Biosimilars: *Costs and controversies*

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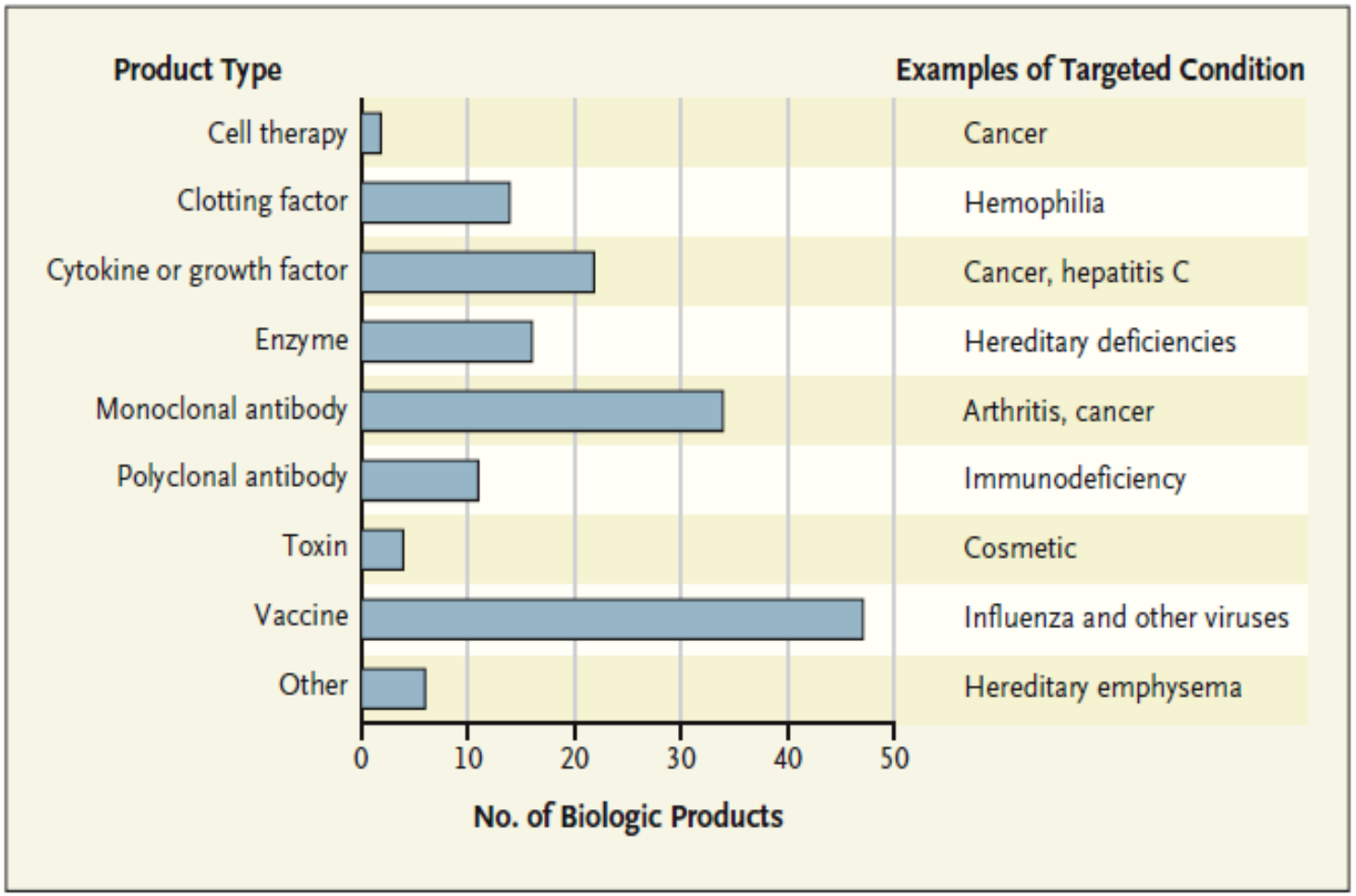
Introduction

- Biosimilars (*aka* follow-on biologics, subsequent-entry biologics, biogenerics) very important for bending the cost curve
  - fastest growing sector of the pharma market
  - high unit costs
  - more complex than chemically synthesized medicines
- No biosimilar approval pathway prior to PPACA
  - FDA rulemaking still TBA
  - major challenges for the regulator (and the science)
- Intellectual property (IP) issues
  - controversy over data vs market exclusivity
  - how long is enough / too long?

