis, and that was which was going to be discussed at the advisory committee, which ultimately was canceled because the team conveyed to the company that this was going to be the discussion. They were understanding of that, agreed that it could be discussed at the advisory committee, and then the advisory committee was canceled, and they agreed to withdraw that indication.”

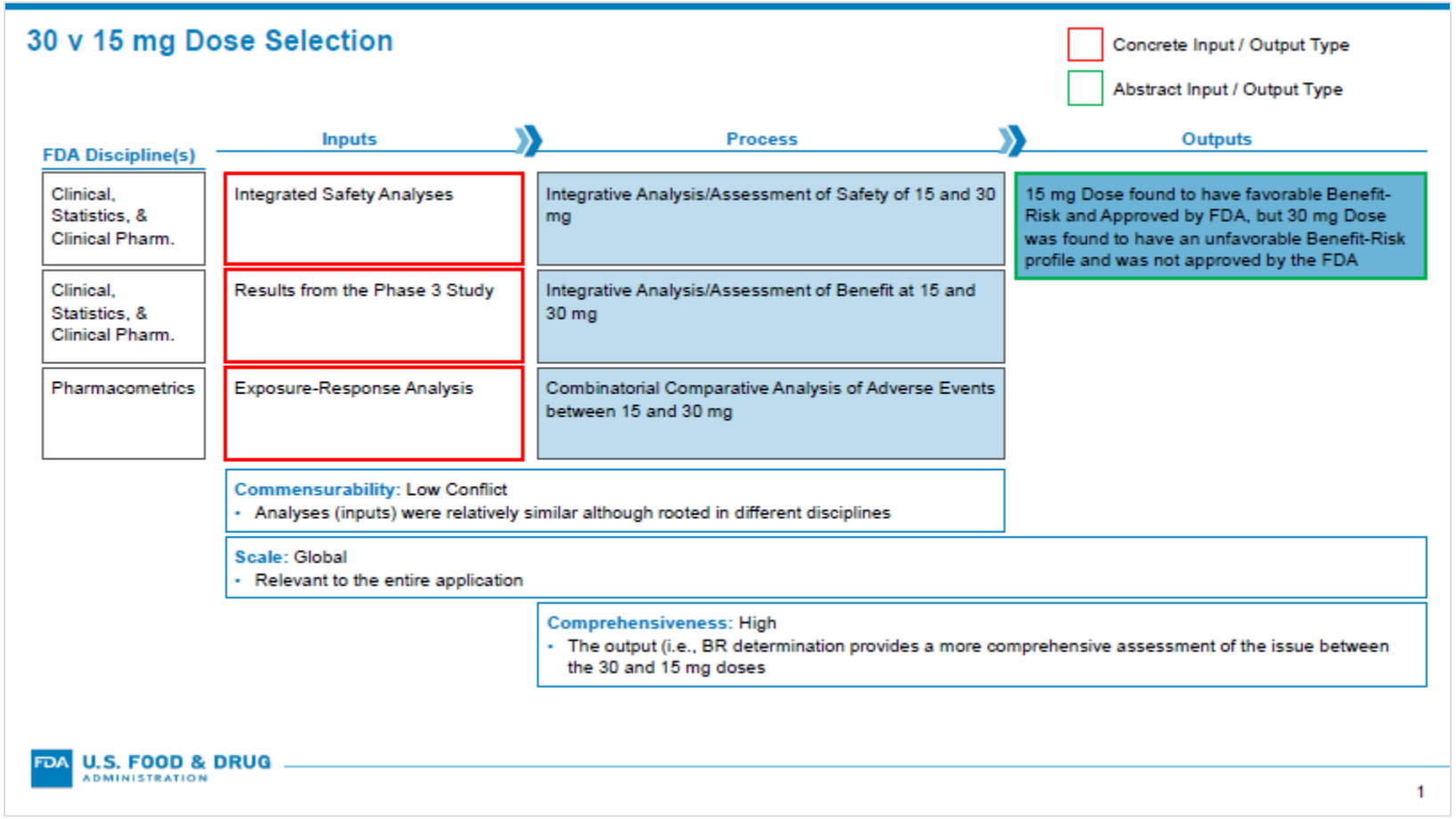
Output 1:

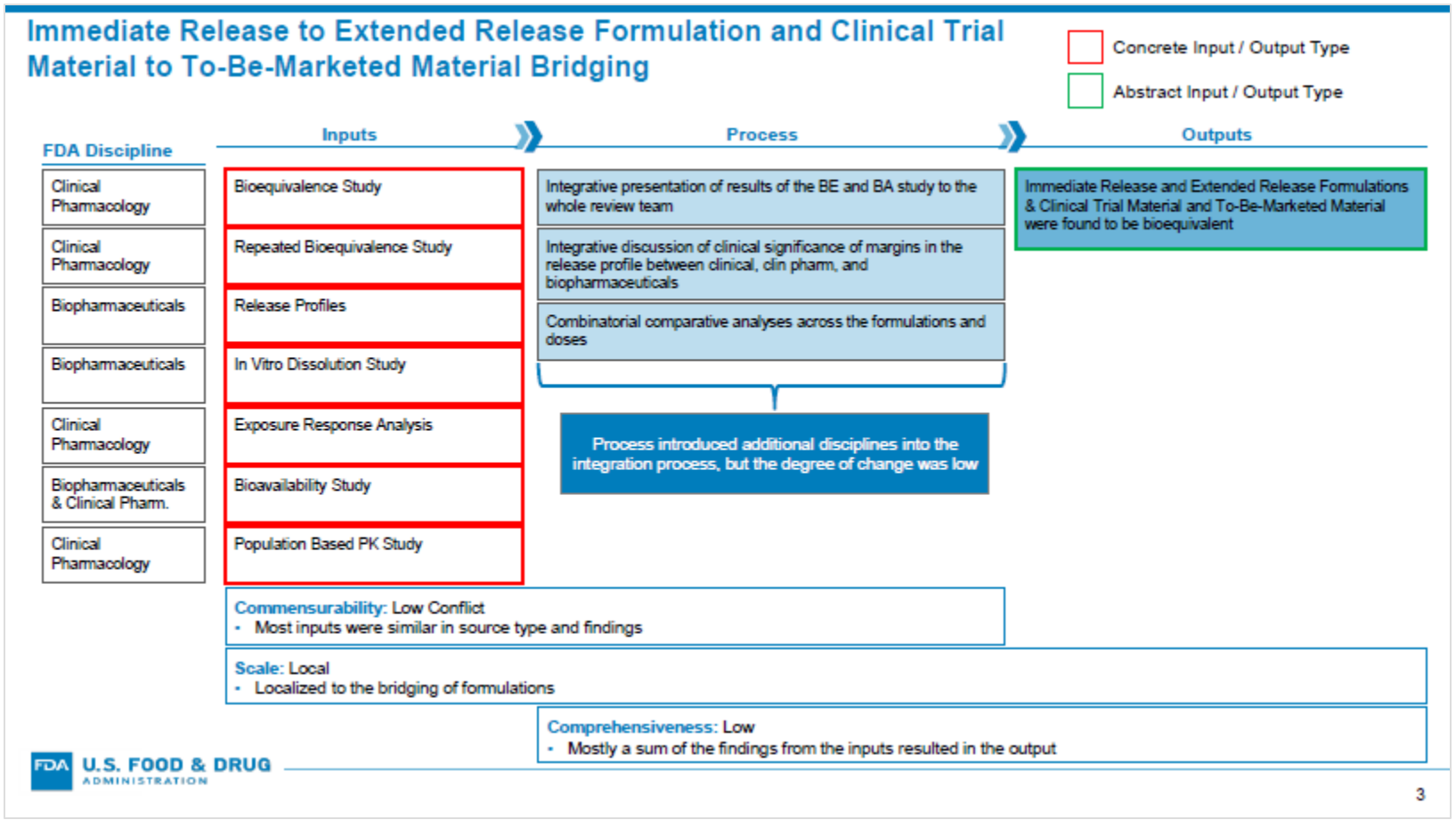
- [redacted]

