

Follow-On Biologics: Stumbling Blocks to Approval

Duke IP Law Symposium

“Generic Biologics: Possible ? Desirable? How?”

February 6, 2009

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Introduction

- Disclaimer: Remarks not attributable to Alston & Bird

Introduction

- Terms:
 - Generic biologics -- follow-on biologics (FOBs) -- biosimilars
 - E.g., Biosimilar (comparable and non-interchangeable)
 - E.g., Biogeneric (equivalent and interchangeable)
 - Interchangeable, substitutable, comparable, therapeutic equivalent
- Abbreviated pathway to approval for generic biologics in 2009?
 - Biologics going off patent
 - Health care costs
 - New administration
- Very different perspectives

Introduction

- Essential considerations
 - Patient safety
 - Health care costs of biologics
 - Balance of innovation v. competition
- Patient safety comes first
- Establish scientific and regulatory guidelines based on safety and efficacy considerations
- Competition analysis impacts:
 - Exclusivity provisions
 - Patent litigation provisions

Introduction

- Should FOB abbreviated pathway be based on Hatch-Waxman?
 - Easier legislative fix, but will it properly
 - protect patient safety?
 - balance innovation and competition?
 - Biologics are different from small molecules
 - Hatch-Waxman regime based on “sameness” of brand product and generic copy
 - FOB regime likely to be based on “similarity” standard
 - Patent protection alone may not be sufficient
 - Longer period of data exclusivity necessary? Desirable?
 - Marketing exclusivity for biogeneric necessary? Desirable?
 - Patent dispute resolution process needs improvement

Issues

- In April 2008, Congress solicited comments
 - Science and Safety
 - Regulatory/Administrative
 - Interchangeability
 - Patents
 - Incentives/Exclusivities
 - Competition
- In August 2008, FTC solicited comments concerning effect of competition provided by abbreviated FOB pathway

Issues

- Immunogenicity
- Separate testing for separate indications
- Mechanisms of action
- Naming of FOBs
- Clinical trials
- Guidances
- Interchangeability
- Patent Dispute Resolution
- Exclusivities

Immunogenicity

- Is testing necessary? Should it be mandated as part of legislation for follow-on biologics?
- Innovator perspective
 - Clinical safety testing is necessary for approval of every new biologic
 - Proteins stimulate immune responses in the body which can have serious consequences
 - Without clinical testing, unable to predict whether a FOB will cause adverse effects
 - FDA should have discretion on a case-by-case basis to determine which clinical studies and what amount of data are needed
 - Should require clinical immunogenicity testing for FOBs to ensure safety and efficacy

Immunogenicity

- Biogeneric perspective
 - Issue of immunogenicity overstated by innovator companies
 - Sometimes biologics can cause immunogenic reactions
 - Often temporary and no adverse effect
 - Requirement for testing should be at FDA discretion
 - Case-by-case basis based on latest scientific knowledge

Immunogenicity

- FDA perspective
 - Ability to predict immunogenicity of protein product is limited
 - Extent of testing will depend on
 - Intended indication
 - length of administration
 - overall assessment of product's immunogenic potential
 - possibility of generating cross-reaction
 - Clinical immunogenicity studies should be mandated in statute
 - FDA should have discretion to determine how much data necessary on case-by-case basis

Separate Indications

- Should separate testing be required for each indication?
- Innovator perspective
 - FOBs should be approved indication by indication
 - Safety and effectiveness may vary with different patient populations
- Biogeneric perspective
 - Biologics that are comparable have comparable structure and biologic activity
 - Not necessary to replicate all safety and efficacy studies in all indications
 - When clinical trials are necessary, only one indication need be evaluated
- FDA perspective
 - Extent of clinical information needed to support approval of product for multiple indications depends on understanding:
 - Mechanism of action
 - Benefits and toxicities in each clinical setting
 - Relationship between product's physiochemical characteristics and its clinical activity

Mechanisms of Action

- Innovator perspective
 - FOB and reference product must have same mechanism of action
 - FOB manufacturer must demonstrate FOB has same mechanism of action as reference product
- Biogeneric perspective
 - Many biologics approved without knowledge of actual mechanism of action
 - FOB manufacturer should not be required to prove mechanism of action where innovator product approved without known mechanism of action
- FDA perspective
 - Reference product and FOB must have same mechanism of action
 - If mechanism of action is different, product cannot be considered a FOB
 - Where mechanism of action of reference product is unknown, clinical studies may be necessary

Naming of FOBs

- Innovator perspective
 - FOBs should have distinct non-proprietary names
- Biogeneric perspective
 - Separate and distinct names for FOBs unnecessary when FDA determines comparable to reference product
 - Causes patient and physician concern over difference between products
- FDA perspective
 - Pharmacovigilance issues
 - Require assignment of distinguishable, non-proprietary name to FOBs for safety purposes
 - Prevent switch to a product not interchangeable with the approved biological product

