5th EGA Symposium on Biosimilars

Perspectives on the Waxman Legislation and EU Implications

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May 3rd, 2007

London, UK

Outline

- Biologics and Biotechnology in the US
- The US Regulatory Environment
- What is new about Follow-on Biologics today
- Economics
- Legislation
- Conclusions

BIOLOGICS

What is a Biological Product?

The FDA Description of a Biologic Product

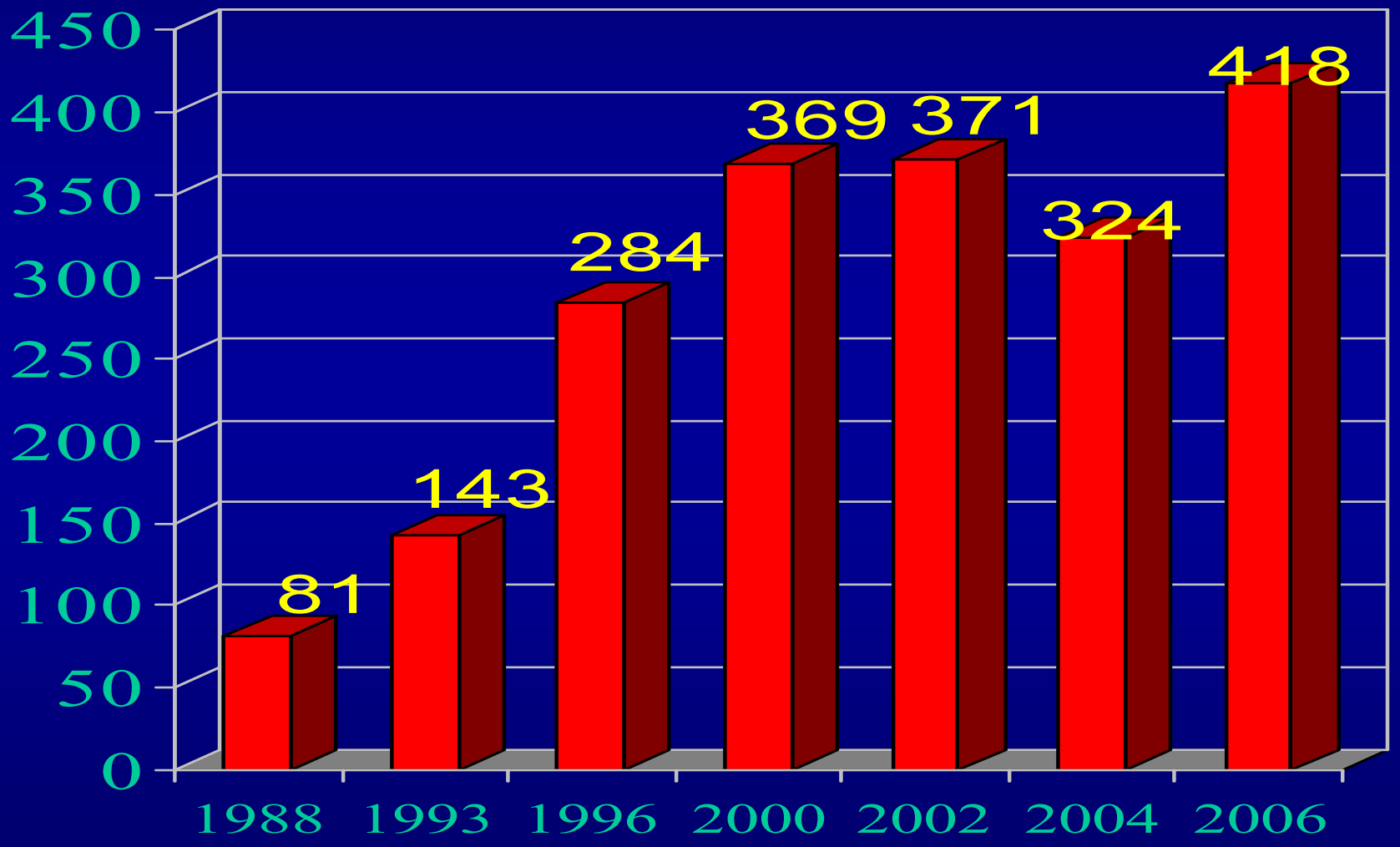
Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies.

i.e. Biologics are a lot more than biotech

Biotech Products are a Subset of Biologics

- Biologics have been important components of healthcare for centuries, but historically were derived from natural sources, for example, Smallpox Vaccine 1798, blood transfusion 1901
- Biotechnology enables unlimited production of homogeneous, complex biologics without the infectious disease risks of natural sources, and is non-depleting of those natural sources
- Biotechnology enables designer-molecules, i.e. the creation of those that do **not** occur naturally but that may offer therapeutic advantages
- Biotechnology products often have patents, most traditional biologics do not, but these are expiring
- **The biotechnology industry is a follow-on industry**