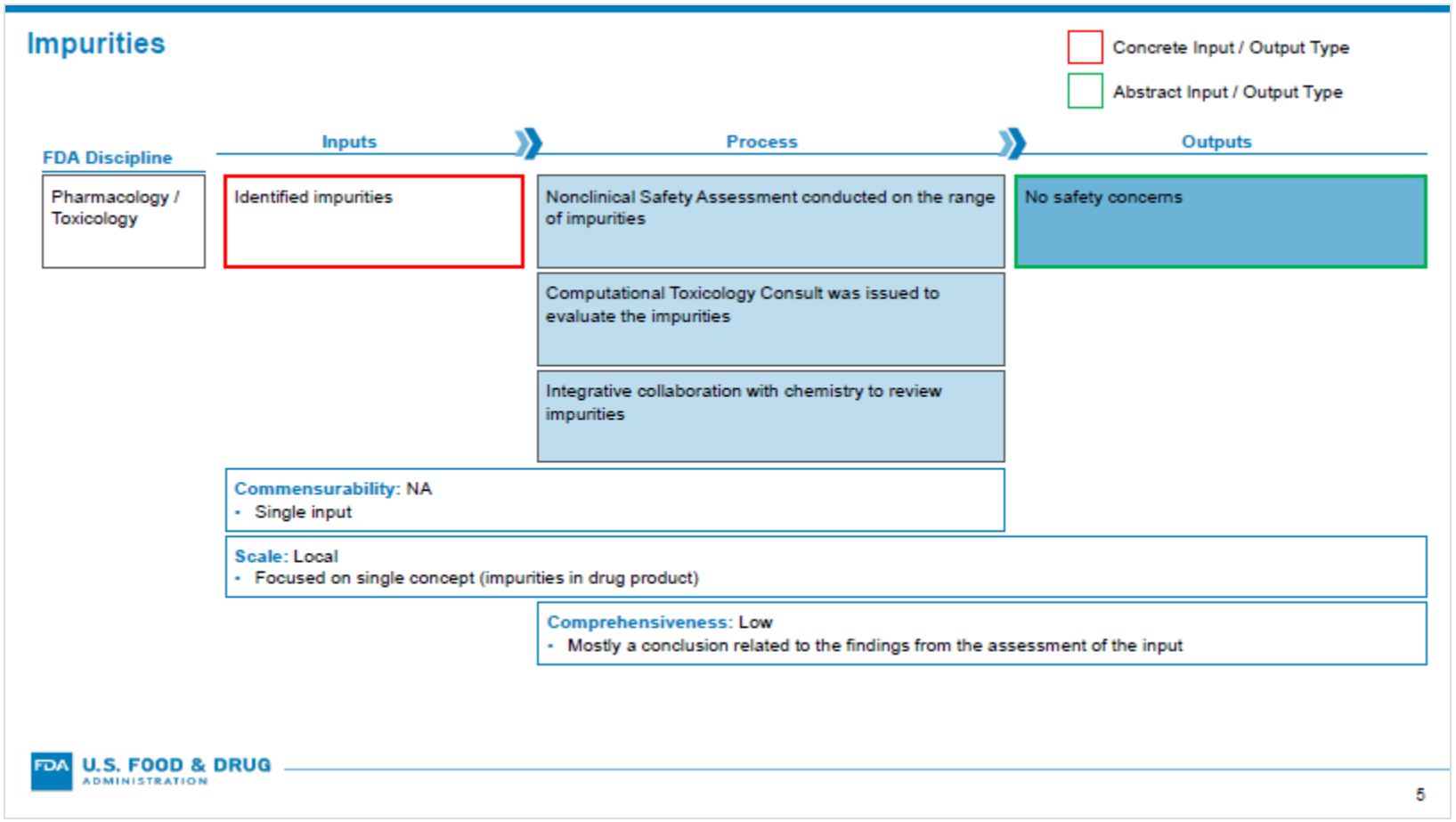
Output 2:

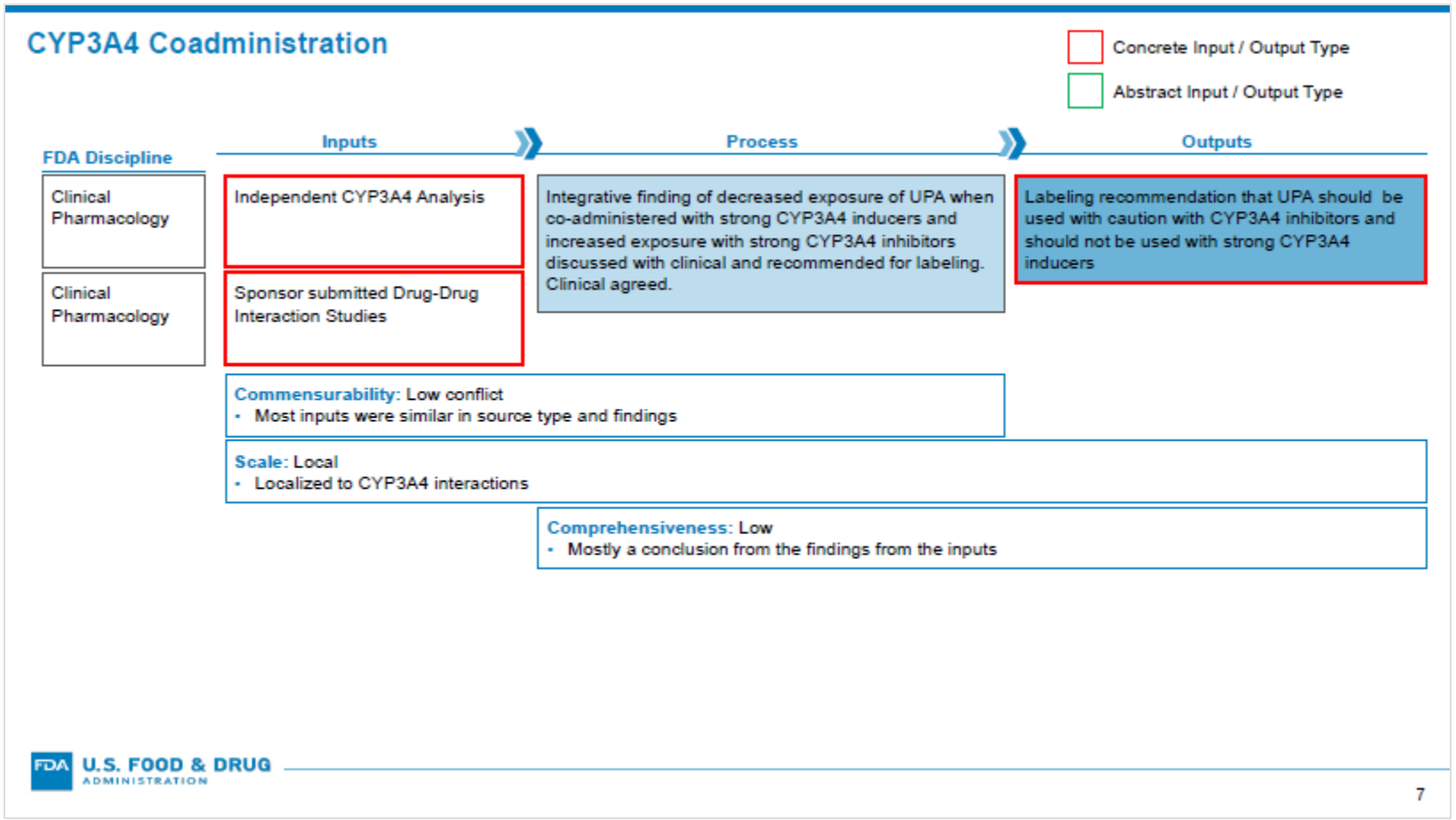
- [redacted]

