
Biosimilars: Navigating FDA's Evolving Approval Pathway, Protecting Patents and Trade Secrets

WEDNESDAY, OCTOBER 9, 2013

1pm Eastern | 12pm Central | 11am Mountain | 10am Pacific

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Biosimilars: Draft FDA Guidance and Emerging Legal Challenges

October 9, 2013

Presented by
Kevin E. Noonan and Howard W. Levine

BPCIA Legislation & FDA Guidance

The Biologics Price Competition and Innovation Act of 2009 (“BPCIA”)

- The BPCIA signed into law on March 23, 2010
 - Amended § 351 of the PHSA (42 U.S.C. § 262) and § 271(e) of the Patent Act
 - Created a statutory framework for FDA approval of new product as “biosimilar” to or “interchangeable” with “reference” products
 - Granted agency discretion in implementing approval pathway
 - Specified procedures for filing patent infringement actions, preliminary injunctions and declaratory judgment actions

Outline of the BPCIA

- Changes to PHSA § 351(i) (42 U.S.C. § 262(i))
 - Provides new and amended definitions
- New PHSA § 351(k) (42 U.S.C. § 262(k))
 - Provides regulatory pathway for biosimilar/ interchangeable products
 - Provides RP exclusivity
- New PHSA § 351(l) (42 U.S.C. § 262(l))
 - Provides patent litigation process

BPCIA Benefits

- Allows for “biosimilar” products
- Allows for “interchangeable” products
- Provides ~ 1 year exclusivity period for first approved “interchangeable” product
- Provides 12 year exclusivity period for RP
- Allows biosimilar applicant to file application 4 years after RP is first licensed
- Authorizes FDA guidances for implementation

BPCIA Definition of “Biological Product”

- A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, ***protein (except any chemically synthesized polypeptide)***, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings
- FDA definition of “protein” (FDA Q&A at 13):
 - “[A]ny alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size”
 - “Compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.”

“Biosimilar” Products

- “Biosimilar” expressly defined in statute:
 - “(A) that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; **and** (B) there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

42 U.S.C. § 262(i)(2)
 - “**Clinically meaningful differences** could include a difference in the expected range of safety, purity, and potency of the proposed and reference products” (*Scientific Considerations* at 8.)
 - **Non-clinically meaningful differences** could include “slight differences in rates of occurrence of adverse events between the two products.” (*Scientific Considerations* at 8.)

Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- Expression System
- Manufacturing Process
- Assessment of Physiochemical Properties
- Functional Activities
- Receptor Binding and Immunochemical Properties
- Impurities
- Reference Product and Reference Standards
- Finished Drug Product
- Stability

Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- Comparison between the putative biosimilar and one reference biologic drug including:
 - Analytical studies that demonstrate putative biosimilar is “highly similar” to reference biologic
 - Animal studies on (at least) toxicity
 - Human clinical trials to assess immunogenicity, pharmacodynamics/ pharmacokinetics
- Data supporting biosimilarity includes:
 - “[A] clinical study or studies [] that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.”

Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- In addition to biosimilarity
 - Biosimilar and reference product use the same mechanism of action (if known)
 - Conditions of use for biosimilar be the same as those previously approved for reference product
 - Identical route of administration, dosage form and strength as approved reference product
 - Biosimilar prepared in a facility that meets standards that insure biosimilar is safe, effective and pure

FDA Guidance on Establishing Biosimilarity

Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

<http://www.fda.gov/Drugs/Outreach/Compliance/RegulatoryInformation/Outreach/default.htm>

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Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity

Guidance for Industry Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity

Guidance for Industry

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

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U.S. Department of Health and Human Services
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February 2012
Biosimilarity

FDA Guidance on Establishing Biosimilarity

- Communication With FDA is Essential
 - “FDA encourages sponsors to consult extensively with the Agency after completion of comparative structural and functional analysis (before finalizing the clinical program), and throughout development as needed.” (*Scientific Considerations* at 7-8.)
 - “FDA also advises sponsors intending ... to meet with FDA to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency. FDA anticipates that early discussions with FDA about product development plans and about the appropriate scientific justifications will facilitate biosimilar development.” (*Scientific Considerations* at 21.)

FDA Guidance on Establishing Biosimilarity

- “FDA intends to use a risk-based, **totality-of-the evidence** approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.” (*Scientific Considerations* at 8.)
- “The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.” (*Scientific Considerations* at 8.)
 - “[M]any product-specific factors can influence the components of a product development program intended to establish that a proposed product is biosimilar to a reference product. Therefore, FDA will ordinarily provide feedback on a case-by-case basis on the components of a development program for a proposed product.” *Scientific Considerations* at 21.

FDA Guidance on Establishing Biosimilarity

▪ **Structural and Functional Characterization**

- “The more comprehensive and robust the comparative structural and functional characterization . . . the more useful such characterization will be in determining what additional studies may be needed.” *Scientific Considerations* at 7.
- Primary structures, such as amino acid sequence
- Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
- Enzymatic post-translational modifications, such as glycosylation and phosphorylation
- Other potential variants, such as protein deamidation and oxidation
- Intentional chemical modifications, such as PEGylation sites and characteristics” (*Scientific Considerations* at 9.)

FDA Guidance on Establishing Biosimilarity

- **Animal data:** “The sponsor should then consider the role of *animal data* in assessing toxicity and, in some cases, in providing additional support for demonstrating biosimilarity and in contributing to the immunogenicity assessment.” (*Scientific Considerations* at 7.)
 - **Animal Toxicity Studies:** “As a scientific matter, animal toxicity data are considered useful when, based on the results of extensive structural and functional characterization . . . Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the protein product.” (*Scientific Considerations* at 11.)
 - **Animal Immunogenicity Studies:** “Animal immunogenicity assessments generally do not predict potential immunogenic responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, measurement of anti-protein antibody responses in animals may provide useful information relevant to patient safety.” (*Scientific Considerations* at 12.)
 - **Animal PK and PD Measures:** “Under certain circumstances, a single-dose study in animals comparing the proposed product and reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity.” (*Scientific Considerations* at 12.)

FDA Guidance on Establishing Biosimilarity

▪ Human Studies

- “In general, **the clinical program for a 351(k) application must include a clinical study or studies** (including an assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product, as set forth in the PHS Act. ***The scope and magnitude of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterization and possible animal studies.***”
(*Scientific Considerations* at 12.)

FDA Guidance on Establishing Biosimilarity

▪ Human Studies (cont.)

- **PK / PD studies:** “We have determined that both PK and PD studies . . . ***generally will be expected*** to establish biosimilarity, unless a sponsor can scientifically justify that an element is unnecessary.”
(*Scientific Considerations* at 13.)
- **Clinical immunogenicity studies:** “[A]t least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product ***will generally be expected.***”
(*Scientific Considerations* at 14.)

FDA Guidance on Establishing Biosimilarity

- **Human Studies (cont.)**
 - **Comparative clinical safety and effectiveness data**
 - “**If there are residual uncertainties about the biosimilarity** of the two products after conducting structural and functional studies, animal toxicity studies, human PK and PD studies, and clinical immunogenicity assessment, the sponsor should **then consider what comparative clinical safety and effectiveness data** may be adequate.” (*Scientific Considerations* at 7.)
 - “Clinical studies should be designed such that they can demonstrate that the ***proposed product has neither decreased nor increased activity compared to the reference product.***” (*Scientific Considerations* at 17.)