Biotechs are an Increasing Proportion of the US Pipeline



* Reference PhRMA

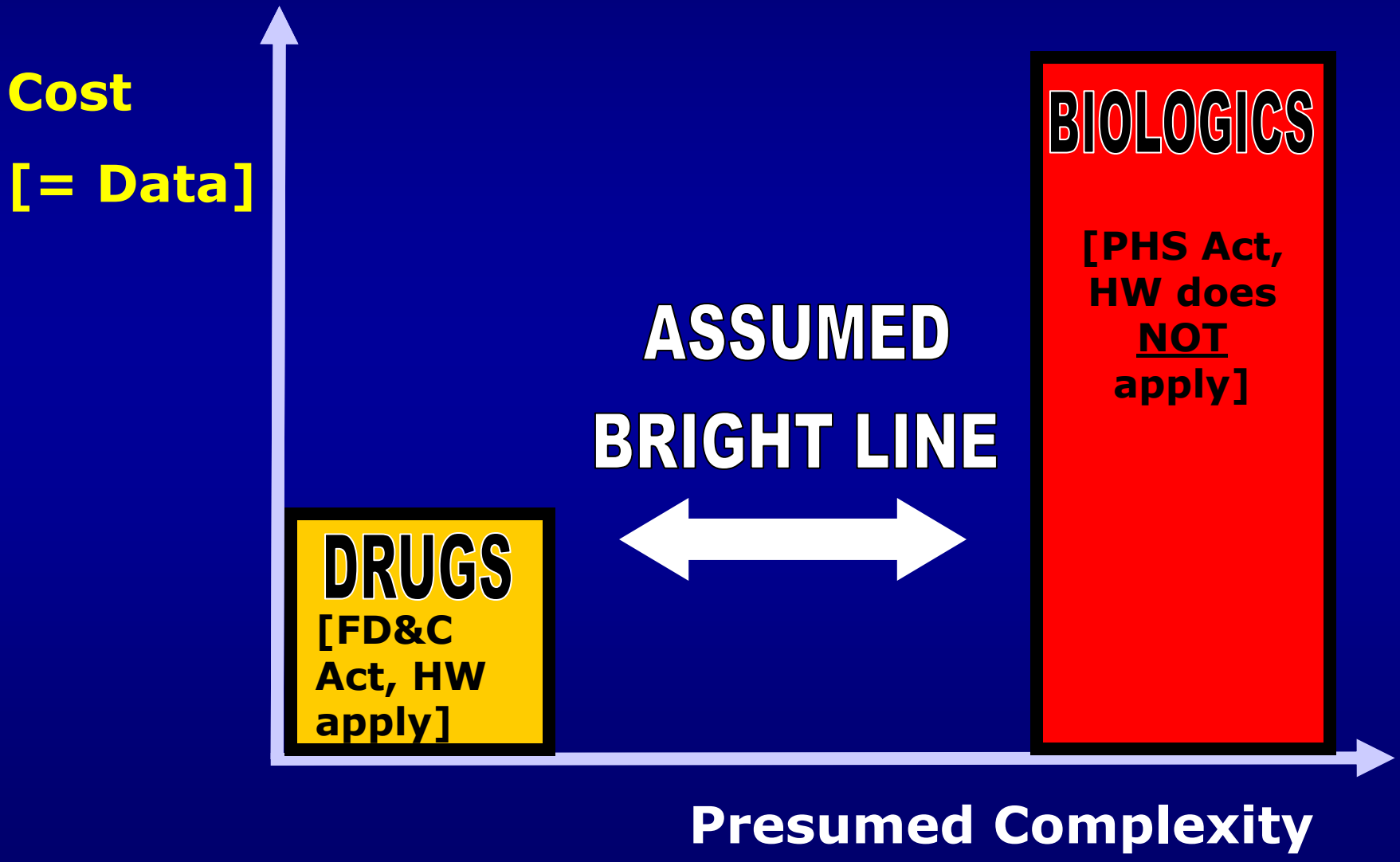
The US Regulatory Environment

FDA determines what choices will be available in the market place to both payors and patients