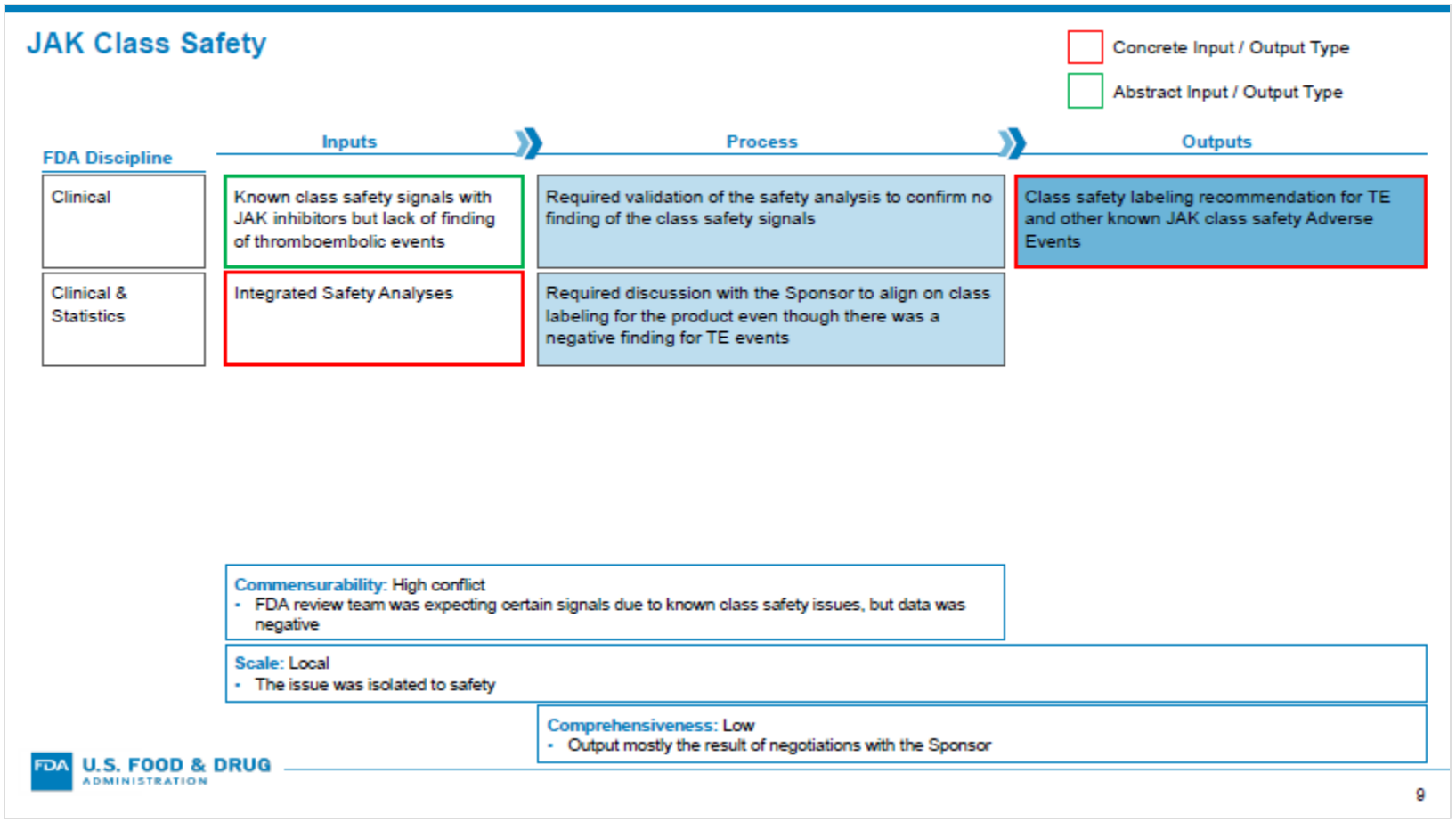
Appendix 6: RINVOQ IPO Models for Member Checking