FDA Guidance on Establishing Biosimilarity

- What must be assessed:

Binding Antibody

- Titer
- Specificity
- Relevant Isotype Distribution
- Time Course of Development
- Persistence
- Disappearance
- Association with clinical sequelae

Neutralizing Antibody

- (all Binding Antibody points)
- Plus neutralizing capacity to all relevant functions
- Uptake and catalytic activity
- Neutralization for replacement enzyme therapeutics

- Immunogenicity assays developed and validated for biosimilar and reference product

Canonical Timeline

- Bioanalytical assay for PK analysis (5 – 8 months)
 - Reagent preparation (3 – 4 months) – May have reagents from release testing
 - Method development and validation (2 – 4 months)
- Immunogenicity testing assay (6 – 9 months)
 - Reagent preparation (3 – 4 months) – may have reagents from release testing
 - Method development and validation (3 – 5 months)

Canonical Timeline

- Cell based assays for functional activity (11 – 15 months)
 - Selection of the assay procedure (1 month)
 - Breeding of cell lines and feasibility study (2 – 3 months)
 - Final selection of cell line and reference antibodies (2 – 3 months)
 - Optimization and final development of assay (4 – 6 months)
 - GLP validation (2 months)
- (If reagents and cell lines are available, applicant could save up to 6 months)

“Interchangeable” Products

- “Interchangeable” means:
 - Biosimilar to RP and
 - Can be expected to produce **the same clinical result as the RP in any given patient, and**
 - For a biological product that is administered more than once to an individual, **the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the RP is not greater than the risk of using the RP without such alteration or switch.**

42 U.S.C. § 262(k)(4)

“Interchangeable” Products

- What’s the benefit for “interchangeability”?
 - The interchangeable product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”
 - A biosimilar product cannot be switched for RP without doctor intervention

42 U.S.C. § 262(i)(3)

- FDA has *not yet issued* guidance on Interchangeability
 - “At this time it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application. . . . ***FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.***” Q & A at 11-12.

“Interchangeable” Products

- Exclusivity for first approved “interchangeable” product
 - No subsequent FOB can be found to be interchangeable until **earlier** of
 - 1 year after first commercial marketing of first interchangeable FOB
 - 18 months after final court decision or dismissal with or without prejudice on patents involved in suit against first interchangeable FOB
 - 42 months after approval of first interchangeable FOB if patent litigation is still ongoing within the 42 month period or 18 months after such approval if no patent suit was filed against first interchangeable FOB

42 U.S.C. § 262(k)(6)

FDA Guidance Misc. Issues

- Reliance on Non-US Licensed Product Comparisons
 - “In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed protein product with the reference product. . . However, under certain circumstances, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed protein product with a non-U.S. licensed product . . . **In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.**” (*Quality Considerations* at 9.)

GPhA Citizen Petition

▪ **Petition dated September 17, 2013**

- The World Health Organization (WHO) administers the international naming convention known as the International Non-proprietary Naming (INN) system
- Action Requested:
 - “that FDA implement its INN naming policy equally to all biologics; and”
 - “that because all biologics approved under the Section 351(k) pathway are ‘highly similar;’ and thus, have no clinically meaningful differences from the reference protein product (RPP) that they share the same INN name as the RPP, just as comparable originator products produced by a change in a manufacturing process or facility (post-change product) share the same INN as the original RPP (pre-change product).”

GPhA Citizen Petition

- “[A] major goal of the BPCIA is to create competition in the marketplace for biologics, thereby expanding access to, and increasing the affordability of, these critical medicines.”
- “Adoption of unique names for each biosimilar could frustrate this goal as well as jeopardize patient safety, inhibit market competition and innovation, and disrupt the current global naming system.”
- “GPhA proposes that the same scientific principles that underlie the 60-year-old policy of INNs, as applied throughout the world to drugs and biologics, also must apply to biosimilars. This means that as a fundamental element of its licensure, each biosimilar product should have the same INN as the single RPP to which it has been demonstrated to be highly similar and to have no clinically meaningful differences.”

GPhA Citizen Petition

- “This would compromise patient safety in that: (1) clinician confusion may lead to prescribing errors, (2) access could be compromised and patients go untreated, and/or (3) safety data for these molecules would be disaggregated from the current system that allows for pooling of data, ensuring rapid identification and communication of class effects and lower frequency safety signals.”
- “Specifically, a patient's health could be jeopardized if, for example, a physician inadvertently double dosed a patient by prescribing two highly similar products because he thought, based on their different INNs, that they contained different active ingredients.”

GPhA Citizen Petition

- **Amgen Statement on GPhA Citizen Petition on Naming for Biologics**
- “We are pleased that the Generic Pharmaceutical Association (GPhA) agrees with Amgen's longstanding view that the U.S. Food and Drug Administration should apply a consistent naming policy to all biologic medicines ***As a biologics and biosimilars manufacturer, we feel strongly that all biologic medicines need a distinguishable component in their non proprietary (proper) name.*** This means that patients, caregivers, healthcare professionals, regulators and industry can more readily and accurately identify, investigate and report adverse events. To that end we are seeking distinguishable non proprietary names (common root and a distinguishable component) for our biosimilar products”

Reference Product (RP) Exclusivity

- 12 year exclusivity for RP
 - The RP is entitled to 12 years exclusivity starting from the date when the RP was first licensed by the FDA
 - Potential for 6 additional months of pediatric exclusivity
- No additional exclusivity for:
 - Supplemental BLA
 - A new BLA filed by same RPS (or related entity) for
 - A change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength; or
 - A modification to the structure of the biological product that does not result in a change in safety, purity, or potency

42 U.S.C. § 262(k)(7)

RP Exclusivity

- Potential additional exclusivity for new BLA if
 - Change involves a modification in structure that results **in a change in safety, purity or potency** compared to the previously approved biologic product
- If modified BLA results in new RP
 - Pending FOB applicant may have to resubmit application (FOB may only be evaluated against 1 RP)

42 U.S.C. § 262(k)(5)(A)
 - Offers real opportunity for additional exclusivity
 - Investigate potential avenues for structural change
 - How much of a change in safety (including side effects), purity or efficacy is required?

