

Biosimilars 2007, George Washington University

**Achieving A Middle Ground On
Biosimilars Legislation:
Balancing A Robust Scientific Pathway
And Respect For IP Rights
(Promoting Continued BioPharma Innovation
While Advancing Access To Medicines)**

JOHN M. ENGEL, ESQ.

MANAGING PARTNER

ENGEL & NOVITT, LLP

THE LAW FIRM THAT KNOWS ITS SCIENCE

September 24, 2007

Washington, DC

OUTLINE

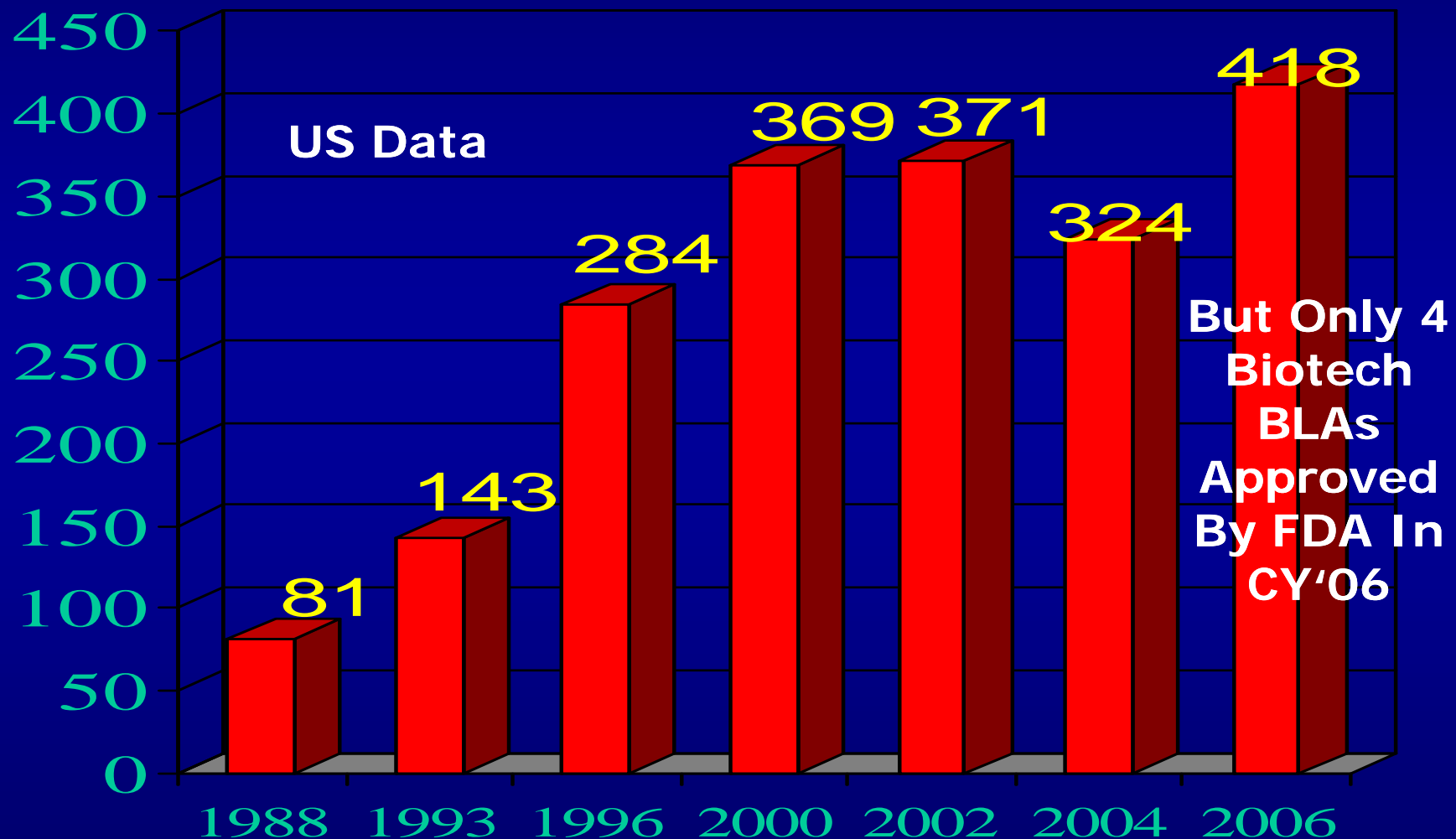
- Biopharmaceuticals Play A Crucial Role In An Era Of Significant Scientific And R&D Advances
- Barriers To Entry For Biosimilars Will Be Overcome As The Industry Evolves And As Science Advances
- Biosimilars Represent A Myriad Of Opportunities For The Breadth Of The BioPharma Industry
- Data-Driven Scientific Standards Can Be Applied Consistently In A Robust Biosimilars Pathway
- Balancing Intellectual Property Rights (IPRs) To Enable Innovation And Access To Medicines
- Legislative Options And Opportunities – A Robust Biosimilars Pathway With Data Exclusivity And Decoupling Of Patents
- Conclusions – A Middle Ground On Biosimilars Legislation Is Achievable

The material and viewpoints set forth in this slide deck and conveyed during this presentation are presented by the author in his capacity as Managing Partner of Engel & Novitt, LLP. They do not represent and do not purport to represent the views of the law firm or any current or former-client of the firm, and should not be construed as such.