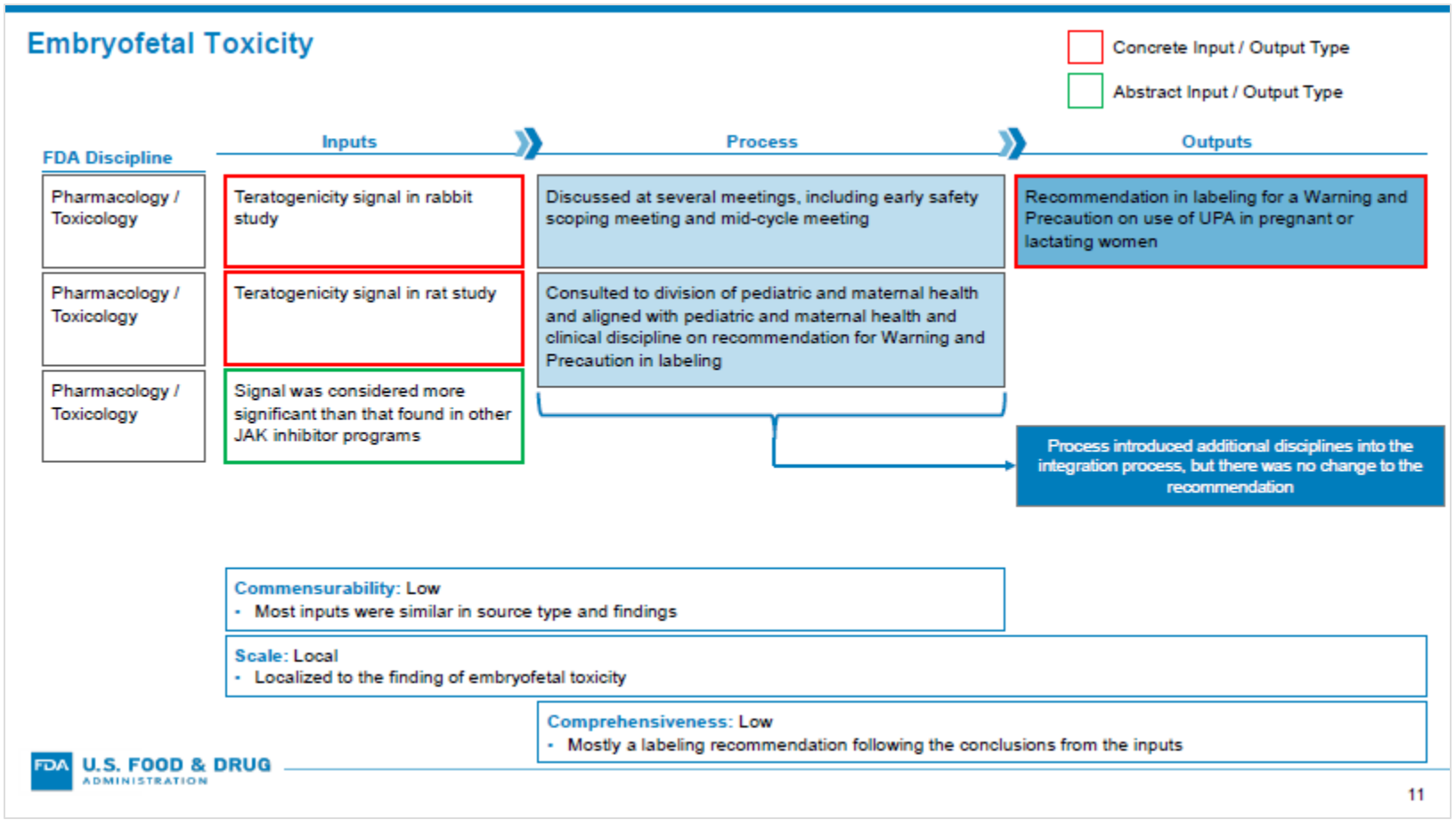



Immediate Release to Extended Release Formulation and Clinical Trial Material to To-Be-Marketed Material Bridging
Concrete Input / Output Type
Abstract Input / Output Type
FDA Discipline
Inputs
Process
Outputs
Clinical Pharmacology
Bioequivalence Study
Integrative presentation of results of the BE and BA study to the whole review team
Immediate Release and Extended Release Formulations & Clinical Trial Material and To-Be-Marketed Material were found to be bioequivalent
Clinical Pharmacology
Repeated Bioequivalence Study
Integrative discussion of clinical significance of margins in the release profile between clinical, clin pharm, and biopharmaceuticals
Biopharmaceuticals
Release Profiles
Combinatorial comparative analyses across the formulations and doses
Biopharmaceuticals
In Vitro Dissolution Study
Clinical Pharmacology
Exposure Response Analysis
Process introduced additional disciplines into the integration process, but the degree of change was low
Biopharmaceuticals & Clinical Pharm.
Bioavailability Study
Clinical Pharmacology
Population Based PK Study
Commensurability: Low Conflict
Most inputs were similar in source type and findings
Scale: Local
Localized to the bridging of formulations
Comprehensiveness: Low
Mostly a sum of the findings from the inputs resulted in the output
FDA U.S. FOOD & DRUG ADMINISTRATION
3

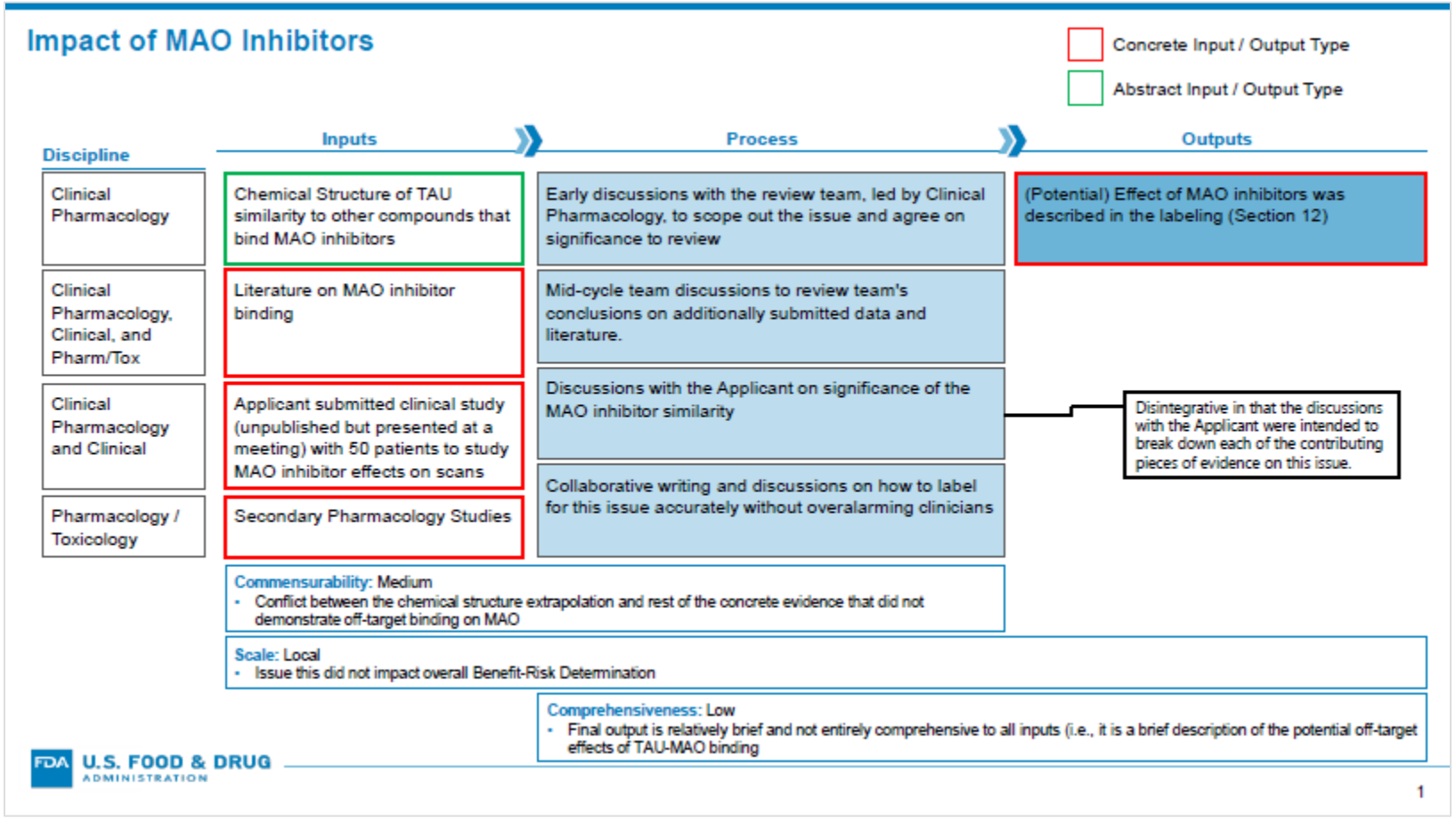

Impurities
Concrete Input / Output Type
Abstract Input / Output Type
FDA Discipline
Inputs
Process
Outputs
Pharmacology / Toxicology
Identified impurities
Nonclinical Safety Assessment conducted on the range of impurities
No safety concerns
Computational Toxicology Consult was issued to evaluate the impurities
Integrative collaboration with chemistry to review impurities
Commensurability: NA
• Single input
Scale: Local
• Focused on single concept (impurities in drug product)
Comprehensiveness: Low
• Mostly a conclusion related to the findings from the assessment of the input
FDA U.S. FOOD & DRUG ADMINISTRATION
5