Clinical Trials

- **Innovator Perspective**
 - Require clinical trial data as part of approval process to evaluate safety and effectiveness of FOBs
- **Biogeneric Perspective**
 - FDA should have discretion to determine whether clinical trials necessary on a case-by-case basis
- **FDA Perspective**
 - Clinical information required depends on extent of knowledge of :
 - Mechanism of action
 - Structural similarity
 - Comparative pharmacokinetic and pharmacodynamic data
 - Immunogenicity
 - Some clinical information will be needed to assess safety and efficacy of most FOBs
 - Require clinical trials with FDA discretion to determine which clinical trials necessary

Guidances

- Innovator perspective
 - FDA must develop guidances prior to approval of FOBs
 - Guidances should be specific to particular product or product group
- Biogeneric perspective
 - FOB applicant should provide data that establish that reference product and FOB comparable
 - FDA should not be required to develop guidances and regulations before considering FOBs
- FDA perspective
 - Guidances should be developed in public process to set forth criteria for specific classes of products
 - FDA should have flexibility to adjust process
 - Guidance process would indicate product classes appropriate for FOB applications
 - Guidance process should occur before acting on any FOB applications

Interchangeability

- Innovator perspective
 - Interchangeability not defined
 - FOBs should be expressly prescribed by physician
 - If FOB substitutable, FOB may be substituted at pharmacy without physician or patient consent
 - Current state of science does not support substitutability for biologics
 - Switching between biologic and FOB has risks
 - If FDA allowed to make interchangeability determinations, FDA should develop guidances describing requirements for interchangeability

Interchangeability

- Biogeneric perspective
 - Interchangeability determinations possible for some biologics now
 - Interchangeability testing will depend on complexity of product and should be determined on a case-by-case basis
 - FDA should determine interchangeability as technology permits and based on FDA's scientific expertise
 - Interchangeable FOBs allow pharmacists and doctors to switch to lower cost generic equivalent

Interchangeability

■ FDA Perspective

- Generic drugs “interchangeable” or “substitutable” because chemical composition is the same
- Biologics more complex and frequently immunogenic
- Even if FOB is biosimilar to reference product, immunogenicity may preclude switching between products
- For most proteins, unlikely FOB manufacturer can demonstrate FOB is identical
- Substitution of FOBs determined to be biosimilar but not interchangeable may result in serious injury or death
- Patients should not be switched from innovator product to FOB without express consent and advice of patient’s physician

Patent Protection/Data Exclusivity

- How long is effective patent term for pharmaceuticals?
- Does Hatch Waxman provide good model for biologic manufacturers in restoring innovator patents up to 14 years and providing manufacturers with 5 years of data exclusivity?
- Are patents for biologics sufficient protection if abbreviated pathway is created?

Patent Protection/Data Exclusivity

- Innovator perspective
 - Substantial period of data exclusivity necessary to preserve and encourage innovation
 - FOB may be able to obtain approval and avoid infringing innovator patents due to “similarity” standard
 - FOB need only be similar not the same
 - Patent protection for biologics is often narrower and easier to design around
 - 14 year period of data exclusivity
 - Break-even point for return on investment is between 12.9 and 16.2 years
 - Patent term restoration provides up to 14 years of patent protection following marketing approval

Patent Protection/Data Exclusivity

- Biogeneric perspective
 - Effective patent term varies from product to product
 - 5 year period of data exclusivity is sufficient
 - Patent protection of biologics not weaker than for small molecules
 - No additional exclusivity period for modifications to approved products
- FDA perspective
 - Statute should include incentives to develop biologic products
 - Innovators should be eligible for a significant period of market and/or data exclusivity in addition to patent protection
 - Additional exclusivity period should be provided for new indications
 - Patent protection differs from market exclusivity in that patents may be challenged

Timing of Patent Dispute Resolution

■ Innovator perspective

- Encourage timely resolution of patent disputes but avoid premature litigation
- Before FOB launch
 - Premature FOB launch can damage public and parties
 - Market share loss and price erosion to innovator product
 - Risk of significant damages for FOB manufacturer
 - Change in product availability and confusion for patients
- After market exclusivity expires
- After determination that FOB application is complete and ready for review without additional clinical studies
- Create incentive for submission of high quality, approvable FOB applications
- If patent found valid and infringed, approval of FOB application effective on date of patent expiration or expiration of exclusivity period, whichever is later

Timing of Patent Dispute Resolution

- Biogeneric perspective
 - Clear and timely resolution of patent disputes before market launch
 - Prohibit litigation from delaying competition
 - At-risk launch subjects company to massive damages
 - Generic company should decide which patents litigated before launch
 - Only patents that prevent launch until questions of validity, infringement and enforcement are decided
 - Litigation on remaining patents should take place after launch

Exclusivity for Biogeneric

- Innovator perspective
 - Exclusivity incentive not necessary
 - Tying exclusivity period to patent challenges leads to premature litigation
- Biogeneric perspective
 - Exclusivity for first approved interchangeable generic biologic
 - Exclusivity does not prevent immediate approval of non-interchangeable, comparable generic biologic product

Thank you!

The End