Scientific Advances Continue Affecting Regulatory/Marketplace R&D Outputs

- Medical science is entering an exciting era of discovery and research advances barely imaginable 20 years ago
- Biomarkers, genomics, molecular targeting, nanotechnology, personalized medicine, proteomics, and a myriad of other advances have taken R&D to the threshold of a revolution of advanced biology
- The inherent risks associated with innovating on this cutting edge become even greater as technology continues advancing and regulatory paradigms strive to catch up while maintaining the “Precautionary Principle”
 - More biopharmaceuticals fail later in development
 - Biopharmaceuticals making it through the pipeline probably will be targeted at increasingly-limited patient populations and precise sub-populations

Biotech Medicines' R&D Portfolio Is Growing – Approvals Not Keeping Pace



Reference: PhRMA Drugs In Development


Biopharmaceuticals – Key Assets In Industry Portfolios As Science Advances

- Within this evolving R&D and regulatory environment, biopharmaceuticals are a critical component of the entire industry's portfolio
 - This applies to both traditional “innovator” and “generic” manufacturers
 - A vibrant biopharmaceuticals business is necessary for growth and development
- Ability to target biopharmaceuticals R&D opens up a range of opportunities in the marketplace
 - Lower-cost interchangeable FOBs once legitimate IP expires
 - Clinically superior non-interchangeable FOBs
 - Premium-priced second-generation biologics

Existing Artificial Barriers To Entry For Biosimilars Can Be Overcome

- Biosimilars are an option for the entire breadth of the BioPharma industry, as more target-products and sponsors emerge as more patents expire
- Biosimilars are the greatest opportunity to the most capable and “innovative” companies across industry
 - “Innovators” have extensive biologics experience and will be able to produce biosimilars, and can be expected to do so, especially with a hiccup in their pipeline and attendant excess capacity
 - Emerging biotech companies will use biosimilars as a stepping stone and for cash flow during the development of their own innovative pipeline
 - “Generics” and CMOs have capacity and experience, some extensively in biologics, and their investment timeframes are often shorter

Biosimilars Present Novel LCM And Development Opportunities

- As the biosimilars debate moves forward in the U.S. and globally and political “trades” are negotiated, well-positioned and forward-thinking BioPharmas have a unique opportunity
- Meeting the innovation challenge necessitates leveraging opportunities in lead markets – the U.S. and EU – as well as in emerging markets
 - The traditional U.S.  RoW development-marketing paradigm needs rethinking
- Truly “innovative” companies will meet challenge by linking analytics to demonstration of clinical benefit in patients -- capitalizing on biosimilars

Biosimilars Regulatory Considerations – Recognizing & Seizing Opportunities

- Biologics generally are considered complex – and yet FDA and other HAs continue approving innovator biologics, which, by definition, are the ones we know the least about at the time of approval
- Biologics and drugs are presumed to be different, but only the U.S. has distinct regulatory pathways, and the EU is setting “biosimilar” precedents “safely”
- Patient safety is critically important, but so is access to life-saving medicines – and cost matters
- Approvals of biosimilars 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

PHS Act Licensing Criteria For A Biologic

[42 U.S.C. §262(a)(2)(A)] – *Broad Delegation Of Authority*

The Secretary shall approve a biologics license application--

- (i) on the basis of a demonstration that--
 - (I) the biological product that is the subject of the application is safe, pure, and potent; and
 - (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and
- (ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c) of this section.

Implications Of Existing Regulatory Framework For Biologics' Approvals

- The burden is always on the sponsor to demonstrate safety, purity, potency under the PHS Act (or safety and efficacy under the FD&C Act)
- Data is always generated on a **case-by-case basis**, always confidential, and always dependent upon what is being requested by the sponsor for its label
- FDA can apply the same criteria to biosimilars
- However, what FDA is lacking is **authority to approve PHS Act biologics as interchangeable** – nothing more, nothing less

Consistent Regulatory Standards Can Be The Touchstone Of Biologics' Regulation

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

Regulatory Opportunities Exists For The Entire BioPharma Industry

- Approval of FOBs are presumed to be a loss for innovators, and IP incentives a loss for FOBs sponsors
- Revisiting regulatory criteria for biologics and incentivizing research to generate more robust pipelines benefits entire BioPharma industry and patients
 - Innovators can appropriately justify reduction in regulatory burden based on enhanced understanding of biologics' function
 - Biosimilars sponsors can legitimately asked to provide more data than required for traditional generic drugs
 - A comparability pathway can keep R&D investments in the US rather than seeing R&D outsourced abroad