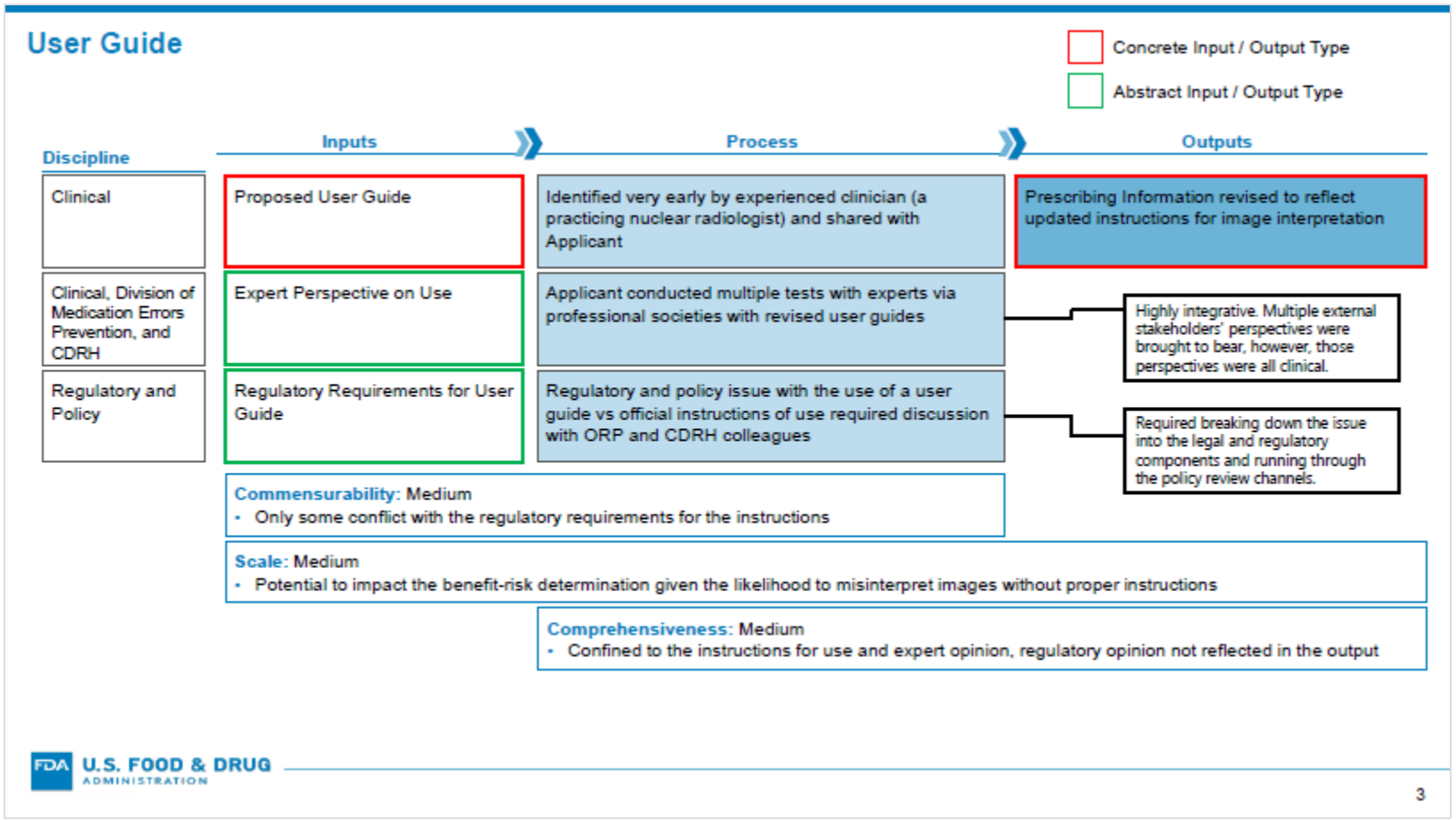

CYP3A4 Coadministration
Concrete Input / Output Type
Abstract Input / Output Type
FDA Discipline
Inputs
Process
Outputs
Clinical Pharmacology
Independent CYP3A4 Analysis
Clinical Pharmacology
Sponsor submitted Drug-Drug Interaction Studies
Integrative finding of decreased exposure of UPA when co-administered with strong CYP3A4 inducers and increased exposure with strong CYP3A4 inhibitors discussed with clinical and recommended for labeling. Clinical agreed.
Labeling recommendation that UPA should be used with caution with CYP3A4 inhibitors and should not be used with strong CYP3A4 inducers
Commensurability: Low conflict
• Most inputs were similar in source type and findings
Scale: Local
• Localized to CYP3A4 interactions
Comprehensiveness: Low
• Mostly a conclusion from the findings from the inputs
FDA U.S. FOOD & DRUG ADMINISTRATION
7