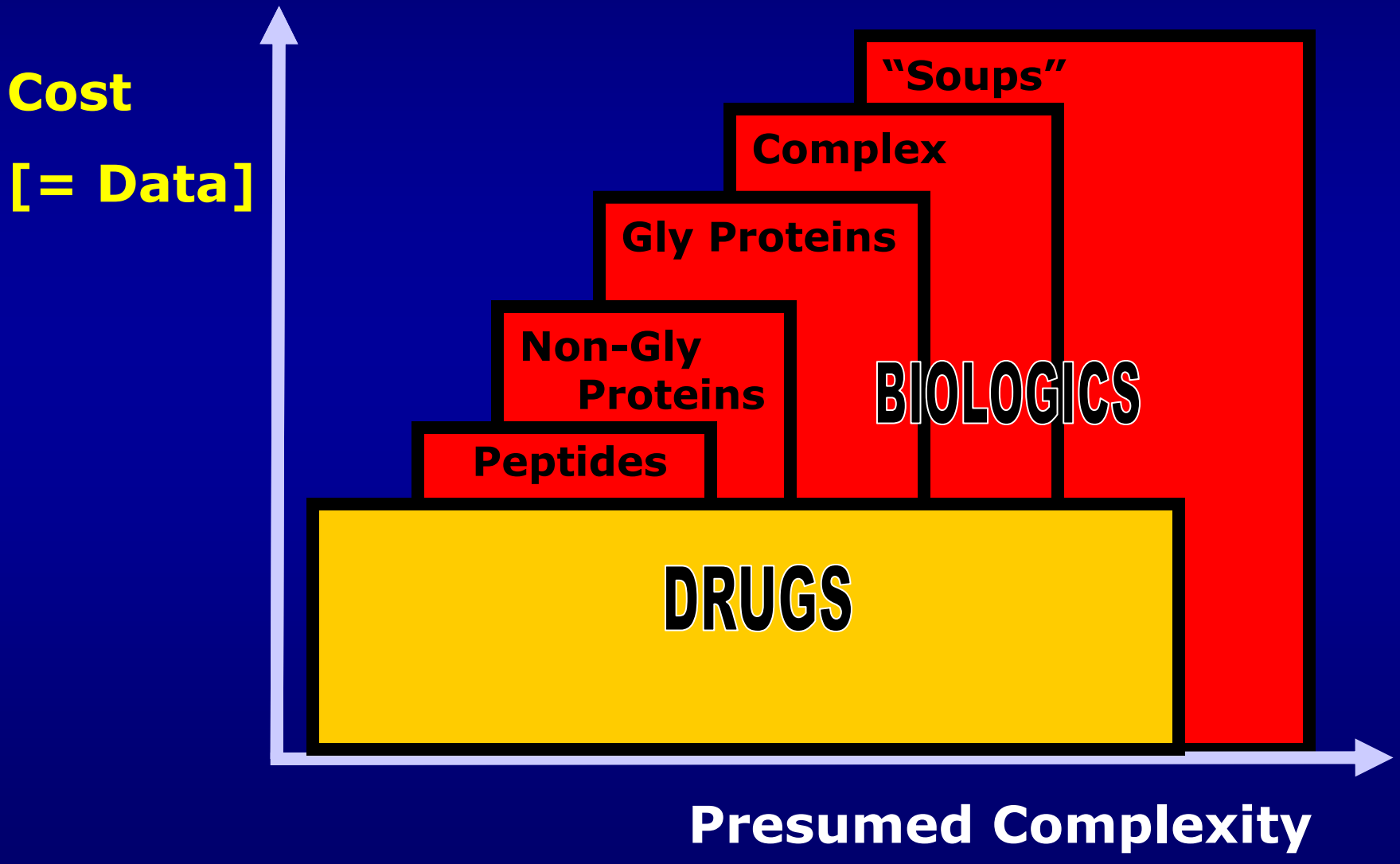
US Regulations for Biologics

- The evolution of regulations in parallel with progress in technology has create situations that appear inconsistent. This becomes particularly difficult to address using scientific parameters in a highly political environment
- Historically, the US regulated drugs and biologics separately, but these distinctions are being lost for largely technical reasons, yet the statutes remain and continue to apply.
- FDA and industry experiences have created precedents that have become the opportunity and legitimate basis for FOBs, especially comparability

Scientific Basis of Regulatory Distinctions - the aspirin vs. Epo view



No Bright Lines…



Two Regulatory Statutes = Two Sets of Regulatory Criteria

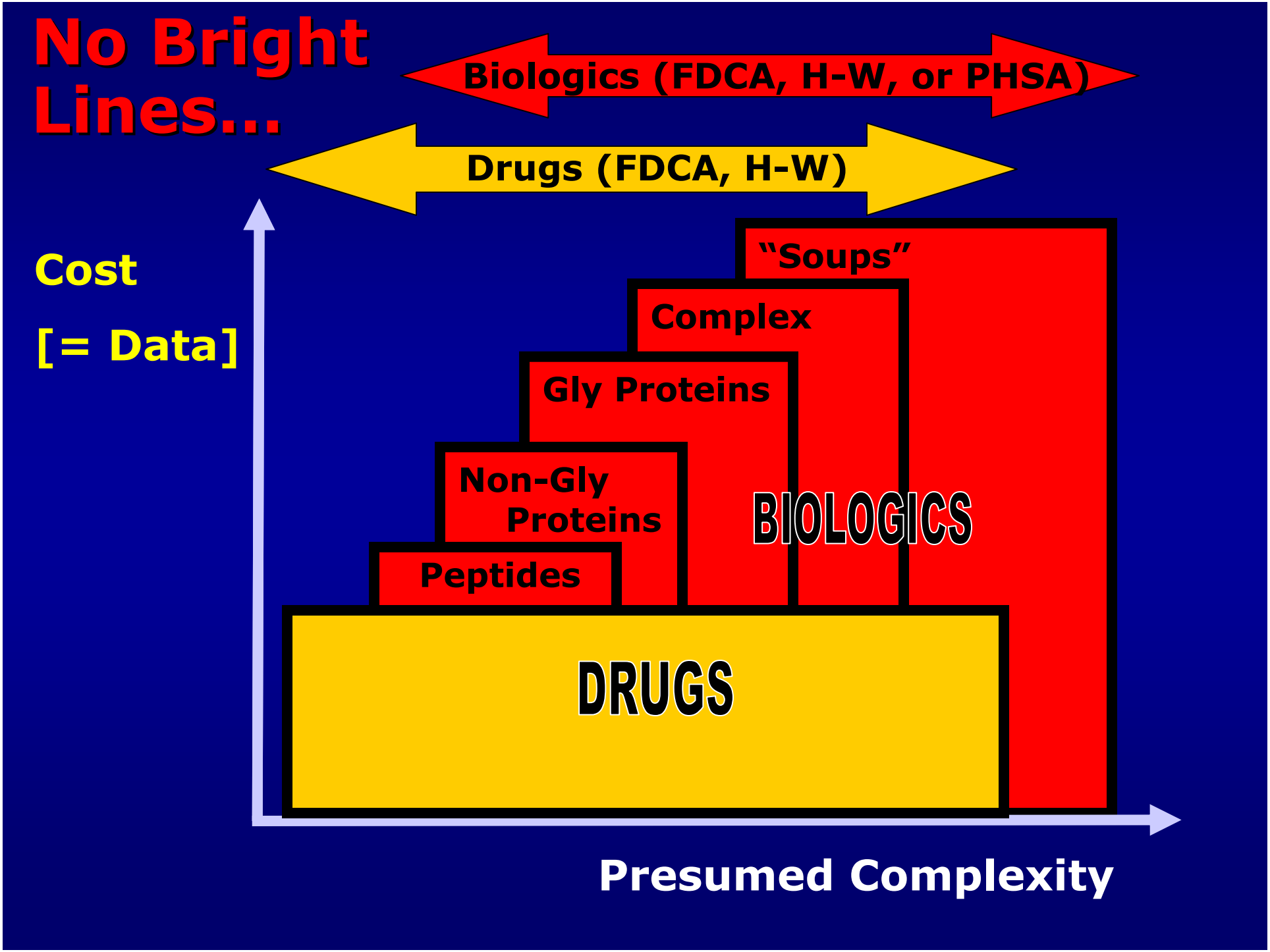
Two statutes govern US approval of medicines, including biologics:

- PHS Act (~1902) — includes traditional biologic products such as vaccines and blood products, as well as recombinants
- FD&C Act (1938) — include small molecule drugs, but also the so-called biologic drugs

Plus:

- Hatch Waxman (1984) – generic drugs, including biologic drugs, and they may or may not be substitutable (ANDA, and 505(b)(2))

No Bright Lines...