Biosimilars Are An Opportunity And Can Facilitate Regulatory Progress

- Biosimilars enable reevaluation of biologics regulations and can enhance the future regulatory framework
- Better regulations will stimulate upgraded facilities and more efficient biologics manufacturing (PAT, QbD, etc.)
- Competitive market-based pricing could enable consumers to become more accepting of higher brand prices for innovative output from R&D investments
 - The perception of indefinite monopolies resulting from the continued absence of pathways for interchangeable biosimilars erodes that acceptance
- The biosimilars debate allows policymakers to restructure the regulatory framework within which BioPharma operates and incentivize its future R&D

The Regulatory Environment Needs To Evolve Just As The Science Is Evolving

- The EU adopted legislative changes in the FML/NML to enable biosimilars and is continuing to approve them
- FDA has shown increasing flexibility applying existing authority and only lacks authority for interchangeability
- Reimbursement is increasingly important and formularies may drive patient options, and may make FDA assessments of “interchangeability” less important
- Important trades make FOBs less than “zero-sum”
 - Regulatory burden can be reduced so BioPharma industry gets updated regulations and old redundant regulations and statutory provisions are repealed
 - Innovation can be stimulated and rewarded across the full breadth of the BioPharma industry
 - Legitimate IP for biologics and patient access can be mutually assured

IPRs Fuel The Engine That Accelerates The Biomedical Research Enterprise

- IPRs are a critical factor in all innovation, especially within the BioPharma industry, ensuring the private sector has the possibility of being rewarded for the major investments needed to develop new medicines vital to patient health
- IPRs represent the legal protection for inventions, including new medicines discovered by biopharmaceutical companies
- The protection afforded by IPRs allows inventors time to recoup their R&D investments, thereby providing investors the assurance they need to risk the capital required to fund both the medical discovery process and new R&D initiatives

"It cannot be doubted by any, I think, that the security of prosperity in inventions has been [elemental to] the advance our country has made in the arts and sciences. Nothing more stimulates effort than security in the results of effort."

President Benjamin Harrison, Opening Address
U.S. Patent System Centennial Celebration (1891)

Nexus Between Scientific Innovation And Intellectual Property Rights (IPRs)

Basic and advanced scientific research have been longstanding drivers of innovations beneficial to society. The past half century has witnessed a myriad of scientific discoveries applied in medicine, information technology, biotechnology, agricultural production, nanotechnology, and a host of other areas. More recently, the processes of creating or acquiring and using scientific discoveries and innovations at various stages of development have expanded with the changing landscape of intellectual property protections in the United States. Scholars have pointed out that “both the inputs and outputs of scientific research” increasingly are being protected through mechanisms including—but not limited to—patenting.

Reference: Stephen A. Hansen, Michael R. Kisielewski, & Jana L. Asher, *Intellectual Property Experiences in the United States Scientific Community: A Report by the Project On Science And Intellectual Property In The Public Interest* (AAAS, 2007) (footnotes omitted).

IPRs Are Essential To The Breadth Of The BioPharma Industry

- As R&D and regulatory risks increase as the technology advances, BioPharmas can become as risk adverse towards R&D as regulators are towards the safety profiles of their products
- IPRs are an essential safety net to protect the substantial investment of time and capital required to bring a biopharmaceutical to market and to mitigate the high risk of failure inherent in biopharmaceutical R&D
- IPRs become increasingly essential to attract risk capital and R&D spend on unproven technologies that ultimately are expected to have much more limited commercialization opportunities
- When the macro-level risks associated with BioPharma R&D are exacerbated by a safety debate or other public health crisis, the BioPharma industry's development of medicines becomes dependent upon respect for and enforcement of legitimate IPRs