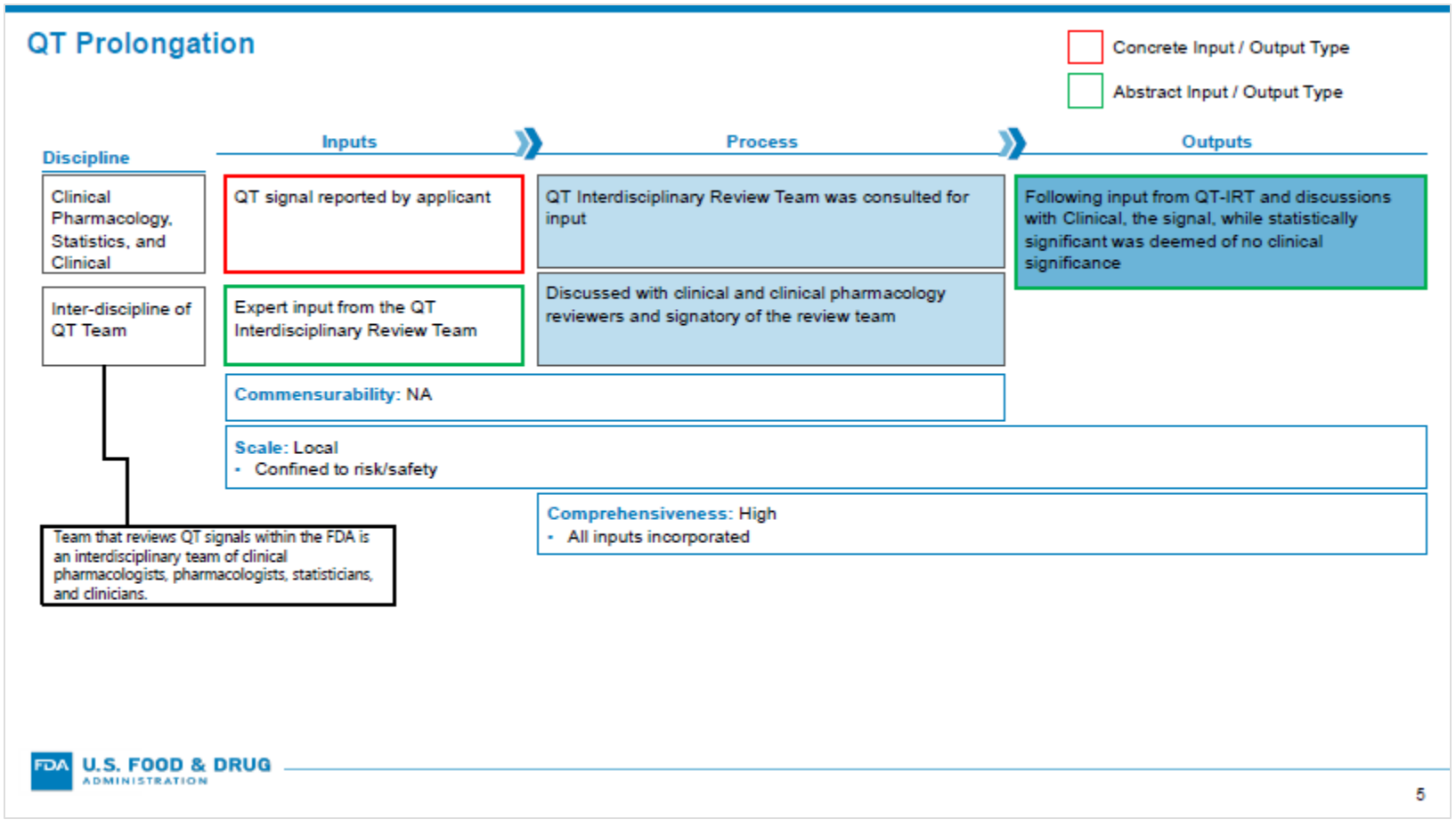

JAK Class Safety
Concrete Input / Output Type
Abstract Input / Output Type
FDA Discipline
Inputs
Process
Outputs
Clinical
Known class safety signals with JAK inhibitors but lack of finding of thromboembolic events
Required validation of the safety analysis to confirm no finding of the class safety signals
Class safety labeling recommendation for TE and other known JAK class safety Adverse Events
Clinical & Statistics
Integrated Safety Analyses
Required discussion with the Sponsor to align on class labeling for the product even though there was a negative finding for TE events
Commensurability: High conflict
• FDA review team was expecting certain signals due to known class safety issues, but data was negative
Scale: Local
• The issue was isolated to safety
Comprehensiveness: Low
• Output mostly the result of negotiations with the Sponsor
FDA U.S. FOOD & DRUG ADMINISTRATION
9

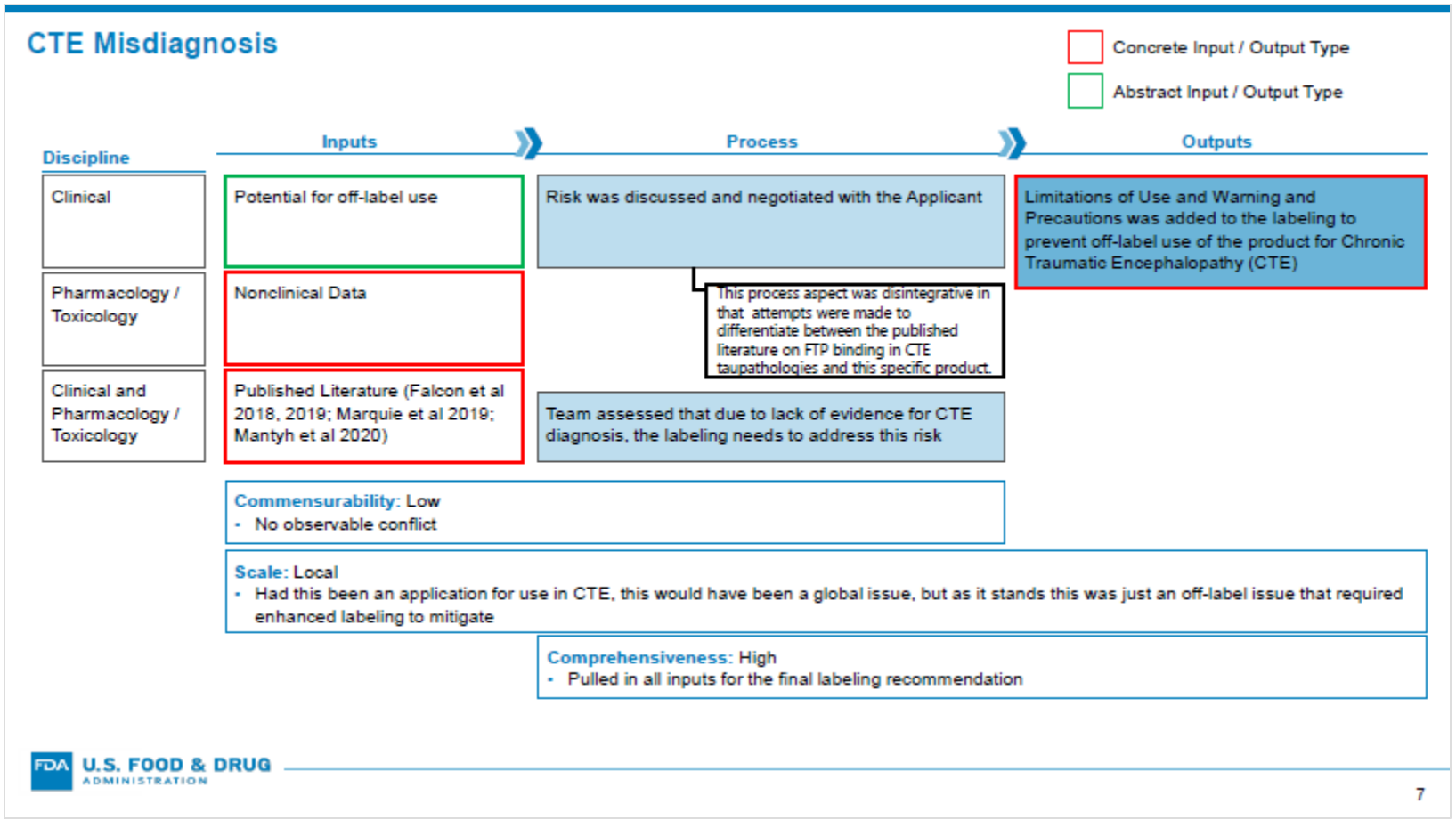

Embryofetal Toxicity
Concrete Input / Output Type
Abstract Input / Output Type
FDA Discipline
Inputs
Process
Outputs
Pharmacology / Toxicology
Teratogenicity signal in rabbit study
Discussed at several meetings, including early safety scoping meeting and mid-cycle meeting
Recommendation in labeling for a Warning and Precaution on use of UPA in pregnant or lactating women
Pharmacology / Toxicology
Teratogenicity signal in rat study
Consulted to division of pediatric and maternal health and aligned with pediatric and maternal health and clinical discipline on recommendation for Warning and Precaution in labeling
Pharmacology / Toxicology
Signal was considered more significant than that found in other JAK inhibitor programs
Process introduced additional disciplines into the integration process, but there was no change to the recommendation
Commensurability: Low
• Most inputs were similar in source type and findings
Scale: Local
• Localized to the finding of embryofetal toxicity
Comprehensiveness: Low
• Mostly a labeling recommendation following the conclusions from the inputs
FDA U.S. FOOD & DRUG ADMINISTRATION
11