FDA Biologic Approvals



Numbers of FDA-Approved Biologic Products of Various Types Available for Treating or Preventing Various Conditions.

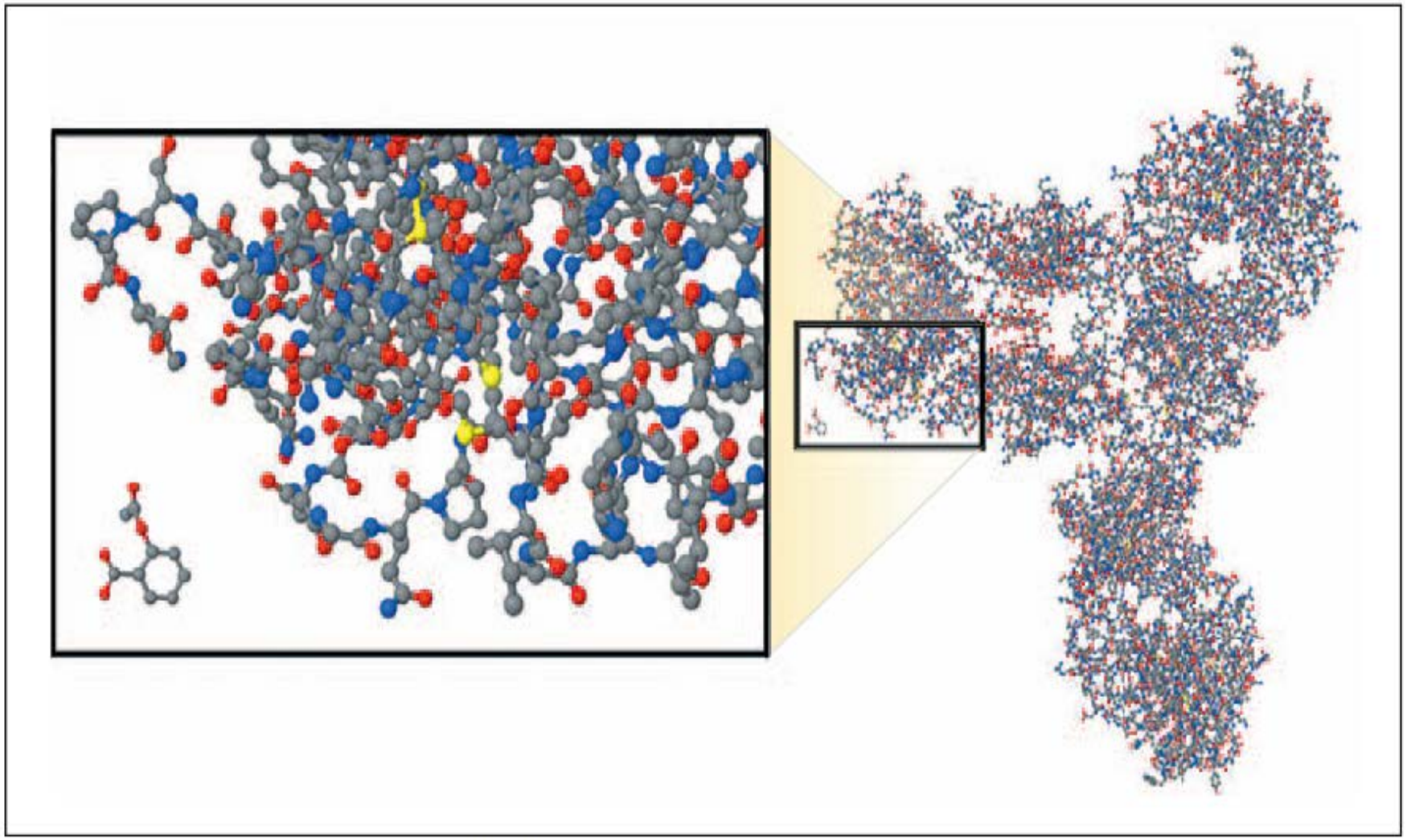
From: Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the Nation's Biosimilars Program. *N Engl J Med* 2011; 365:385-388

"It's a major breakthrough. But we're still years away from being able to justify the outrageous cost per pill."