Balancing IPRs To Enable Innovation And Patient Access To Medicines

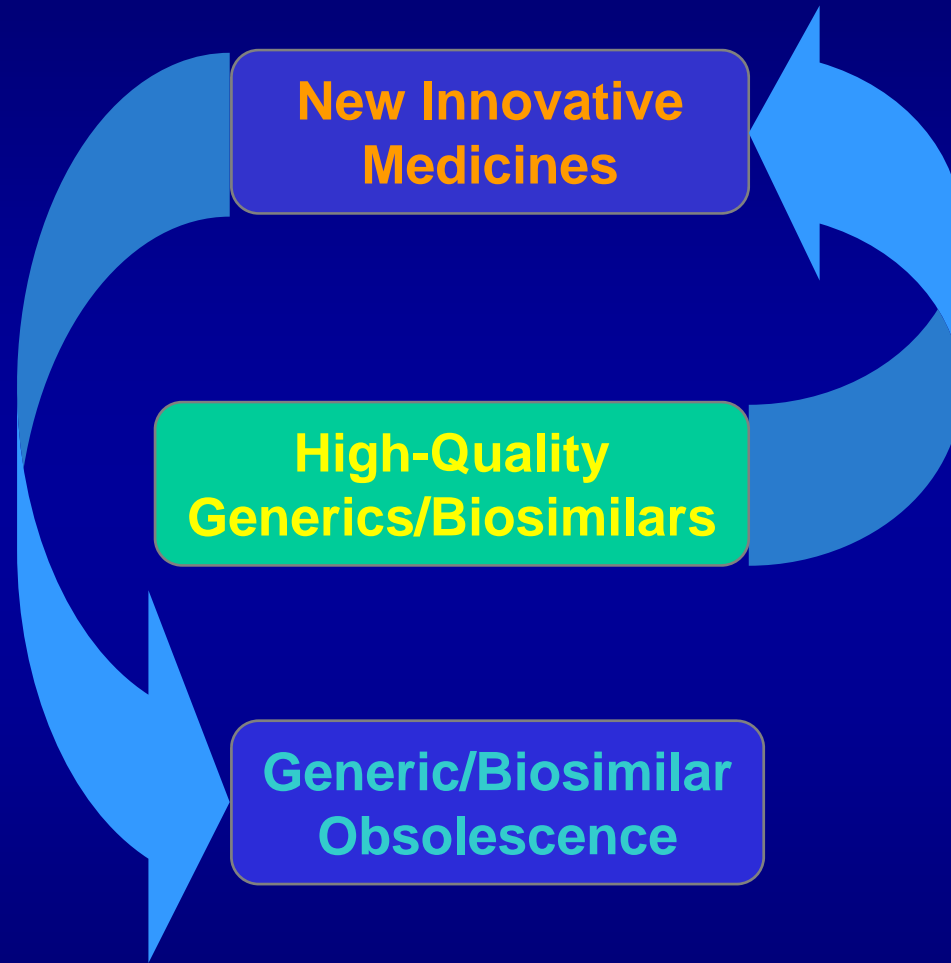
- In return for IPRs (in particular, patent rights), an inventor discloses to the world the patented research and the science underlying the invention
 - This patent-publication process makes important scientific information underlying a new medicine available immediately to researchers worldwide, thereby enabling and encouraging the continuation of scientific discovery
 - In return for disclosing the invention to the public - driving science forward - an inventor receives the right to exclude others from practicing the invention for a limited time
 - »Once patents expire, pathways should exist to allow robust competition to commence in the marketplace
 - »That competition and resulting market forces (supply/demand) can regulate pricing and incentivize continued innovation

Balancing IPRs To Enable Innovation And Patient Access To Medicines

- Denying or overriding IPRs for innovative medicines does not benefit patients or enhance patient access to treatments
- Such action will most likely adversely affect patients by denying patients continuous access to innovative new medicines (or even generic products)
- Nonetheless, as a matter of corporate responsibility, the BioPharma industry must be responsive to serious concerns of rapidly-rising costs for public health systems for countries in the developed world, and the lack of affordability of life-saving medications in developing countries
- Market trends are favoring competing products (including generics and biosimilars), which are one part of the solution
 - Generics/Biosimilars help keep expenditures down by providing affordable medicines, enabling healthcare systems to remain viable
 - Utilization of generics/biosimilars also can free up capital for more innovative treatments

IPRs & Post-Expiry Competition Combine To Facilitate Innovation And Access

Innovation offers improved treatment options rendering generics/biosimilars obsolete



Generics/biosimilars free up funds for innovative medicines

- In a price-sensitive environment, with aging a primary global demographic trend associated with the need for more medicines, **generics/biosimilars contribute to public health in a fundamental way**
- Use of generics/biosimilars when patents expire **free up health care \$s for innovative therapies**
- Generics/Biosimilars trigger further innovation by **stimulating revitalization of legacy portfolios**

Legislative Options & Opportunities – Achieving Balance For Biosimilars

A *Viable* Pathway Has Very Few Real Requirements

- **Delegation** of authority to FDA to license interchangeable biosimilars that reference biologics originally licensed under the PHS Act
 - Authorities for FD&C Act FOBs already exist
- **Balanced** IPR provisions to incentivize continued innovation in an increasingly-risky R&D environment
- **Continued decoupling** of the patent litigation and BLA review process as exists today for biologics
 - The case has not been made for linking patent litigation to FDA review and approval of biologics
 - Hatch-Waxman is not really a viable model for biosimilars beyond the core principle of balance
 - As it does today, decoupling permits patentees to litigate to enforce patents whenever the patent laws permit a case to be initiated