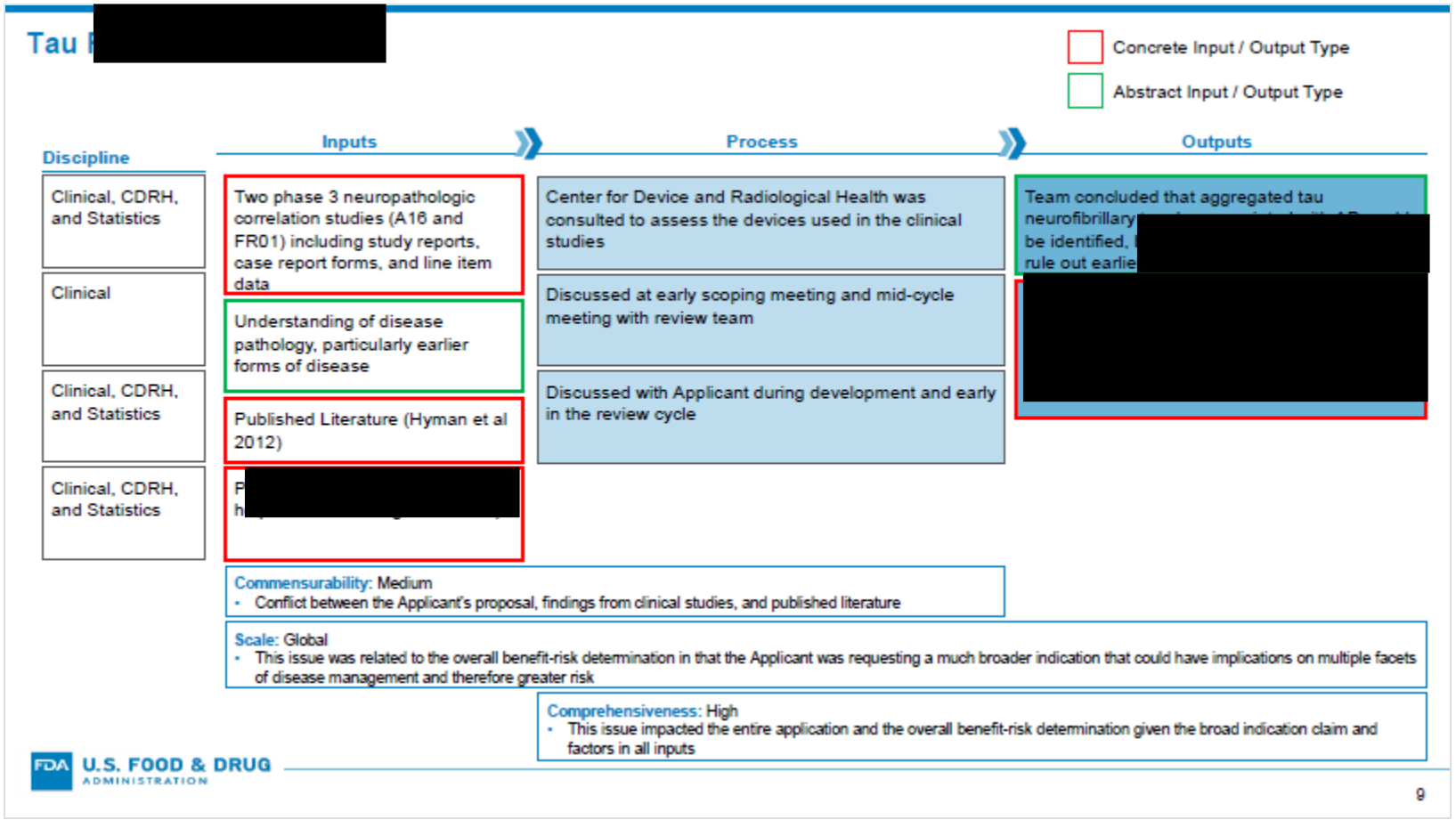
Appendix 7: TAUVID IPO Models for Member Checking




User Guide
Concrete Input / Output Type
Abstract Input / Output Type
Discipline
Inputs
Process
Outputs
Clinical
Proposed User Guide
Identified very early by experienced clinician (a practicing nuclear radiologist) and shared with Applicant
Prescribing Information revised to reflect updated instructions for image interpretation
Clinical, Division of Medication Errors Prevention, and CDRH
Expert Perspective on Use
Applicant conducted multiple tests with experts via professional societies with revised user guides
Highly integrative. Multiple external stakeholders' perspectives were brought to bear, however, those perspectives were all clinical.
Regulatory and Policy
Regulatory Requirements for User Guide
Regulatory and policy issue with the use of a user guide vs official instructions of use required discussion with ORP and CDRH colleagues
Required breaking down the issue into the legal and regulatory components and running through the policy review channels.
Commensurability: Medium
Only some conflict with the regulatory requirements for the instructions
Scale: Medium
Potential to impact the benefit-risk determination given the likelihood to misinterpret images without proper instructions
Comprehensiveness: Medium
Confined to the instructions for use and expert opinion, regulatory opinion not reflected in the output
FDA U.S. FOOD & DRUG ADMINISTRATION
3


QT Prolongation
Concrete Input / Output Type
Abstract Input / Output Type
Discipline
Inputs
Process
Outputs
Clinical Pharmacology, Statistics, and Clinical
QT signal reported by applicant
QT Interdisciplinary Review Team was consulted for input
Following input from QT-IRT and discussions with Clinical, the signal, while statistically significant was deemed of no clinical significance
Inter-discipline of QT Team
Expert input from the QT Interdisciplinary Review Team
Discussed with clinical and clinical pharmacology reviewers and signatory of the review team
Commensurability: NA
Scale: Local
• Confined to risk/safety
Comprehensiveness: High
• All inputs incorporated
Team that reviews QT signals within the FDA is an interdisciplinary team of clinical pharmacologists, pharmacologists, statisticians, and clinicians.
FDA U.S. FOOD & DRUG ADMINISTRATION
5