Biologic Drugs Traditionally Reviewed by CDER as Biologic Drugs under FD&CA

- A variety of products, mainly hormones – including complex naturally-sourced products, and recombinant products, such as:
  - Low Molecular Weight Heparins, Lovenox
  - Naturally-sourced hormones, Menotropins,
  - Naturally-sourced hormones that were subsequently made using recombinant DNA technology, such as Insulin, Human Growth Hormone, Glucagon, FSH
  - Naturally-sourced hormones that were subsequently made synthetically and by recombinant DNA technology, Calcitonin
- **For these the Hatch Waxman pathways already exist – ANDA and 505(b)(2)**

Therapeutic Biologics transferred to CDER but still BLA's under PHS Act

- Therapeutic recombinant biologics were transferred to CBER in 2003. These products are now distributed across the review divisions of CDER. The biologics included are:
  - Monoclonal antibodies for *in-vivo* use
  - Proteins intended for therapeutic use, including cytokines, enzymes, and other novel proteins
  - Immunomodulators
  - Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells *in vivo*
- NOTE: These are different from the biologics drugs that have been reviewed as drugs in CDER since at least 1991 and that are FD&C Act regulated. **The Hatch-Waxman pathways are NOT available**

Follow-On Biologics Have Existed Since 1982

- The original recombinant versions of previously, naturally-derived biologics were the first FOBs, e.g., insulin, rHGH, glucagon, calcitonin, hyaluronidase
- Improved versions of previously-licensed biologics, or second-generation biologics, are also examples of FOBs as they build on specific prior knowledge, e.g. *Aranesp* is a longer-acting epoetin than *Epogen*
- In 2006 the first recombinant follow-on to a recombinant innovator biologic was approved in both EU and US, i.e. *Omnitrope* (somatropin), but it is not an ANDA/generic

So what is new about Follow-on Biologics today…

For The Innovator Industry…

- Biotechnology continues to advance by leaps and bounds, and is enabling more efficient production, as well as technology platforms for improvements
- Use of **comparability** to enable manufacturing changes for innovator products is commonplace (since 1996), and there is no credible conceptual barrier to FOBs

i.e. The product is <u>not</u> the process

- **Patents are expiring** – It is estimated that >$18B will be off-patent by 2010. The patent on EPO has expired in Europe (~2013 US), and its global market alone is ~ $8B
- <u>But</u>, as innovation gets more expensive, innovators vigorously protect their existing franchises

And Likewise For The Generic Drug Industry…

- Competition in the classic generic drugs business is increasing, but the expected future pipeline is more limited, hence the margins are getting tighter
- Biopharmaceuticals represent more of the future pipeline: ~12% of Rx, the market was ~$43B in 2004, and by 2010 it is forecast to be ~$67B
- Well over 1/3 of medicines in development are now biotech-based
- Emerging biotech companies may include FOBs in their business models, but have little capital or experience in manufacturing
- The future generic business model has to include biologics, but not all generic companies can engage

US Regulatory Considerations – Constraints And Opportunities

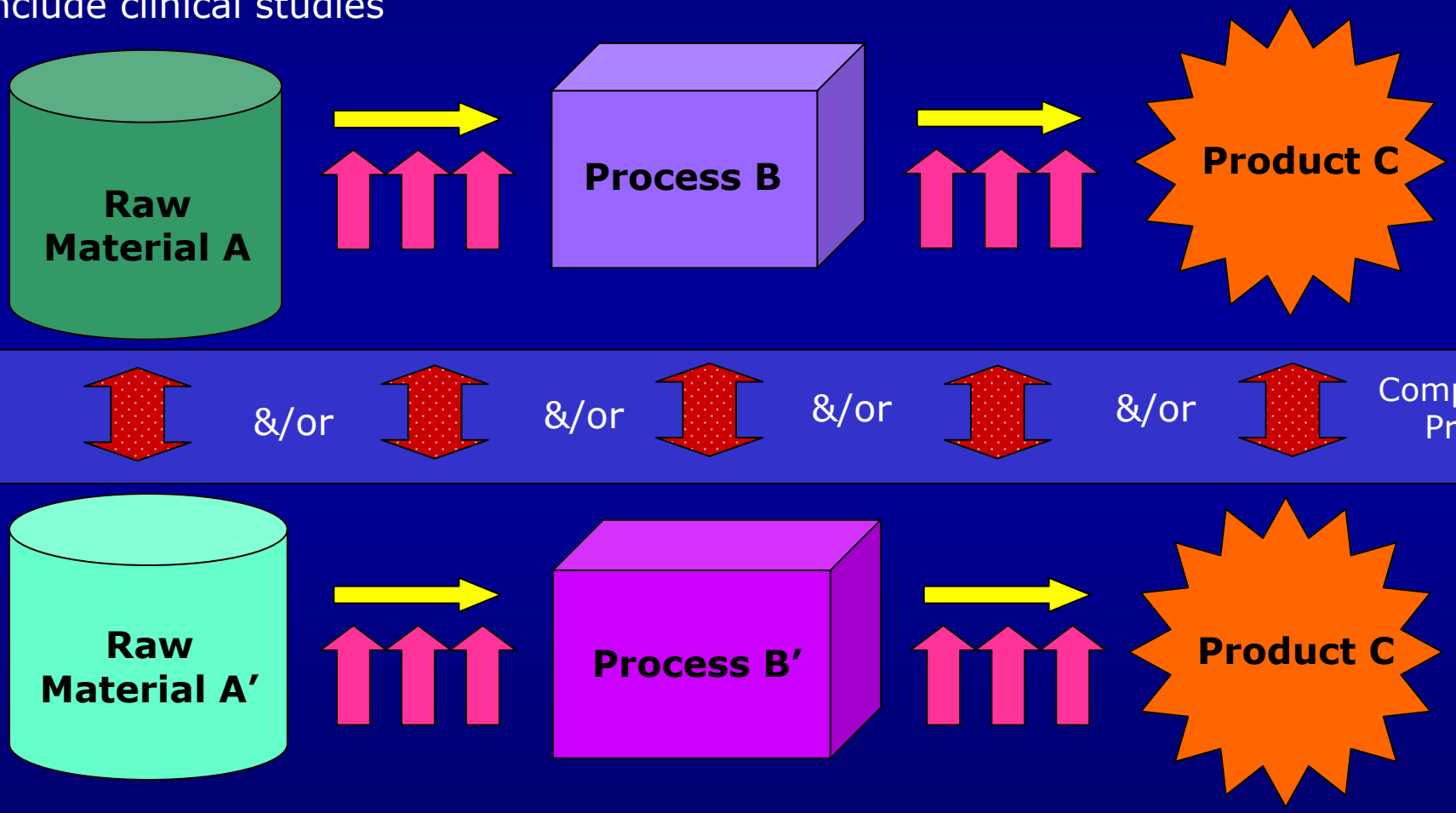
- Biologics are complex, but we continue, albeit slowly, to approve innovator products - by definition the ones we know the least about
- Biologics and drugs are presumed to be different, but only the US has distinct regulatory routes, and the EU is setting "biosimilar" precedents "safely"
- Patient safety is important, but so is access, cost matters
- Approval of FOBs are presumed to be a loss for innovator manufacturers, but a revisiting of the regulatory standards for biologics could benefit innovators… … as well as patients
- **FDA has said they can approve safe interchangeable FOBs today**