Legislative Options & Opportunities – Science-Based Regulatory Standards

- Follow-on versions of biologic drugs approved under the FD&C Act need no new authorities:
 - Standard established is **safety and efficacy**
 - **Comparability** already applies
 - **Interchangeability** is based on **therapeutic equivalence** (pharmaceutical equivalence plus bioequivalence)
- Biosimilar versions of biologics licensed under the PHS Act need authority for interchangeability determination following licensure based on reference to a previously-approved biologic:
 - Standard established is **safety, purity, potency**
 - **Comparability** already applies
 - **Interchangeability** can be based on **comparability** at the **structural, functional, and clinical** levels

Legislative Options & Opportunities – Robust Pathway With FDA Deference

- Build on vast experience with biologics – statutory enactments, regulatory implementation, and administrative precedents over the past 100 years – and appropriately enable regulators and sponsors alike to use prior knowledge
- Enable scientific experts at FDA to apply consistent and predictable standards to all biologics to:
 - Encourage competition
 - Stimulate innovation through better use of prior experience
 - Build in opportunities/incentives for second-generation biologics
 - Facilitate global harmonization

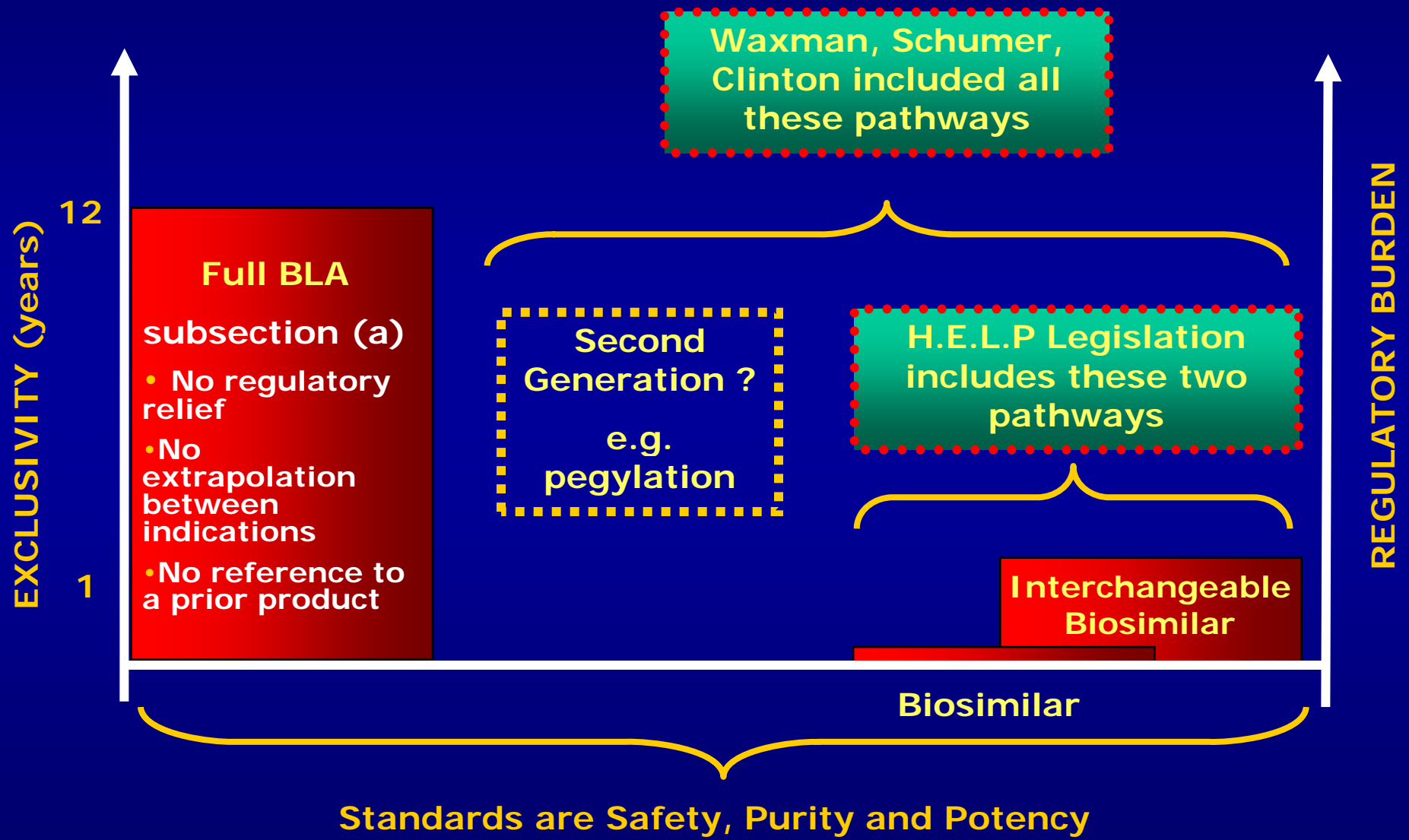
Legislative Options & Opportunities – Granting Exclusivity & Respecting IPRs