Practical and Ethical Considerations for Litigating Under the BPCIA

BPCIA Litigation Overview

1. Biosimilar applicant provides application to RPS
2. RPS and Biosimilar applicant identify potentially relevant patents
3. RPS and Biosimilar applicant “negotiate” final list of patents to actually litigate
4. Biosimilar applicant must notify RPS 180 days before 1st commercial marketing, and RPS may file for preliminary injunction
5. RPS and Biosimilar can negotiate alternative to patent exchange process

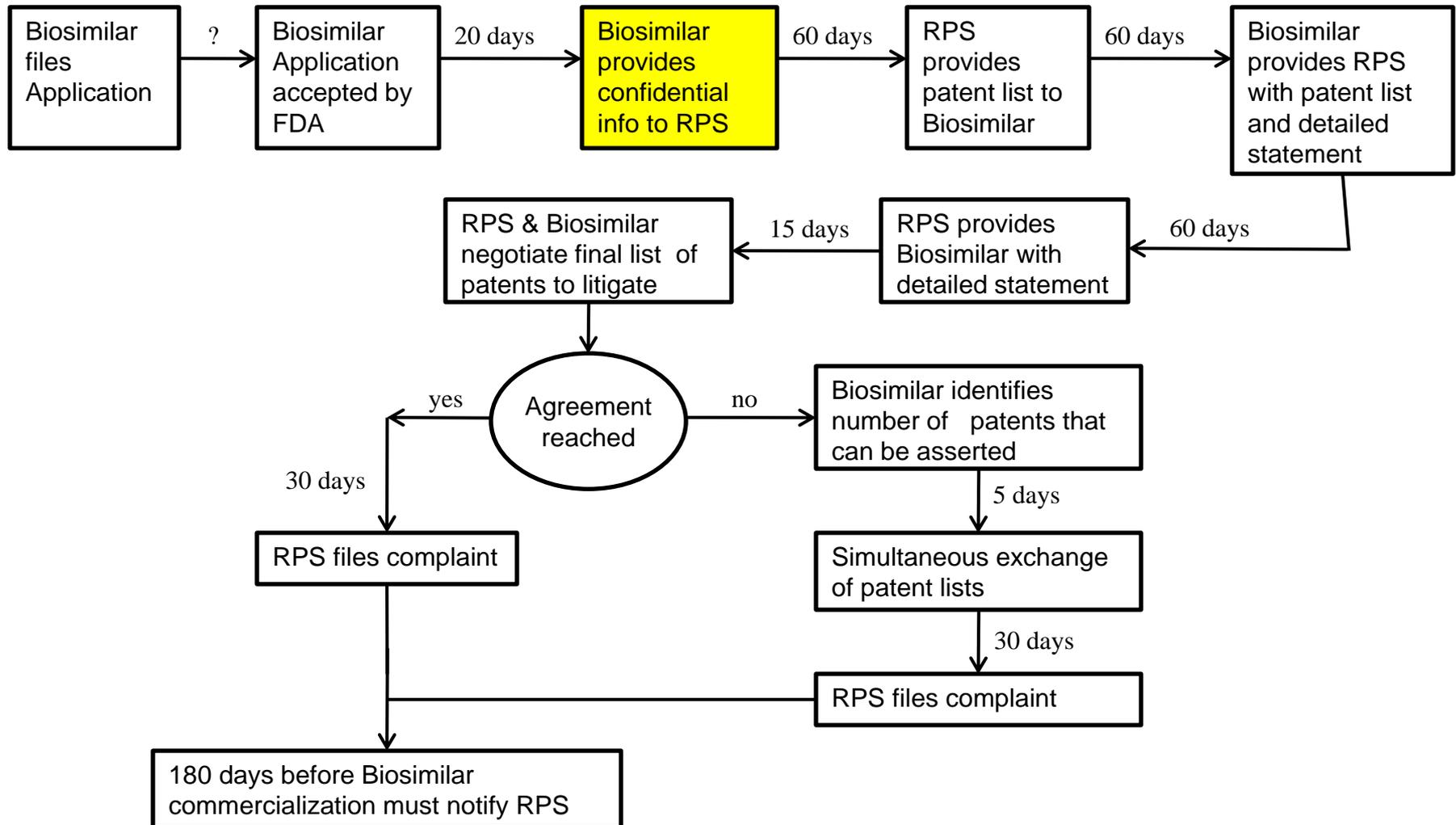
BPCIA Litigation ≠ Hatch Waxman

- No Orange Book listing
 - Biosimilar applicant has burden of identifying relevant patents during development work
 - Negotiated list of patents in suit
- No limitation on types of patents to assert
 - Hatch-Waxman limited to listing patents covering the active ingredient, formulations, and method of use patents
 - BPCIA allows RPS to assert *any* patent having a claim wherein patent infringement “could reasonably be asserted”
- No 30-month stay upon filing suit
- No 180 day exclusivity period for 1st filed biosimilar application

Patent Litigation and FDA Approval

- Patent litigation process cannot start until **four years** after RP is first licensed
- Patent litigation process does not stay FDA approval of biosimilar application
 - Even if Biosimilar applicant indicates it will not market until after patent expiry, FDA can still approve application
- Only way to stop biosimilar product from coming onto the market is injunction from the court

Patent Exchange Process Under 42 U.S.C. § 262(I)



Confidential Disclosure of Biosimilar Application

- Confidential information
 - Within **20 days** after Biosimilar applicant receives notice that application has been accepted for review, Biosimilar applicant “**shall provide**”:
 - Copy of the application
 - Information that describes the process used to manufacture the biological product and
 - “**May provide**” other information requested by the RPS

42 U.S.C. § 262(l)(2)

Confidential Disclosure of Biosimilar Application

- **Access to confidential information** 42 U.S.C. § 262(l)(1)(B)
 - “One” in-house RPS lawyer who does not prosecute “formally or informally” patents related to RP
 - “One or more” outside counsel who do not prosecute patents “formally or informally” related to RP
 - Owner of patent if not RPS and agrees to be bound by confidentiality provisions

Confidential Disclosure of Biosimilar Application

- **“Formally or informally”**
 - What does this mean?
 - Immediate supervisor of prosecuting attorney?
 - Head of in-house IP group?
 - Responsible partner at law firm for client?
- **“Related” to RP**
 - How related?
 - Same basic technology?
 - Any patent that you might sue on?
 - What about patents where claims do not actually cover the product?
- **“Do/Does not prosecute”**
 - Impact of past prosecution work?

Confidential Disclosure of Biosimilar Application

- Concern that confidential information may be used in RPS prosecution
- If new patent issues with claims specifically covering Biosimilar, may be difficult to prove information **not** derived from Biosimilar application
- Better to identify someone **not** involved in prosecution
- Consistent with ANDA litigation, wherein in-house lawyers denied access to confidential material under protective order - *Affymetrix, Inc. v. Illumina, Inc.*, 205 U.S. Dist. LEXIS 15482 (D.Del. 2005)

Confidential Disclosure of Biosimilar Application

- **Limitation on disclosure** 42 U.S.C. § 262(l)(1)(C),(D),(F)
 - No disclosure to anyone else without prior written consent
 - Includes RPS employees, outside experts, or other outside counsel
 - Information “**only**” used to determine identify relevant patents that “**a claim of patent infringement could reasonably be asserted**”
 - Confidentiality provisions govern until court enters protective order
 - But “[u]pon entry of such order, the subsection (k) applicant **may** redesignate confidential information in accordance with the terms of that order.”