Biologics

- Therapeutics containing biotech-derived proteins as the active substance(s)
  - include vaccines, monoclonal antibodies, hormones
- Fastest growing sector of the pharma market
  - Costs high relative to small molecule drugs, so patent expiry important
- Most biologics are licensed under PHSA, but some are approved under the FDCA.
- Late 1970s and early 1980s, recombinant proteins & monoclonal antibodies began to be developed
  - hormones (eg insulin and human growth hormone, heparins
  - drugs/CDER/FDCA
- Antibodies, cytokines, immunomodulators, clotting factors etc.
  - biologics/CBER/PHSA (though many transferred to CDER under the PHSA in 2003)

Biologics vs small molecule meds



Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

From: Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the Nation's Biosimilars Program. *N Engl J Med* 2011; 365:385-388

Licensing of generic medicines

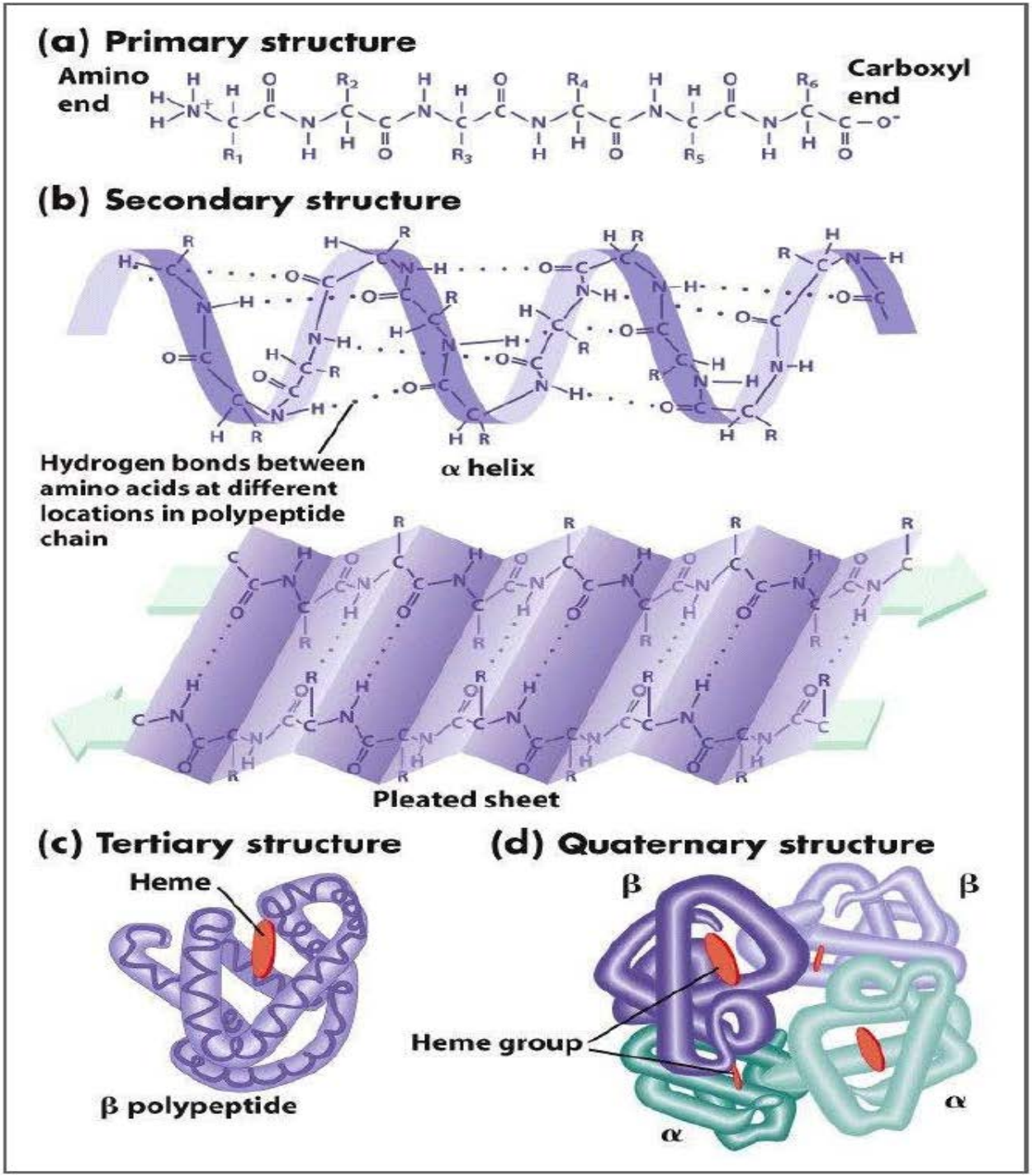
- Modern era of generics since Hatch-Waxman (Drug Price Competition & Patent Term Restoration) Act of 1984.
- Act established ANDA process – for products approved under FDCA
  - allowing a generic to be licensed on the basis of bioequivalence to a reference product
- Bioequivalent = pharmaceutically equivalent and similar bioavailability
  - same amount of same active substance in the same dosage form for the same route of administration and meeting the same or comparable standards and with same bioavailability
  - effect of drug on body the same and effect of body on drug the same
- If bioequivalent, generic may then "rely" on efficacy and safety data submitted by the originator
  - avoids need to repeat costly (and arguably unethical) clinical trials