Comparability as a Regulatory Principle

- Comparability was described by the FDA in their 1996 Guidance and has been used successfully ever since by innovators making manufacturing changes to their own products
- It was a concept adopted in EU, as part of ICH, and ultimately as a basic principle in the evaluation of biosimilars in EU.
- It is rigorous, science-based and enables a data-driven process by which regulators determine comparability is substantiated
- **Comparability presupposes interchangeability** of the product before and after the manufacturing change

Comparability for Biologics in the US today…

The Sponsor of C can change any attribute of A or B, as long as they pre-agree with the FDA how they will assure no change to C by doing specific studies (that *may* include clinical studies



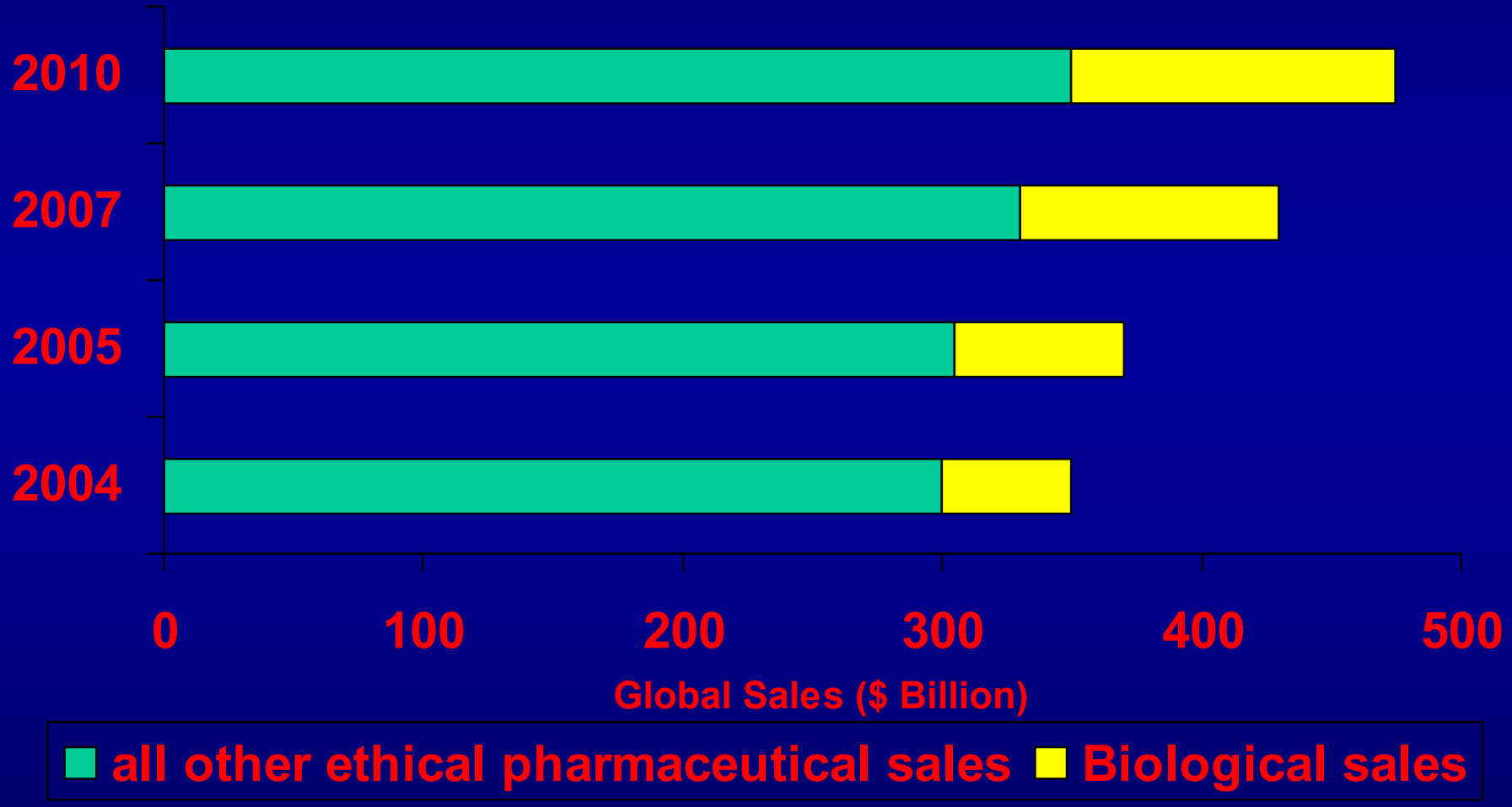
Economics

Ultimately it will be the money that drives the debate

The Economic Drivers for FOBs are Inevitable and Increasing

- Medicines are a critical part of health care worldwide, but prices vary considerably and conspicuously in different countries. US prices tend to be high.
- Healthcare costs are significant and increasing, and growing Rx prices/use in the US are **very visible**, and have garnered political attention at all levels
- Biologics are more expensive on a per patient basis, **biotech products are coming off patent**, and the opportunities for FOBs are increasingly apparent to biopharma companies, payors, and patients
- **Arguments for free-market pricing of drugs evoke an <u>expectation of competition</u> in the market place when patents have ended**