- Various forms of **exclusivity** have been proposed, with the EU model still meriting consideration
 - 8+2+1 provides a preclusion on biosimilar filing double that of the four-year period in the U.S. under the NCE exclusivity provisions, and a preclusion on biosimilar approval double that of the U.S. five-year NCE period
 - Effectively combines data and market exclusivity
 - Incentivizes continued R&D with potential for +1 exclusivity period for significant new uses
- All types of **patents** should be appropriately respected and enforced in every jurisdiction in which they apply
 - When patents expire, competition must be seen to begin
- In all cases, **trade secrets** must continue to be respected by and for all sponsors

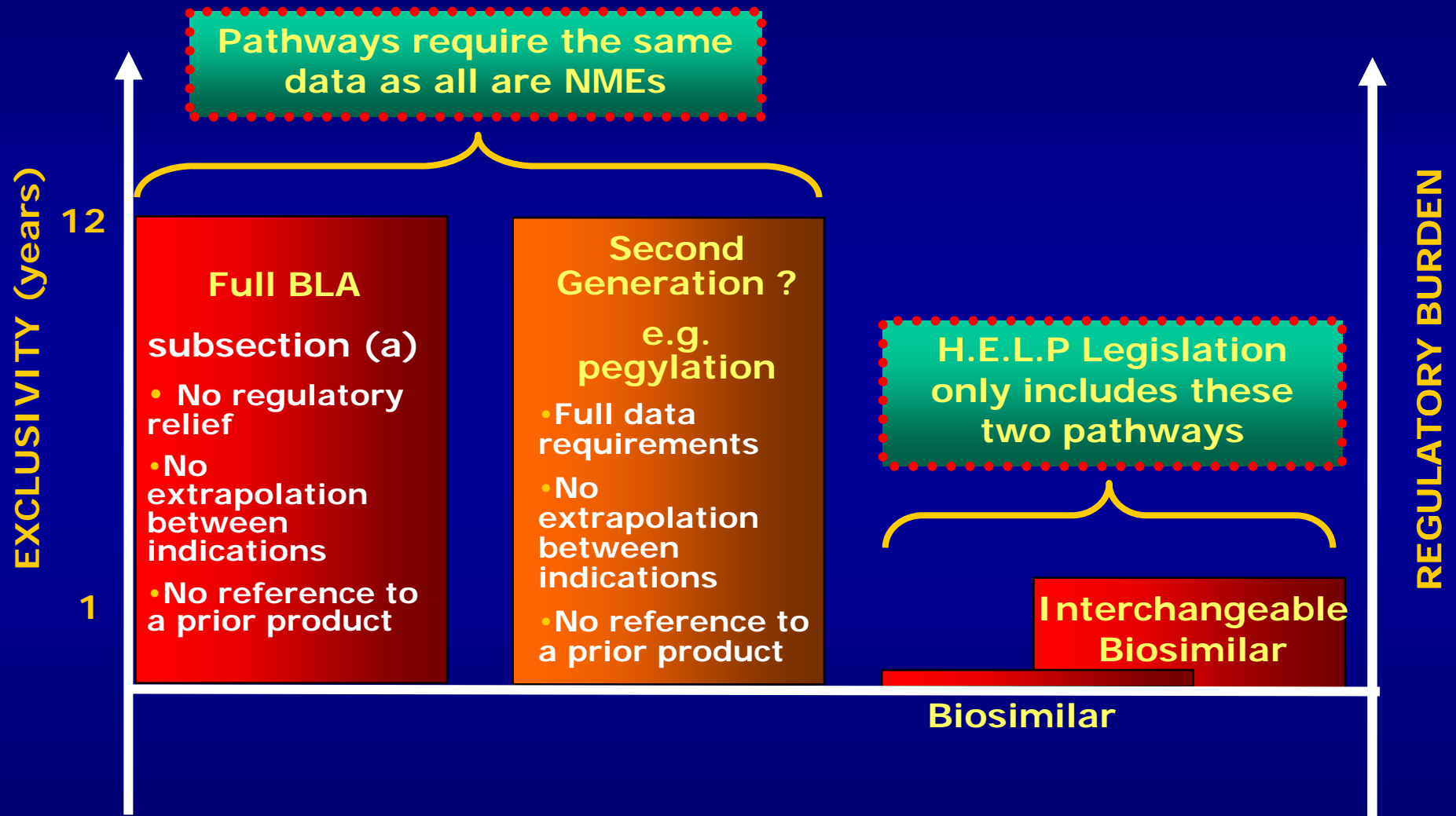
Legislative Options & Opportunities – Decoupling Patents And BLA Licensure

- The biotechnology industry has grown and prospered without any link between patents, patent litigation, and FDA licensure of products
- Decoupling enables FDA to utilize its scientific expertise and resources where it is most appropriate – on its public health mission of reviewing and evaluating sponsor applications
- Courts can continue to enforce biotech patents – pre- and post-approval – just as they do now
 - Like cases before it, *Amgen v Roche* pegylated EPO litigation in Massachusetts Federal District Court demonstrates viability of decoupling