CTE Misdiagnosis
Concrete Input / Output Type
Abstract Input / Output Type
Discipline
Inputs
Process
Outputs
Clinical
Potential for off-label use
Risk was discussed and negotiated with the Applicant
Limitations of Use and Warning and Precautions was added to the labeling to prevent off-label use of the product for Chronic Traumatic Encephalopathy (CTE)
Pharmacology / Toxicology
Nonclinical Data
This process aspect was disintegrative in that attempts were made to differentiate between the published literature on FTP binding in CTE taupathologies and this specific product.
Clinical and Pharmacology / Toxicology
Published Literature (Falcon et al 2018, 2019; Marquie et al 2019; Mantyh et al 2020)
Team assessed that due to lack of evidence for CTE diagnosis, the labeling needs to address this risk
Commensurability: Low
• No observable conflict
Scale: Local
• Had this been an application for use in CTE, this would have been a global issue, but as it stands this was just an off-label issue that required enhanced labeling to mitigate
Comprehensiveness: High
• Pulled in all inputs for the final labeling recommendation
FDA U.S. FOOD & DRUG ADMINISTRATION
7


Tau [redacted]
Concrete Input / Output Type
Abstract Input / Output Type
Discipline
Inputs
Process
Outputs
Clinical, CDRH, and Statistics
Two phase 3 neuropathologic correlation studies (A16 and FR01) including study reports, case report forms, and line item data
Center for Device and Radiological Health was consulted to assess the devices used in the clinical studies
Team concluded that aggregated tau neurofibrillary [redacted] be identified, [redacted] rule out earlie
Clinical
Understanding of disease pathology, particularly earlier forms of disease
Discussed at early scoping meeting and mid-cycle meeting with review team
[redacted]
Clinical, CDRH, and Statistics
Published Literature (Hyman et al 2012)
Discussed with Applicant during development and early in the review cycle
Clinical, CDRH, and Statistics
[redacted]
Commensurability: Medium
• Conflict between the Applicant's proposal, findings from clinical studies, and published literature
Scale: Global
• This issue was related to the overall benefit-risk determination in that the Applicant was requesting a much broader indication that could have implications on multiple facets of disease management and therefore greater risk
Comprehensiveness: High
• This issue impacted the entire application and the overall benefit-risk determination given the broad indication claim and factors in all inputs
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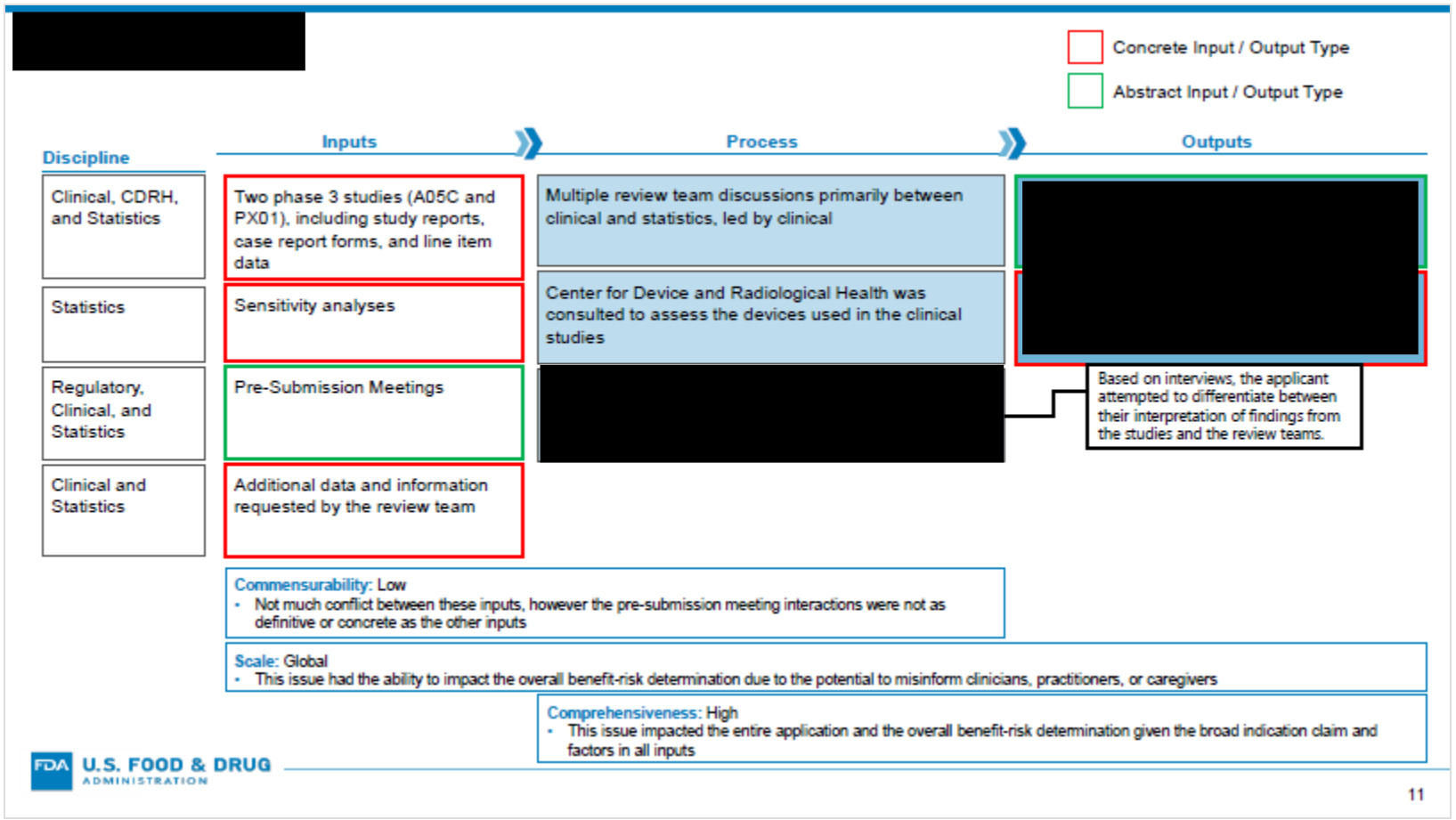
[redacted]
Concrete Input / Output Type
Abstract Input / Output Type
Discipline
Inputs
Process
Outputs
Clinical, CDRH, and Statistics
Two phase 3 studies (A05C and PX01), including study reports, case report forms, and line item data
Multiple review team discussions primarily between clinical and statistics, led by clinical
[redacted]
Statistics
Sensitivity analyses
Center for Device and Radiological Health was consulted to assess the devices used in the clinical studies
[redacted]
Regulatory, Clinical, and Statistics
Pre-Submission Meetings
[redacted]
Based on interviews, the applicant attempted to differentiate between their interpretation of findings from the studies and the review teams.
Clinical and Statistics
Additional data and information requested by the review team
Commensurability: Low
• Not much conflict between these inputs, however the pre-submission meeting interactions were not as definitive or concrete as the other inputs
Scale: Global
• This issue had the ability to impact the overall benefit-risk determination due to the potential to misinform clinicians, practitioners, or caregivers
Comprehensiveness: High
• This issue impacted the entire application and the overall benefit-risk determination given the broad indication claim and factors in all inputs
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