Biotechnology Represents A Growing Percentage Of Rx Sales



* Reference: Data from 2006 Nature Reviews

Summary of Potential Savings with FOBs

Source			
Population	Entire US Population	Entire US population, but reported Federal Government savings	Medicare Part B beneficiaries
Timeline	Rolling 10-year period	2008-2017, with no savings 2007-2012	"next ten years" beginning with pathway available in 2007
Therapies Evaluated	Erythropoietin, Interferons for Multiple Sclerosis, Growth Hormone for growth deficiency, Insulin for diabetes	Non-specific therapies. (Erythropoietin excluded almost entirely due to timeline and gradual market movement)	All PHS Act regulated biologics within the top 200 HCPCs that are currently reimbursed by Medicare Part B
Assumptions	Product specific analysis to calculate movable market share. Substitution rates of 83.4% (directly substitutable) and 49% (therapeutically substitutable). 25% discount on biogeneric products.	Assumes 10% of biologic spend goes off patent per year. Market penetration reaches 60% over 3-year period. Large revenue products reach discounts of 30%, medium revenue products achieve 10% discount.	Assumes only a single competitor to each already-approved biologic when it goes off patent (and that all patents are valid); that the savings will begin at 15% rising to 30% over 10 years
Conclusion	**$71 Billion** savings opportunity in ten years following approval of generic biotech products.	Federal Government can save **$3.6 Billion** over ten years	Medicare Part B can save **$14 Billion** over next 10 years.

Billions in *potential* savings…

- Legislation is proposed, and CBO will "score" it (typically as estimated savings over the 10 years from the date of enactment), billions get attention
- The longer the debate, the more billions we are talking about (especially since the trajectory of biotechnology's success, plus ~20 years patent life is just beginning)
- And the more market exclusivity sought, the greater the cost → ergo the tougher it will be to justify more years of exclusivity the longer the debate continues
- **The Brand leverage is rapidly decreasing, and legitimate opportunities are being lost**

Legislation

The US Congress, both the House and Senate, are engaged

The US Legislative System

- Congress has two chambers – Senate and House
- Members of each can propose legislation, various committees hold hearings, vote on bills, and legislation reaches the "floor" of each chamber
- If the bills passed by the two chambers are different, then they need to be reconciled, often by Conference Committee, before going to the President
- The President can veto, and 2/3 majority in each chamber is needed to over-ride his veto
- If all steps are achieved, legislation is enacted, and then, if necessary, the promulgation of regulations by the responsible agency can begin

FOBs Legislation

- FDA has stated that legislation is necessary for them to approve, as interchangeable, FOBs under PHSA (but can approve substitutable FOBs for biologics drugs under FD&C Act today)
- Innovators have been reluctant to engage in a substantive debate and make FOBs happen sooner
- Generic companies have traditionally resisted any requirement for clinical trials, or indeed anything over and above the statutory requirements for innovator biologics, but are engaged in the legislation in a way the innovators are not
- Legislation was introduced last year and has been reintroduced this year, now in a Democratically controlled Congress

Waxman-Schumer-Clinton "Access To Life-Saving Medicines Act"

- Identical bills re-introduced in House (H.R. 1038) and Senate (S. 623) on 14th February 2007
- Grants FDA the authority to recognize PHS Act biologics as interchangeable, based on comparability data (NOT a "sameness" standard like that for Hatch-Waxman generic drugs)
- Pro-competitive, market-based solution that allows the pathway to be used to license second-generation products too
- Includes other non-pathway-related provisions
  - Optional patent notification process
  - Exclusivity to first sponsor to qualify for interchangeability