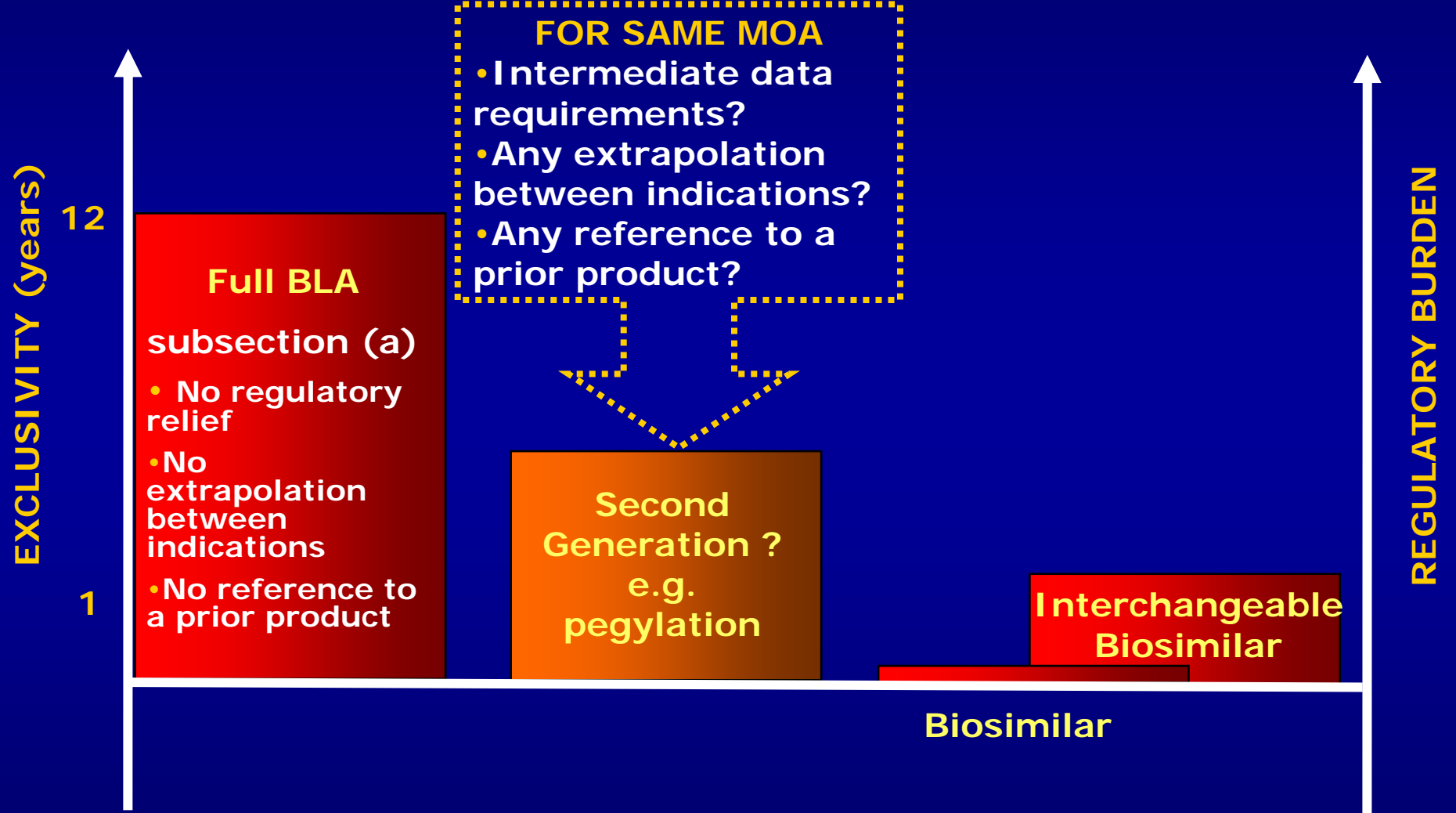
New "Biosimilars" Pathways Addressing "Evergreening" Claims