Licensing of generic medicines

- Pharmaceutical Equivalence (PE): same active ingredients, dosage form, route, strength
- Bioequivalence (BE): same rate & extent of absorption & availability at site
- Therapeutic Equivalence (TE) = PE + BE
- Rule for 505(j) need PE + BE without need for clinical or pre-clinical studies beyond BE
- Substitutability needs Therapeutic Equivalence
- 505(b)(2)-full reports [some without right of ref]
  - Not limited to “sameness”; can be substitutable

Biologics *vs* follow-on biologics

- Follow-on biologics are biological products that are able to demonstrate a degree of similarity to an already-approved product
  - Conceptually similar to generic small molecule medicines, but can't be approved on basis of bioequivalence
- Biologics are more complex than chemically synthesised meds
  - Follow on product may have the same DNA encoding sequence but may differ in other key attributes
  - Unlikely any second manufacturer will be able to reproduce precisely the process used by the originator


(a) Primary structure
Amino end
Carboxyl end
(b) Secondary structure
Hydrogen bonds between amino acids at different locations in polypeptide chain
α helix
Pleated sheet
(c) Tertiary structure
Heme
β polypeptide
(d) Quaternary structure
β
β
Heme group
α
α

Approval Pathway for Biosimilars

- Hatch-Waxman provisions do not capture most biologics
- Pathway set out in PPACA in Title VII (Biologic Price Competition and Innovation Act 2010)
  - amends s351 of PHSA
  - pathway analogous to ANDA process - but with key differences
- BPCIA created serious scientific and policy challenges for FDA
  - evidentiary requirements
  - how similar is similar?
  - is interchangeability possible? (biosimilar may be substituted for the reference product without prescriber's intervention)
  - nomenclature
  - pharmacovigilance
  - data/market exclusivity

Provisions of BPCIA

A follow-on biologic is required to demonstrate it is *biosimilar* to a reference product based on data derived from

i) studies demonstrating that the biological product is *highly similar* to the reference product (notwithstanding minor differences in clinically inactive components);

ii) animal studies (including the assessment of toxicity); and

iii) clinical studies sufficient to demonstrate safety, purity, and potency in one or more conditions for which reference product is licensed.

The biosimilar and reference products must utilize the same

- mechanism(s) of action (to the extent these are known);
- route of administration,
- dosage form,
- strength and
- proposed indication(s) and

the manufacturing facility must meet appropriate standards

Provisions of BPCIA - *Interchangeability*

"A (follow-on) biological product … may be deemed *interchangeable* with the reference product… if it is

- biosimilar to the reference product;
- can be expected to produce the same clinical result in any given patient; and
- where administered more than once to a patient, the risks (in terms of both efficacy and safety) of switching between the follow-on biological product and the reference product are not greater than the risks of using the reference product alone. "

and where '*interchangeable*' is defined as

- "… (able to) be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

Scientific / Regulatory Challenges for FDA

- FDA currently developing evaluation criteria to determine how similar a biosimilar must be
  - these will likely vary according to product type
  - animal & clinical studies required "for the foreseeable future" but scope and extent will vary
  - applicants will need to "carefully tailor" animal & human testing to address any "residual uncertainty.
- Pharmacovigilance
  - even small changes in manufacturing process can affect S&E
  - potential for immunogenicity a key issue
  - critical to have identification of product for PV processes
- For products claiming "interchangeability," additional data requirements.
  - interchangeable products may be substituted for reference product without reference to the prescriber
  - standards to ensure biosimilar products that are not interchangeable, are not substituted w/o prescriber's consent.