Confidential Disclosure of Biosimilar Application

- **What if you need help from a technical employee or outside expert?**
 - Need to obtain permission from Biosimilar applicant
 - Could be difficult to obtain, particularly if technical person is an employee of RPS (paradoxically, this may be the best person to provide the required information)
 - Perhaps both parties use a single expert for the purpose of deciding which patents should be part of litigation

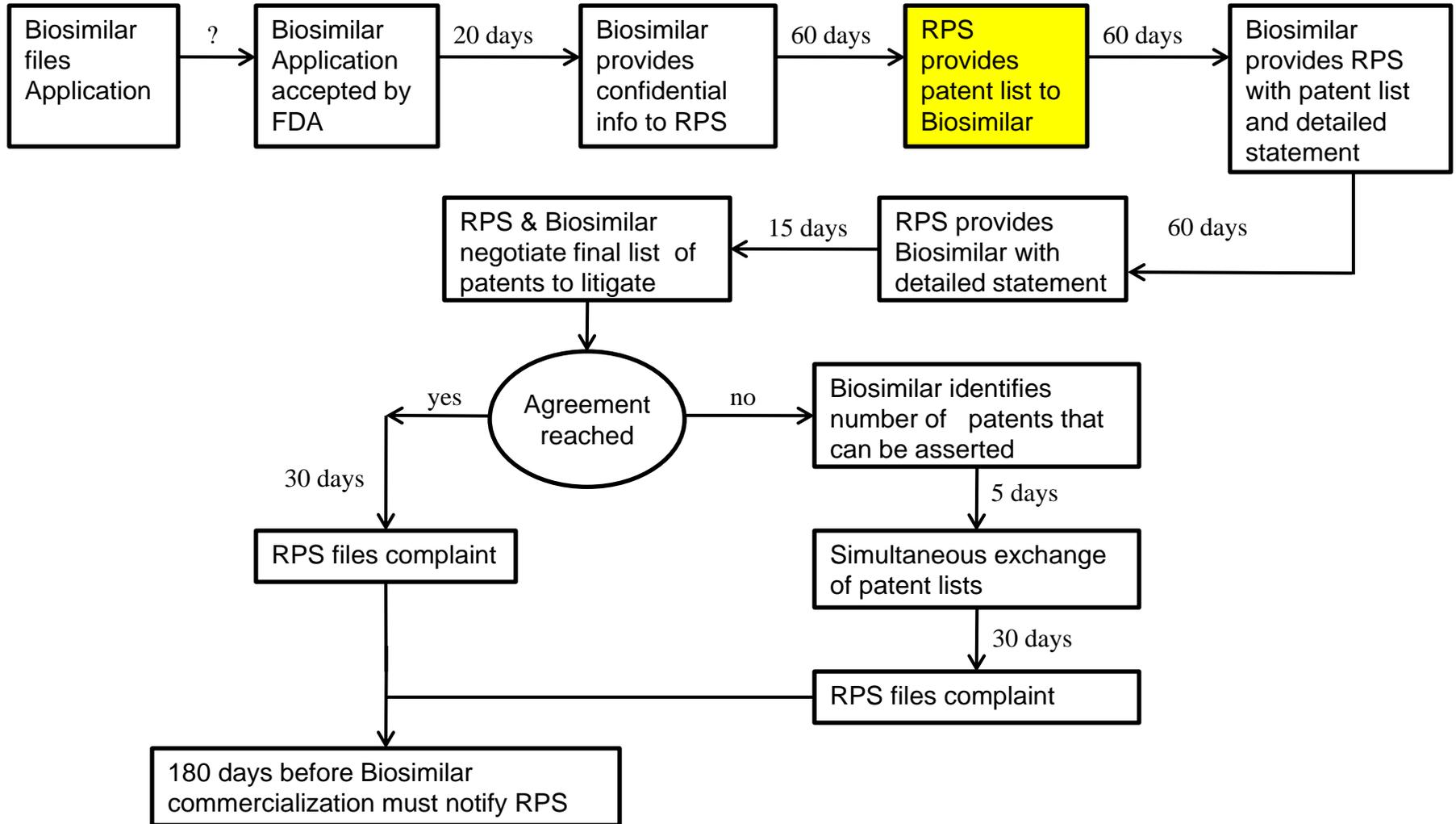
Confidential Disclosure of Biosimilar Application

- **No bar from practicing before the FDA concerning regulatory matters**
 - Can have regulatory counsel review the information under the statute, **but** information “**only**” used to determine identify relevant patents that “**a claim of patent infringement could reasonably be asserted**”
 - What about Citizen’s Petition?
 - If regulatory counsel has access will there be a presumption that information came from Biosimilar’s application ?
 - What if you need (health risk, etc.) to file a Citizen’s Petition with the FDA based on biosimilar application –how do you do it?

Confidential Disclosure of Biosimilar Application

- **Penalties for improper disclosure** 42 U.S.C. § 262(l)(1)(H)
 - Improper disclosure is presumed to cause Biosimilar applicant “irreparable harm” (trade secret?)
 - Court “shall enter” immediate injunctive relief appropriate and necessary to remedy violation
 - How do you obtain an injunction if no lawsuit filed?
 - File a new lawsuit with a TRO?
 - Jurisdictional issues – may need to file in a different jurisdiction than where lawsuit will be filed, depending on where the breach occurred

Patent Exchange Process



RPS List of Patents

- Within **60 days** after receiving copy of Biosimilar application RPS “**shall provide**”:
 - “A list of patents for which the reference product sponsor believes a claim of ***patent infringement could reasonably be asserted***” and
 - “Identification of the patents . . . that the reference product sponsor would be ***prepared to license*** to the” Biosimilar applicant

RPS List of Patents

- RPS must list their own patents as well as patents owned by third parties that could reasonably be asserted

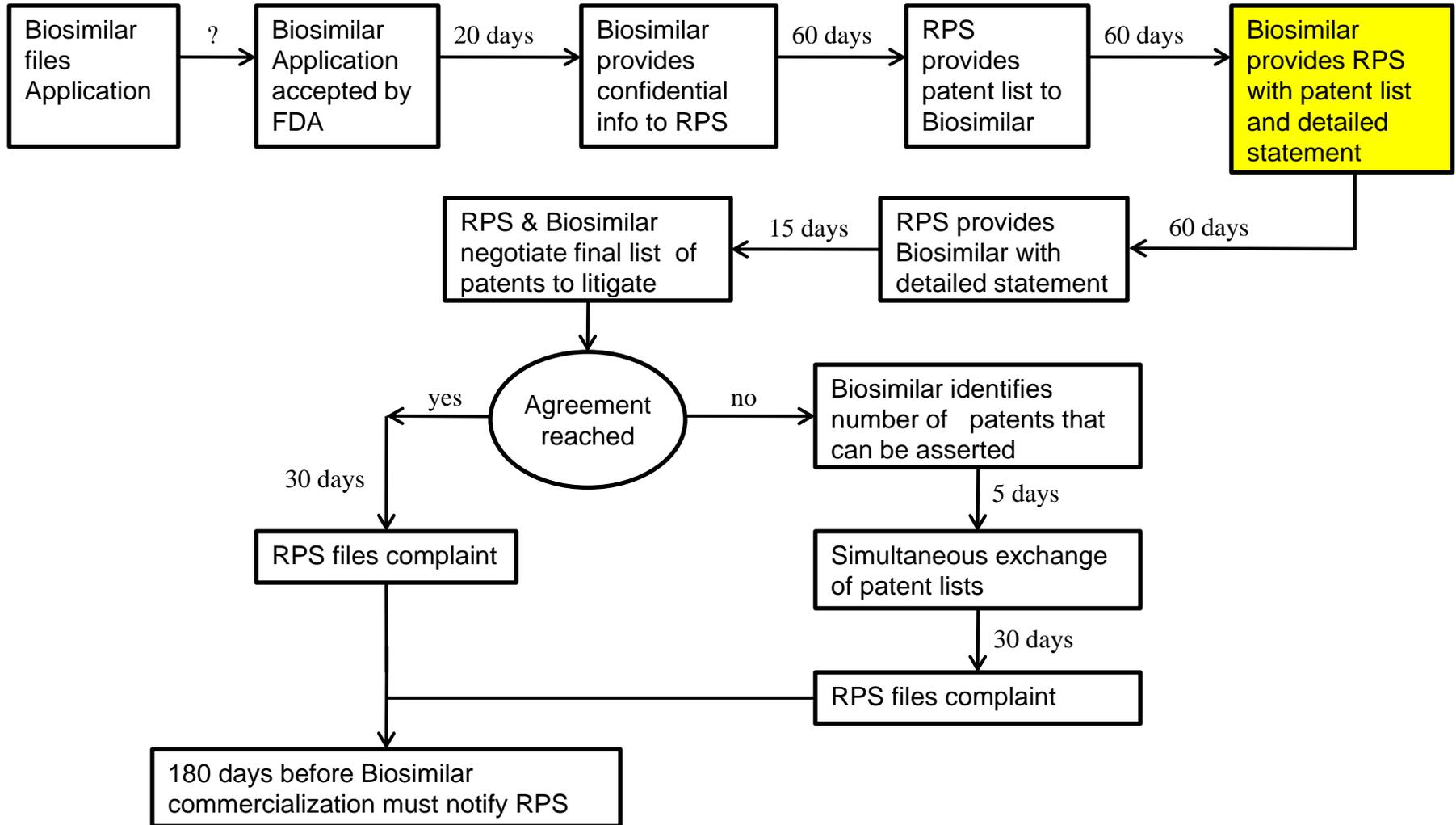
42 U.S.C. § 262(l)(3)(A)