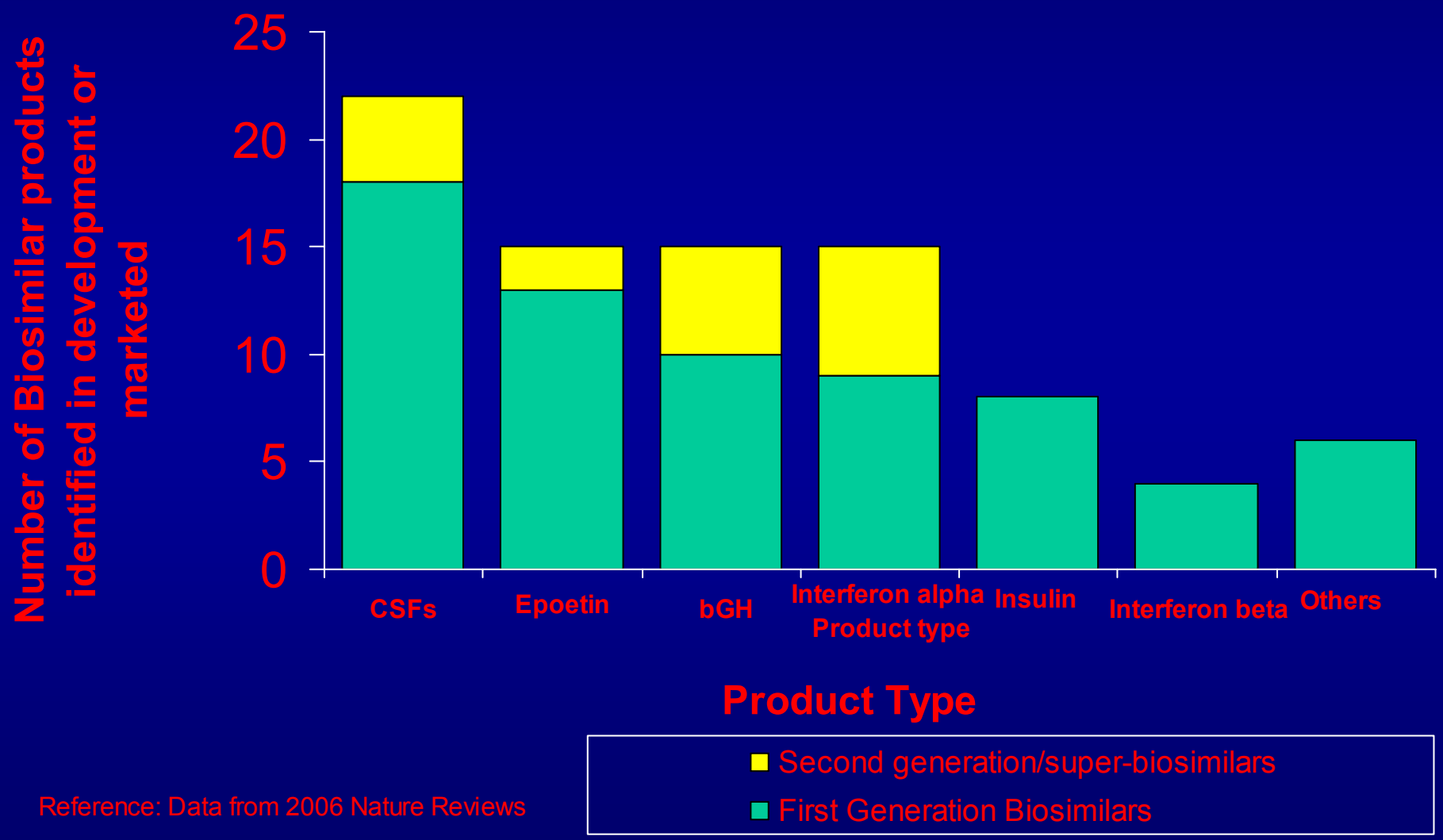
What Next For The Legislation…

- Senate H.E.L.P Committee (Chair Kennedy) held a hearing March 8th, 2007
- House Oversight and Govt Reform Committee (Chair Waxman) held a hearing March 26th, 2007 at which FDA testified and said they would be able to approve interchangeable FOBs safely today
- Administration Statement of Policy (SAP) saying the science needs "more discussion"
- House Committee on Energy and Commerce (Chair Pallone) Hearing May 2nd, 2007
- Kennedy has said that a FOBs bill will be added to PDUFA ("MegaDUFA") which is "must pass" legislation, but that may have changed. October 1, 2007 FDA needs PDUFA fees to maintain 52% of the review staff