Safety / Immunogenicity

- An immune response to a therapeutic protein can range from clinically insignificant antibodies to a substantive impact on safety and/or efficacy
  - neutralising antibody responses can reduce efficacy
- Adverse immunogenic responses can include
  - immediate or delayed hypersensitivity reactions
  - cross-reaction with an endogenous protein
- The ability to predict immunogenicity is very limited
  - some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed.
  - epoetin alfa *
- For a biosimilar to be interchangeable (substitutable)
  - repeated switching from the follow-on product to the reference product (and vice versa) w/o adverse effects

* Macdougall IC. Pure red cell aplasia with anti-erythropoietin antibodies occurs more commonly with one formulation of epoetin alfa than another. *Current Medical Research and Opinion* 2004 20;1:83-86.

Casadevall N, Nataf J, Viron B, et al. Pure red cell aplasia and anti-erythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346:469-75

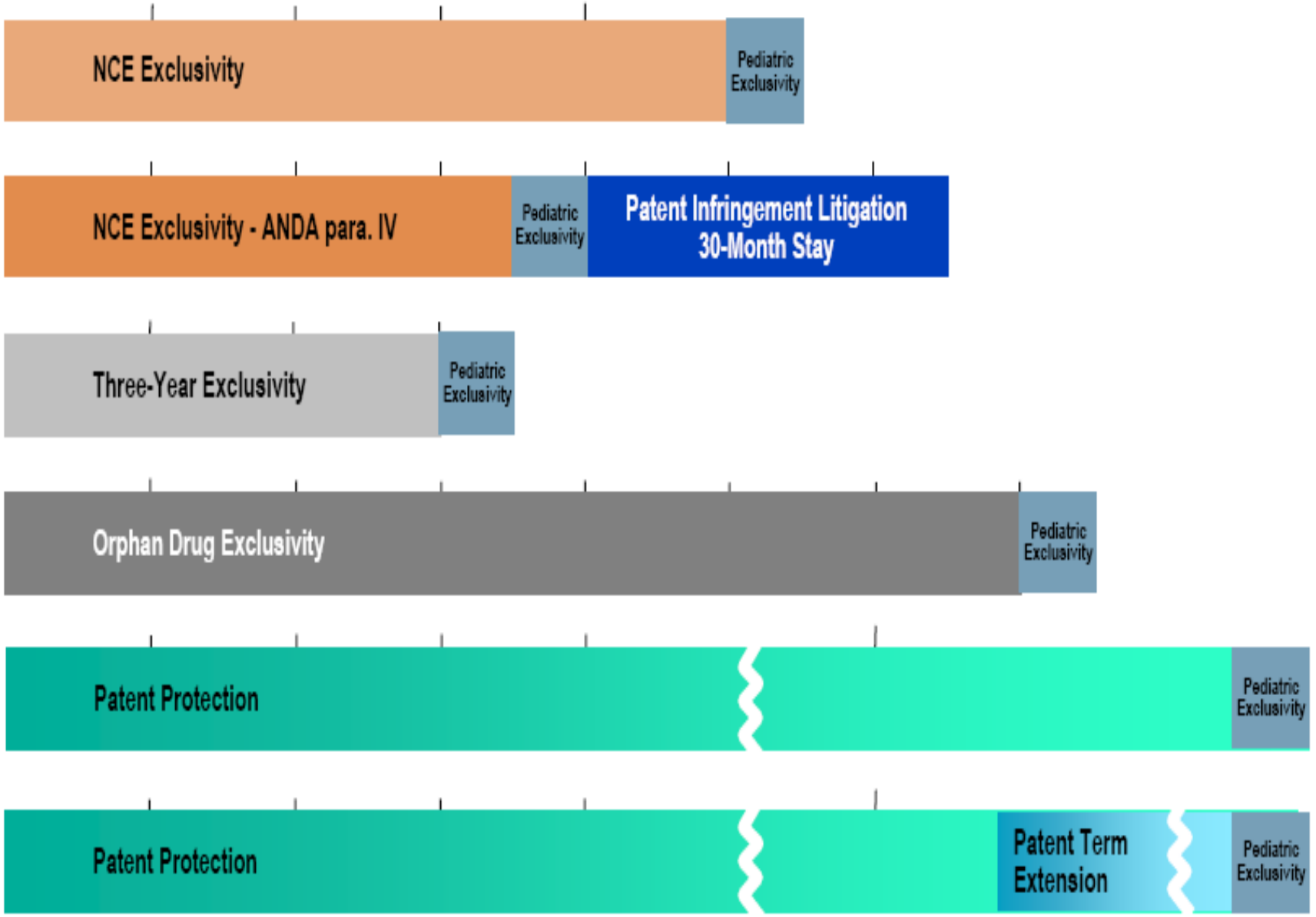
Hatch-Waxman and Data/Market Exclusivity