- Communicate with Third Party patent owners before you receive Biosimilar application
 - Do you take a license
 - Do you renegotiate license terms
 - Determine if you are you obligated to assert licensed patents against infringers

RPS List of Patents

- Duty to supplement patent lists
 - Reference product sponsor must notify Biosimilar applicant of newly issued /licensed patents (for which a claim of patent infringement could be reasonably asserted) within **30 days** of issuance/licensing 42 U.S.C. § 262(l)(7)
- RPS's failure to list patents
 - If RPS fails to list patents or supplement list then owner of that patent “***may not bring an action under this section for infringement of the patent with respect to the biological product***” 35 U.S.C. § 271(e)(6)(C)
 - Could RPS file an action under 35 USC § 271(a) after Biosimilar product on market or a DJ action if launch is imminent?

Patent Exchange Process

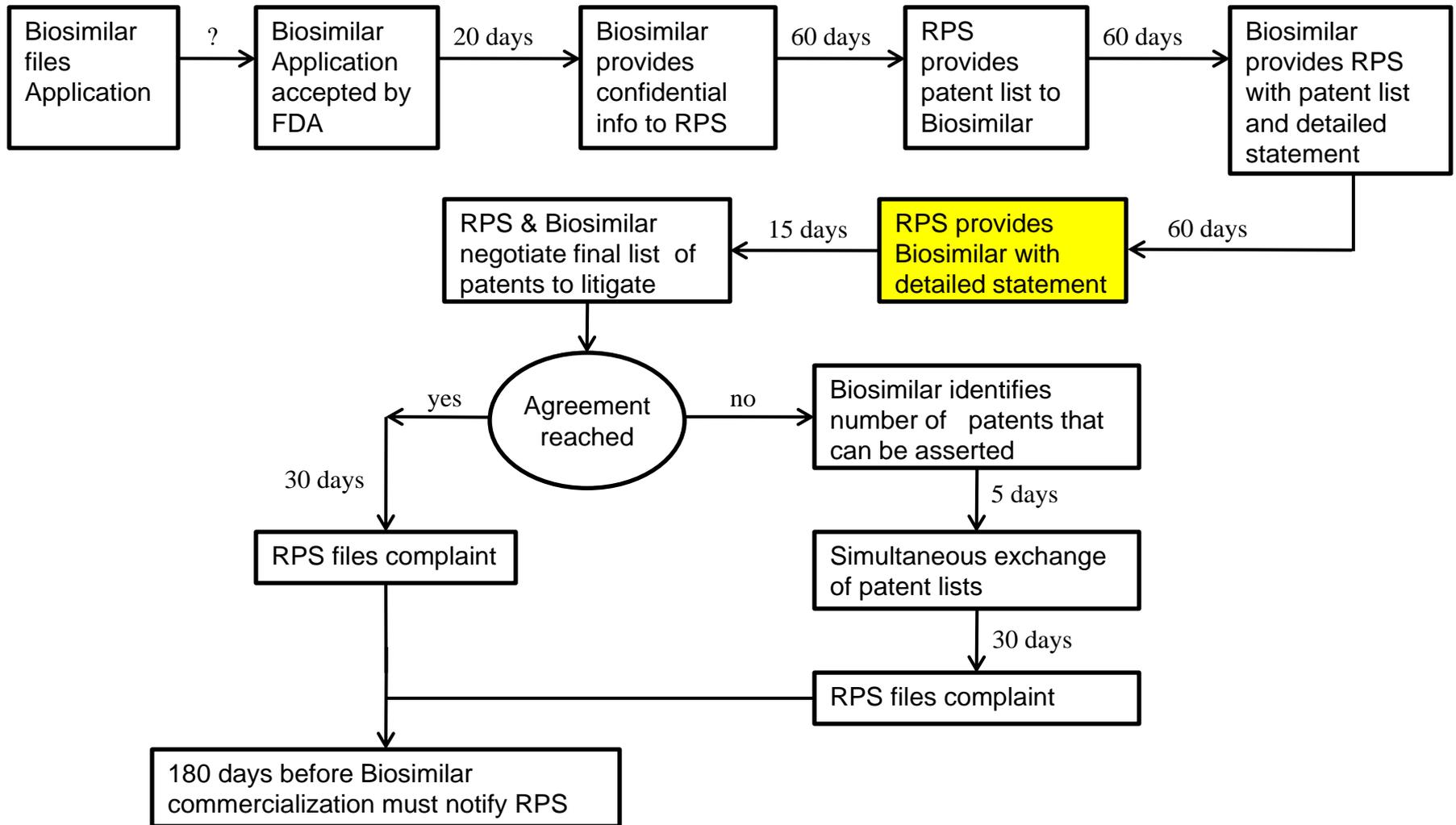


Biosimilar Applicant List of Patents and Detailed Statement

- Within **60 days** after receiving patent list from RPS, Biosimilar applicant “**shall provide**”:
 - A **detailed statement** that describes, on a claim by claim basis, the factual and legal basis of the opinion . . . that [each listed] patent is invalid, unenforceable, or will not be infringed” **or**
 - “A statement that the [Biosimilar] applicant does not intend to begin commercial marketing of the biological product before the date that such patent expires;” and
 - Response regarding any licensing offer
- Biosimilar applicant “**may provide**”:
 - “A **list of patents** for which the . . . [Biosimilar] applicant believes a claim of **patent infringement could reasonably be asserted**”