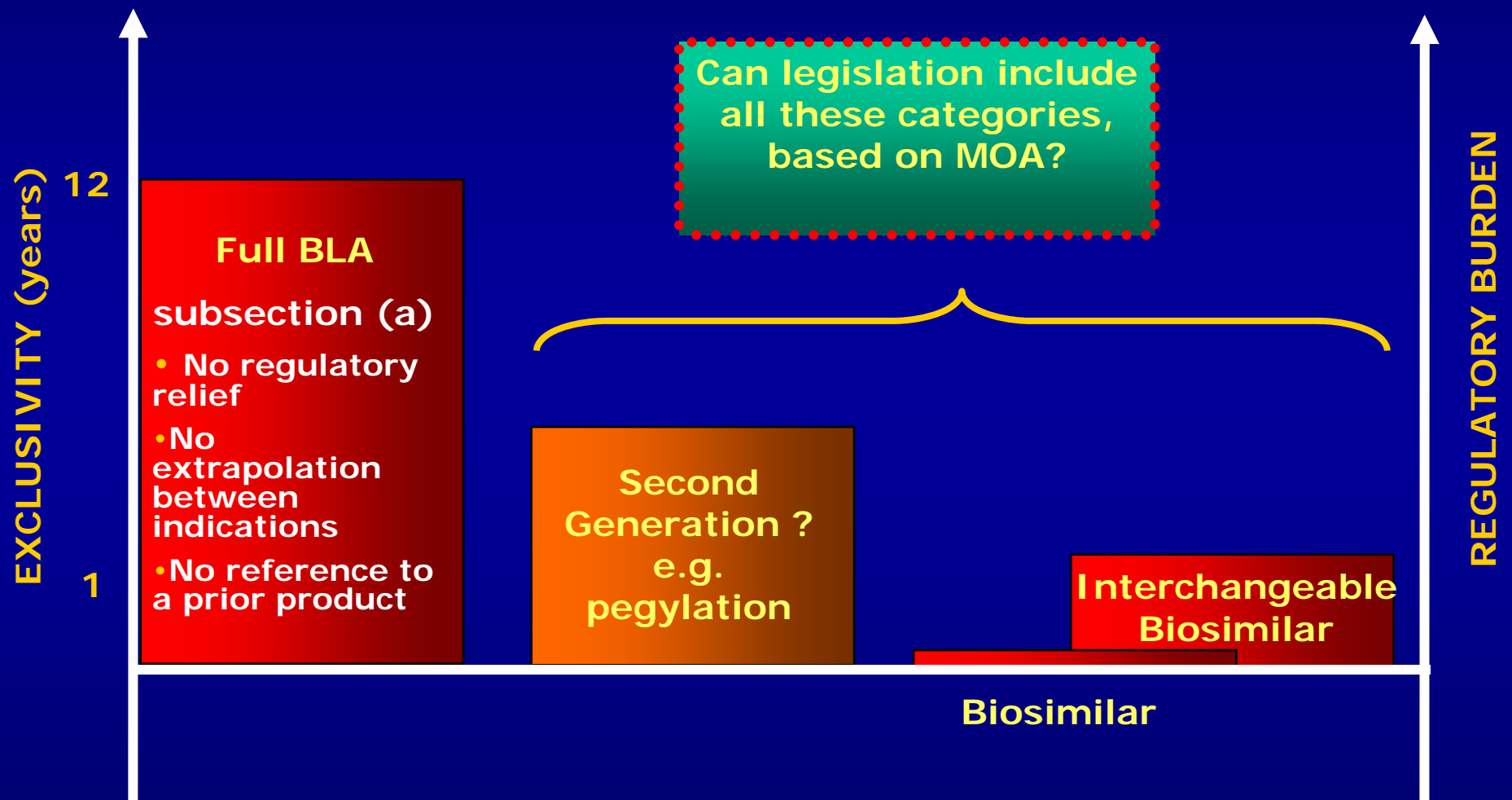
Exclusivity & Pathway Data Standards For Second-Generation Biologics



Exclusivity & Flexible Data Standards For Second-Generation Biologics



Exclusivity And Second-Generation Biologics – Pathway Opportunities



Conclusions – A Middle Ground On Biosimilars Legislation Is Achievable

- A constructive solution for the BioPharma industry, regulators, health care providers, and patients is readily achievable
- Respect for legitimate IPRs and ensuing market-based competition following patent expiry are both achievable
- An appropriate balance can drive continued innovation and enable patient access to innovative and affordable medicines
- Competition from high-quality biosimilars should be encouraged
 - » Neither “side” should fear a competitive marketplace
- The global biotechnology-based industry can afford to recognize its own success and help design its future
 - » Support consistent regulatory standards for all biologics
 - » Seize opportunity to use state-of-the art technology to reduce regulatory burdens appropriately for all biologics
 - » Embrace global health authorities’ adoption of comparability principles to limit trials and size
 - » Reevaluate development/launch strategies based on evolving regulatory paradigms especially in RoW
 - » Develop improved and superior biologics

Thank You!

John M. Engel, Esq.

Managing Partner

ENGEL & NOVITT, LLP

THE LAW FIRM THAT KNOWS ITS SCIENCE

www.engelnovitt.com

202.207.3303

jengel@engelnovitt.com

The material and viewpoints set forth in this slide deck and conveyed during this presentation are presented by the author in his capacity as Managing Partner of Engel & Novitt, LLP. They do not represent and do not purport to represent the views of the law firm or any current or former-client of the firm, and should not be construed as such.