- Hatch-Waxman established minimum periods of exclusivity for new chemical entities (NCEs).
- Period commences on first day of registration of NCE
  - during which FDA may not accept an ANDA – or may not approve it – irrespective of patent status of originator.
- Confers monopoly protection via the regulatory process in addition to that conferred by a patent
- US has complex exclusivity schema

Data/Market Exclusivity

- Market exclusivity for NCE – 5 years – with 4 years data exclusivity
- Plus 3 years for change in an approved drug product
  - eg new indication, dosage strength, dosage form, route of administration, patient population, conditions of use
- Orphan drug exclusivity – 7 years
- Pediatric exclusivity – 6 months
  - subject to FDA request for pediatric studies but trials *need not result in a labeling change*
  - extends Hatch-Waxman exclusivity by 6 months
  - extends orphan drug exclusivity by 6 months
  - *also extends patent term by 6 months*
  - extends to all approved formulations, dosage forms and indications
  - more than one period of pediatric exclusivity possible

Exclusivity Schema before Biosimilars



And for biosimilars …

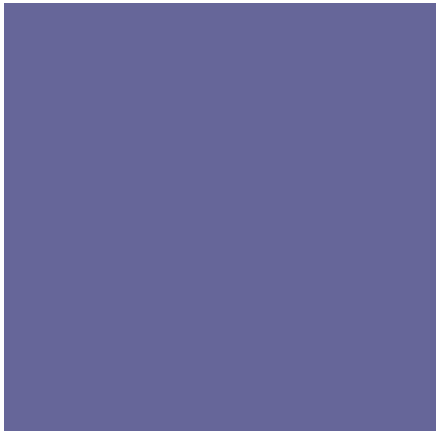
- Under BPCIA approval of a follow-on biologic application
  - "… may not be made effective … until 12 years after … the reference product was first licensed", and
  - "an application may not be submitted to the Secretary until 4 years" after that date".
  - seems to be describing *4 years of DE* and *12 years of ME*
- Yet members of Congress say this "inconsistent with their intentions"
  - intended to provide 12 years of *data exclusivity*, not *market exclusivity*.
  - to prevent the FDA from allowing another manufacturer to rely on the data of an originator to support approval of another product
  - but not to "*… prevent another manufacturer from developing its own data to justify FDA approval of a similar or competitive product*."
- President Obama's 2012 budget proposal seeks to reduce the 12 years of exclusivity to 7

Implications for the biosimilar market

- Competition between originators and FOBs unlikely to model that of generic and branded small molecules; originators likely to maintain significant market share
- BPCIA gives FDA substantial discretion but
  - evidentiary requirements much greater than for small molecule generics
  - clinical trials to support claims of interchangeability and exclude differences in immunogenicity much more expensive and longer than the bioequivalence trials
- Uncertainty and costs associated with biosimilars may limit the number of players – enough to generate price competition?
- Issue of acceptability of biosimilars to prescribers and patients.
- FTC view that costs of FDA approval and developing manufacturing capacity likely to limit the number of market entrants;
  - lack of automatic substitution will limit rate and extent of acquisition of market share;
  - considers 12 years ME unnecessary to "*protect innovation*"

Thank you

Questions?



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