42 U.S.C. § 262(l)(3)(B)

Patent Exchange Process

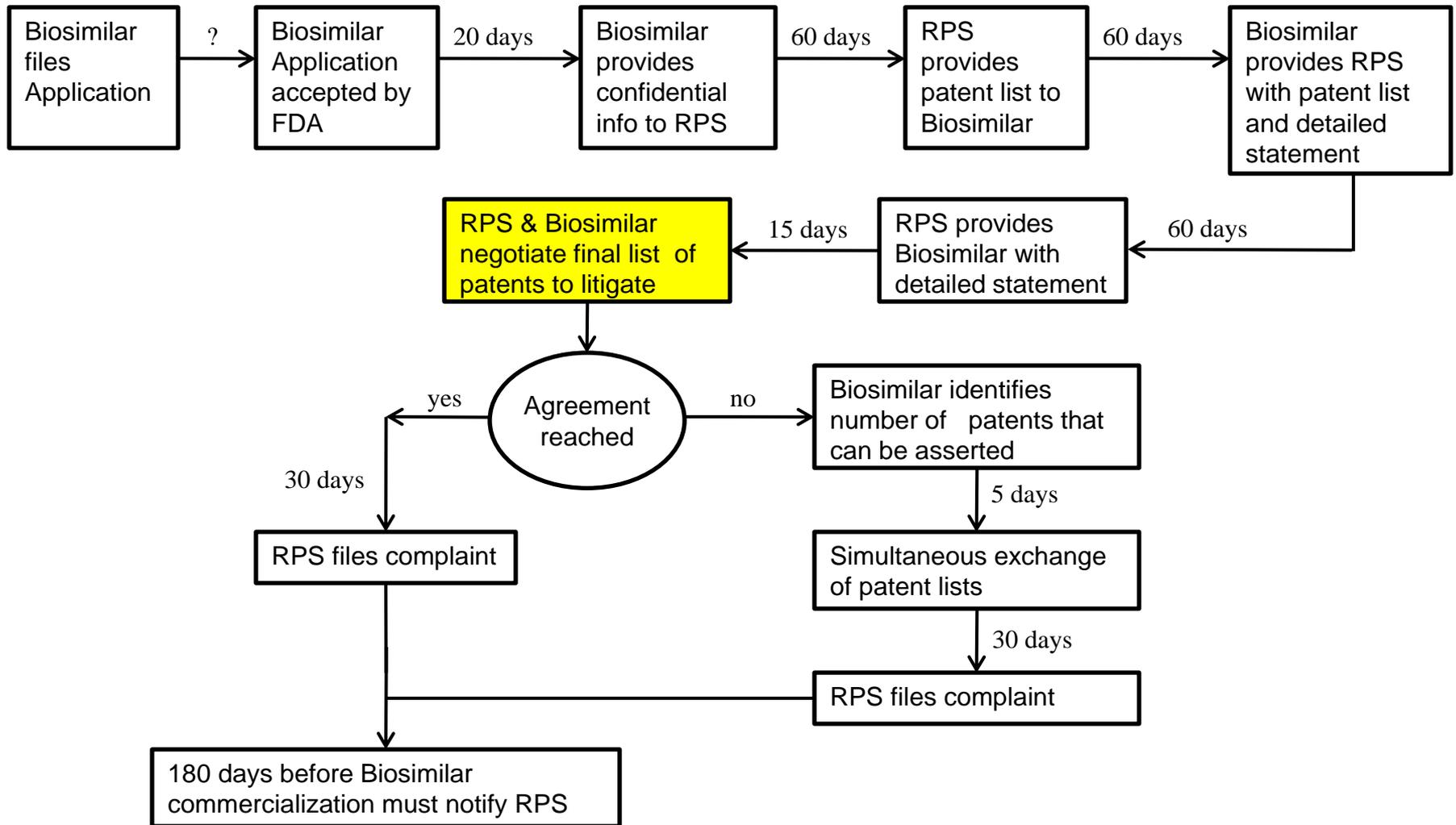


RPS Detailed Statement

- Within **60 days** after receiving list and detailed statement from Biosimilar applicant RPS “**shall provide**”:
 - “A **detailed statement** that describes . . . on a claim by claim basis, the factual and legal basis of the opinion of the [RPS] that [each listed] patent will be infringed” by the Biosimilar and
 - “A **response**” to any allegation by the Biosimilar applicant that patents are invalid or unenforceable

42 U.S.C. § 262(l)(3)(C)

Patent Exchange Process



Duty to Negotiate Prior to Filing Suit

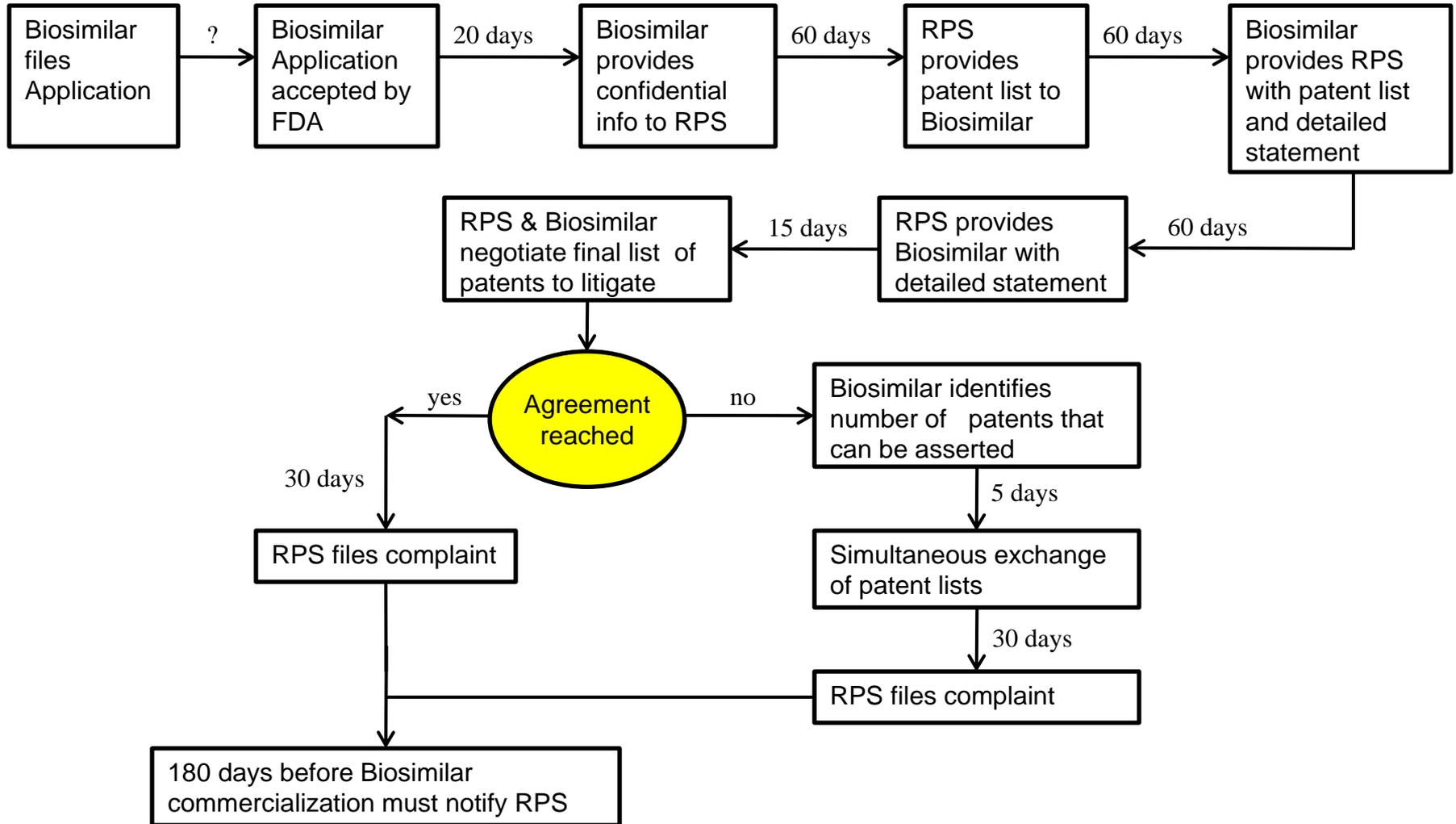
- **15 days** for RPS and Biosimilar applicant to negotiate in good faith upon list of patents for litigation
 - Patents to litigate selected from patents identified during exchange period