The Future

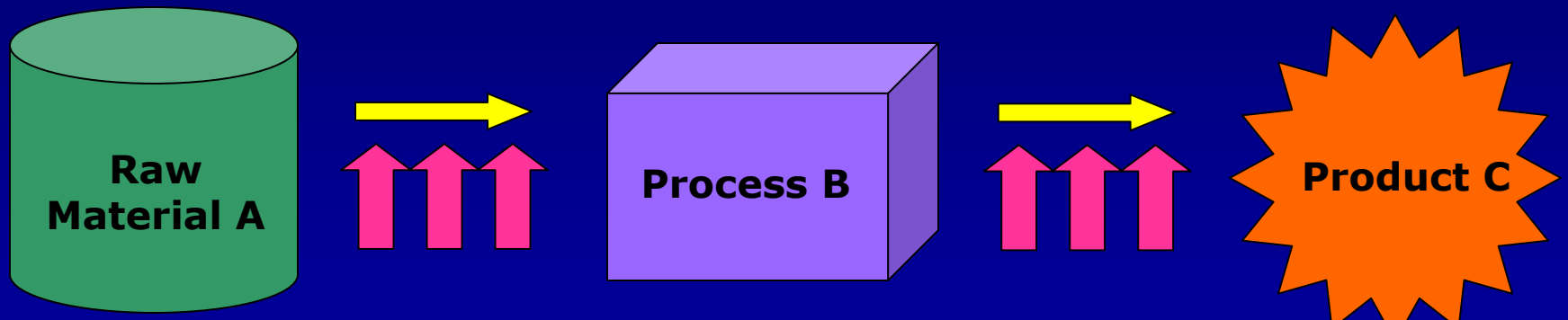
Is happening now…

FOBs In Development

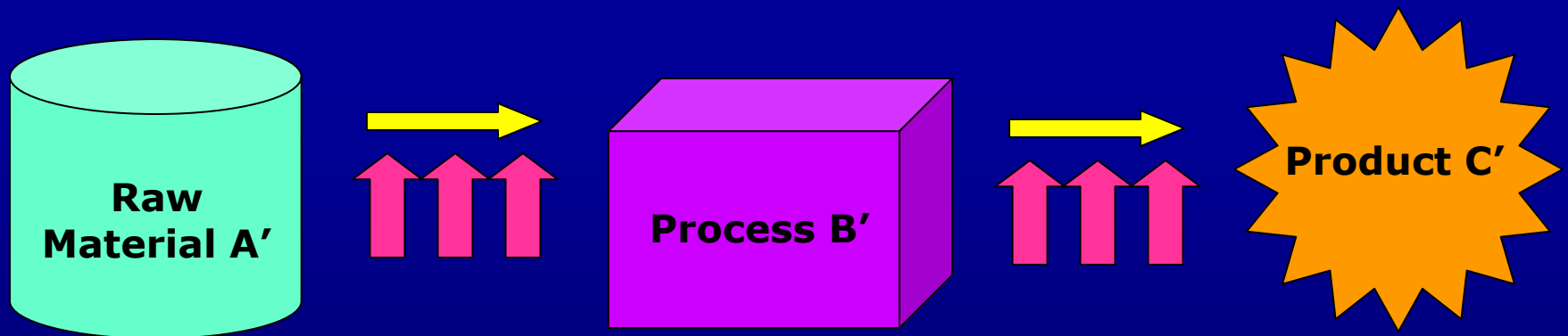


Reference: Data from 2006 Nature Reviews

US has non-interchangeable FOBs…



As long as A and B stay the same, C can be sold without more clinical trials

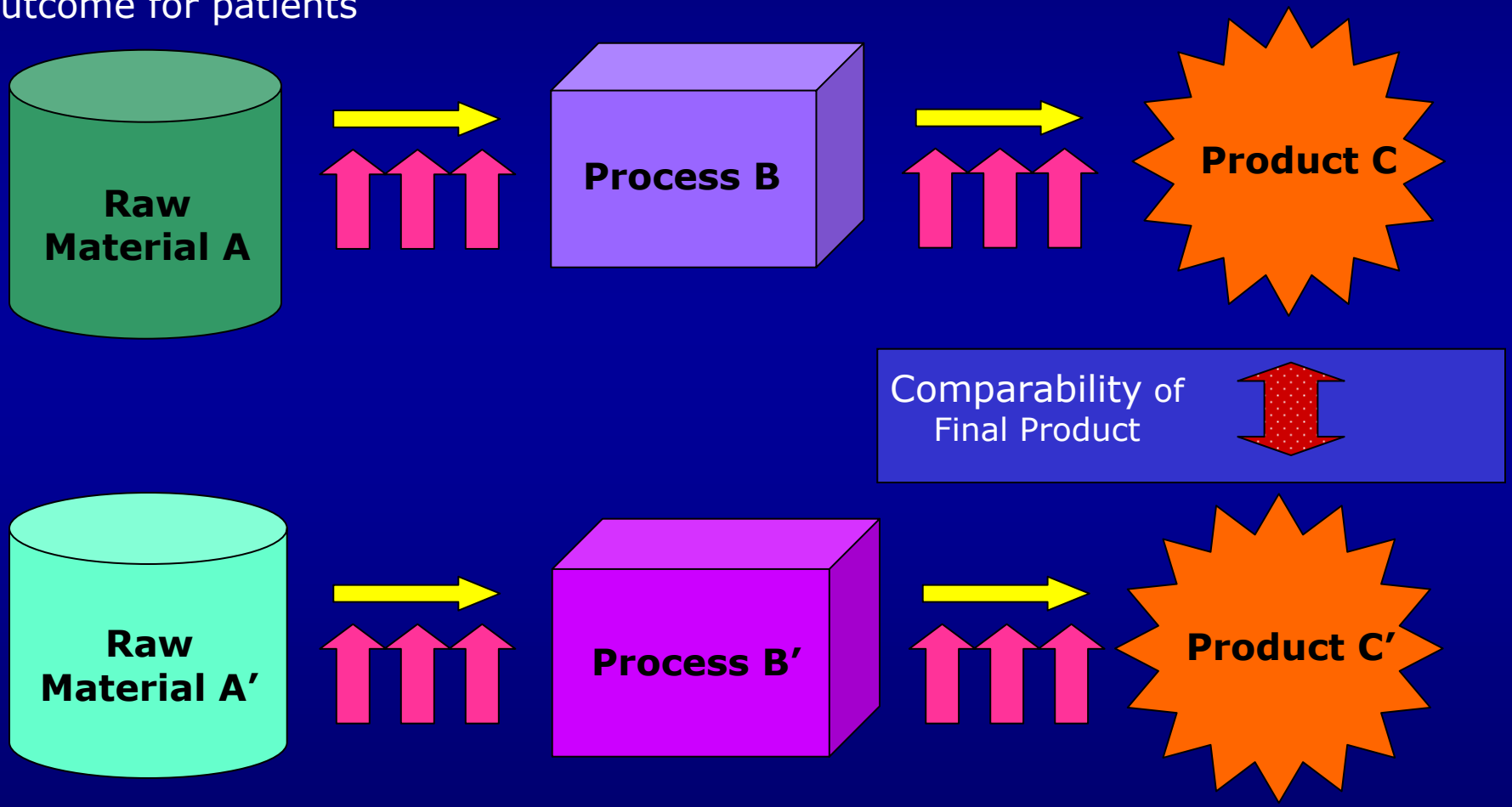


C' can be made and licensed today.

The only question is by what criteria at C and C' judged to be interchangeable

Comparability proposed for FOBs…

The Sponsor of C' will change A or B, but must provide data, including clinical, to demonstrate to FDA that C and C' are comparable and give the same clinically outcome for patients



= comparability tests final product – analytical, preclinical and clinical

The Debate is Getting Simpler…

- FDA approves innovator products based on their evaluation of the data submitted, and the innovator companies with FDA developed the concept of comparability. FDA can continue this leadership by being allowed to approve interchangeable FOBs to PHS Act products
- Market-based pricing is best justified by free-market competition: The best arguments for premium, market-based pricing of innovator products will be competition, and a willingness of the innovators to further innovate, when the patents on the original products have expired.
- The EU regulatory system suits the EU healthcare environment of single payor systems and price controls, the US has important differences: Science is global, the biopharmaceutical industry is global and the market place is global. Products available in Europe and not in the US will get political attention. Pressures for importation will increase including through mail order and internet routes.

Politics Matters to the biopharma industry

- For the patient, what matters is that all biotech products are made to consistent and appropriately high regulatory standards, and that those standards rely on data that supports the statutory requirements of safety, purity and potency
- Unless industry works with regulators, and other stakeholders, regulatory requirements will continue to increase for no net benefit in safety, or efficacy – especially in a post-Vioxx world
- The truly innovator medicine is the one we will always know the least about at licensure
- It is highly risky for innovators' own portfolios to overplay safety fears on FOBs, as innovator BLAs are stumbling as a result of those arguments

Conclusions

- An aging population will continue to demand more health care and Rx will continue to be an increasing proportion of that care; and biologics, including specialty pharma, a higher proportion of that Rx
- Medicare Drug Benefit makes the Federal Government role in reimbursement more significant, and many more aware of costs
- The biotechnology-based industry can afford to recognize its own success and help design its own future
  - Including legitimate, high-quality FOBs but impose consistent regulatory standards on all biologics
  - Be seen to encourage competition
  - Seize the opportunity to use comparable state-of-the art technology to reduce the regulatory burden appropriately on innovator products

Any Questions?

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