42 U.S.C. § 262(l)(4)
- If RPS and Biosimilar agree, RPS must file suit on agreed upon patents within 30 days

42 U.S.C. § 262(l)(6)
- If no agreement reached follow alternative procedures

42 U.S.C. § 262(l)(5)

Patent Exchange Process



Duty to Negotiate Prior to Filing Suit

- No agreement on patent list
 - If the RPS and Biosimilar applicant **do not agree** on patents for litigation within 15 days then:
 - Biosimilar applicant “shall notify” RPS of number of patents it will provide to RPS
 - Five days later RPS and Biosimilar simultaneously exchange
 - List of patents RPS believes should be in suit
 - List of patent Biosimilar believes should be in suit
 - RPS list cannot exceed number of patents identified by Biosimilar
 - **Except** if Biosimilar provides no patents, then RPS can list one patent

42 U.S.C. § 262(l)(5)

Infringement Actions

- Infringement action when no agreement on patent list
 - Upon completion of exchange RPS “shall bring an action for patent infringement with respect to each patent that is included on such lists”

42 U.S.C. § 262(l)(6)(B)

- How often will RPS and Biosimilar not agree on the list of patents to be litigated?

Remedies for Timely Lawsuit

- RPS is entitled to **mandatory permanent injunction** against infringement if:
 - (a) Suit filed within 30 days,
 - (b) Final judgment of infringement from which no appeal can be taken (excluding certiorari to the Supreme Court), and
 - (c) FDA has yet to approve Biosimilar because of 12 year exclusivity
 - Depending on when Biosimilar filed application RPSs may need to litigate quickly

35 U.S.C. § 271(e)(4)(D)

- Might obtain permanent injunction under *eBay* if (a)-(c) not met

Remedies for Timely Lawsuit

- Do you file application early or late in 12-year exclusivity period
 - If file early, you may have the opportunity to be 1st approved interchangeable
 - If file late, you may preclude RPS from obtaining injunction

Limitations on Remedies

- RPS's remedy for infringement shall be limited to a **reasonable royalty** if:
 - Suit was filed **after the 30 day period**, or
 - Suit was filed within 30 day period, but was **dismissed without prejudice** or **was not prosecuted to judgment in good faith**

35 U.S.C. § 271(e)(6)(A)-(B)

- Airtight complaint and personal jurisdiction are of paramount importance

Preliminary Injunctions

- Biosimilar applicant must give RPS 180-day notice before date of first commercial marketing of Biosimilar
- After receiving 180-day notice, and before commercial marketing by Biosimilar, RPS may seek a preliminary injunction with respect to any patent
 - Identified during patent exchange but Biosimilar applicant excluded from the list of patents to litigate
- RPS and Biosimilar applicant have a duty to cooperate in expediting discovery for purposes of preliminary injunction

42 U.S.C. § 262(l)(8)

Declaratory Judgment Actions-Permitted

- Declaratory judgment actions are permitted in very specific circumstances
- **Timing:**
 - RPS and Biosimilar applicant **cannot file** DJ actions until 180 days before 1st commercial marketing **if** Biosimilar applicant provides RPS with copy of Biosimilar application
42 U.S.C. § 262(l)(9)(A)
 - If Biosimilar applicant does **not** provide copy of Biosimilar application, RPS **may** file DJ action before the 180 day period
42 U.S.C. § 262(l)(9)(A),(C)

Declaratory Judgment Actions-Permitted

- RPS **can file** DJ on any patent on list it provided to Biosimilar applicant **if** Biosimilar applicant fails to:
 - Complete exchange of patent information or
 - Provide detailed statement, or
 - Notify FDA that RPS filed suit, or
 - Provide the required notice of first commercial marketing

42 U.S.C. § 262(l)(9)(B)

- RPS **can file** DJ on any patent that “claims the biological product or a use of the biological product” **if** Biosimilar applicant fails to provide the Biosimilar application to the RPS
 - No DJ on process patents

42 U.S.C. § 262(l)(9)(C)

Could There Be Three Rounds of Litigation?

- Round 1: Initial suit after the patent exchange process
- Round 2: Preliminary injunction 180 days before 1st commercial marketing on patents exchanged but not litigated
- Round 3: Traditional §271(a),(b), and/or (c) suit after commercial launch of Biosimilar product on new patents

Could There Be A Fourth Round?

- Round 0: Declaratory judgment action before filing of Biosimilar application?
- *Sandoz v. Amgen*
 - Sandoz filed a declaratory judgment action challenging the validity of two patents that cover Enbrel®
 - Sandoz made large investment in phase III clinical trials
 - Product unlikely to change
 - Phase III trials merely confirmatory of results of phase II trials
 - Amgen filed a motion to dismiss

Could There Be A Fourth Round?

- “Neither Amgen nor Roche has made any threats to Plaintiff. Thus, there is not any controversy between the parties that has sufficient immediacy or reality to invoke this Court’s declaratory judgment jurisdiction.”
- “This action is simply an attempt to obtain an advisory opinion on two of several patents owned by or licensed to Roche and/or Amgen that may be problems for Plaintiff should its biosimilar candidate survive further clinical testing.”
- “If Plaintiff ultimately produces sufficient experimental evidence (pre-clinical, clinical, and quality) to support the filing of an application for FDA approval of a biosimilar etanercept product, a patent dispute will likely ripen—but that point is years away and will likely involve other relevant patents”

Could There Be A Fourth Round?

- “To accept this case at this juncture would set a bad precedent in a variety of ways. In a time of decreasing judicial resources and increasing caseloads, it would encourage resource-consuming patent litigation that could be wholly mooted by either (1) a Phase III clinical trial failure; (2) the declaratory judgment plaintiff’s inability, for whatever reason, to submit an FDA application; or (3) the FDA’s refusal to approve a product submitted for approval.”

Could There Be A Fourth Round?

- “[T]he statutory schemes for resolution of patent disputes involving biologics seeking approval pursuant to the “biosimilar” pathway, as well as the statutory scheme for resolution of patent disputes involving generic pharmaceuticals, set the triggering act for statutory jurisdiction at the filing of an application for FDA approval to market the product candidate.
- “These statutory schemes reflect the Congressional judgment that the appropriate time for the courts to have jurisdiction to resolve patent disputes is at the filing of an FDA application, coincident with the applicant’s representation to the FDA that it has completed sufficient clinical testing and analysis of its product candidate to justify FDA approval.”

Consequences of Patent Negotiations

- Statute requires multiple disclosures of patent-related information from both parties
- What types of liability could these representations raise?
 - Rule 11
 - Admissions

Rule 11

- Relevance to biosimilars negotiations can be found in parallel standards applied to Paragraph IV certifications in ANDA litigation
- Requires exercise of an appropriate “duty of care” - *Yamanouchi Pharma. Co. v. Danbury Pharmacal. Inc.*, 231 F.3d 1339 (Fed. Cir. 2000)
- Inadequate basis and/or investigation raises possibility of sanctions; see, *View Eng’g. Inc. v. Robotic Vision Sys. Inc.*, 208 F.3d 981 (Fed. Cir. 2000); *Dome Patent LP v. Permeable Tech Inc.*, 190 F.R.D. 88 (W.D.N.Y. 1999)
- Bad faith or baseless certification subject to sanctions - *Takeda Chem. Indust., Ltd. v. Mylan Labs. Inc.*, 549 F.3d 1381 (Fed. Cir. 2008)(sanctions based on “baseless” certification of obviousness)

- One distinction with Paragraph IV certifications in ANDA litigation is that courts recognize they are made in the absence of discovery
- Under the BPPCIA the required disclosures may be the equivalent to discovery
- RPS “detailed statement” identifying patents infringed by biosimilar requires claim construction and applying construed claims to biosimilar product
- Both assertions can raise ethical issues that may be subject to sanction
- But the standards for deserving sanctions differ

- Claim construction standard is that the construction asserted not be “frivolous” - *Antonius v. Spaulding Evenflo Co., Inc.*, 275 F.3d 1066 (Fed Cir. 2002)
- Frivolous claim construction can include ignoring plain meaning of a claim term or an express definition of a term in the specification
- However, recognizes the provisional nature of claim construction even when performed by a district court, and accordingly sanctions not available merely because the RPS’s claim construction not the ultimate construction
- Good faith effort all that’s required

Rule 11

- Infringement involves questions of fact requiring at least some analysis of how accused biosimilar product reads on construed claims
- Absence of such an analysis raises possibility of sanctions - *View Eng'g. Inc. v. Robotic Vision Sys. Inc.*, 208 F.3d 981 (Fed. Cir. 2000)
- Relying on lay (i.e., non-expert) opinion can also raise possibility of sanctions - *Antonius v. Spaulding Evenflo Co., Inc.*, 275 F.3d 1066 (Fed Cir. 2002)
- Actual comparison sufficient even if no infringement found, *Dome Patent LP v. Permeable Tech Inc.*, 190 F.R.D. 88 (W.D.N.Y. 1999)

Rule 11

- Additional potential for sanctions involving manufacturing methods
- Typically, infringement assessment of method of manufacturing claims subject to higher standard for deserving sanction due to the difficulties of a patentee discerning whether its patented methods are being used by the accused infringer - *Dome Patent LP v. Permeable Tech Inc.*, 190 F.R.D. 88 (W.D.N.Y. 1999)
- Some investigation required - *Hoffman La Roche Inc. v. Invamed, Inc.*, 213 F.3d 1359 (Fed. Cir. 2000)
- The “reasonable inference” test - *Antonius v. Spaulding Evenflo Co., Inc.*, 275 F.3d 1066 (Fed Cir. 2002)
- But part of the required disclosure from the biosimilar applicant to the RPS is a description of its manufacturing processes

Admissions and Waiver

- Both RPS and biosimilar applicant required by statute to make affirmative representations of law and fact regarding:
 - The RPS must identify a list of patents for which claim of infringement could reasonably be asserted against person engaged in unlicensed making, using, offering to sell, selling, or importation
 - The biosimilar applicant must provide a detailed statement describing, on a claim by claim basis, the factual and legal basis for opinion that each listed patent is invalid, unenforceable, or will not be infringed by commercial marketing of biosimilar
 - Biosimilar applicant has immunity under the statute but not RPS (no Rule 708 FRE exception for either)

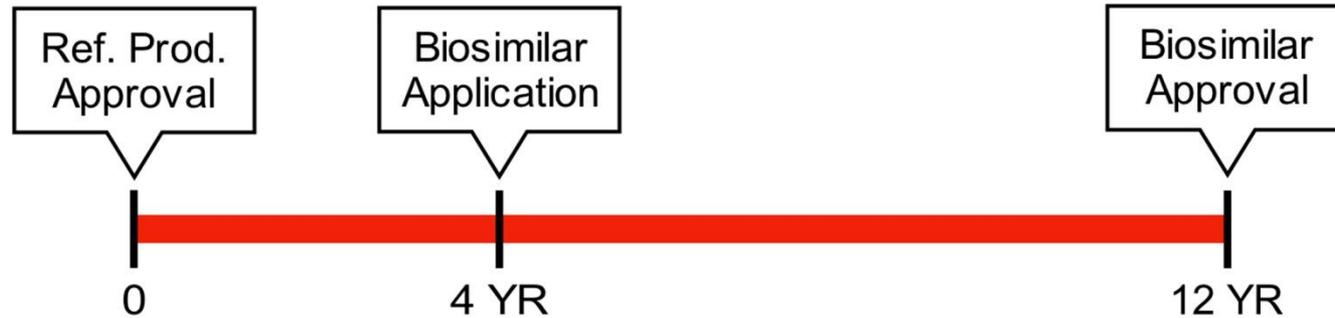
Long Term Predictions

- Changing biosimilar patent strategy: drift towards trade secrets to avoid disclosing manufacturing secrets and enjoy statutory exclusivity instead
- Prior User Rights defense from AIA also incentivizes trade secret protection for manufacturing methods
- *Myriad* – broad "product of nature" preclusion could have negative effects on biologic drugs

Less Reliance on Patent Exclusivity

- Strong likelihood that the combination:
 - Non-specific guidances;
 - Reduced scope of patent protection;
 - Possibility of protecting manufacturing methods by asserting prior user rights defense; and
 - Complex litigation provisions of the law
- provide incentives for biologic drug innovators to rely more heavily on the market exclusivity provisions of the Act than on patents

Statutory Exclusivity



- Prohibits biosimilar filings until 4 years after reference product is licensed
- Prohibits biosimilar approval until 12 years after reference product is licensed

Less Reliance on Patent Exclusivity

- **What will be the relevance of patents in the future of Biosimilars?**
- If innovators eschew patenting altogether
- What must be shared:
 - How the biologic was made
 - Characterization of the biologic (with the FDA)
- But NOT the cell itself
- Advantages:
 - Obstacles to biosimilar applicants
 - Avoiding biosimilars litigation under the statute

Universities and Startups

- **"If Patents Become Irrelevant in a Biosimilars Future, What About University Patents and Startups?"**
- Statutes:
 - BPCIA
 - Hatch-Waxman Act
 - Bayh-Dole
- Biotech patenting plays a vital role in early development, especially licensing, but then is de-emphasized for later stage development
- Startups have become the feeder for new technologies for large pharmaceutical companies
- Startups could flounder if patents become less important in biologics development

www.patentdocs.org, Dec. 21, 2011

- **The importance of patent protection cannot be understated or minimized**
- But patent exclusivity might not hold the preeminent role it does with small molecule drugs

Thank You!



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