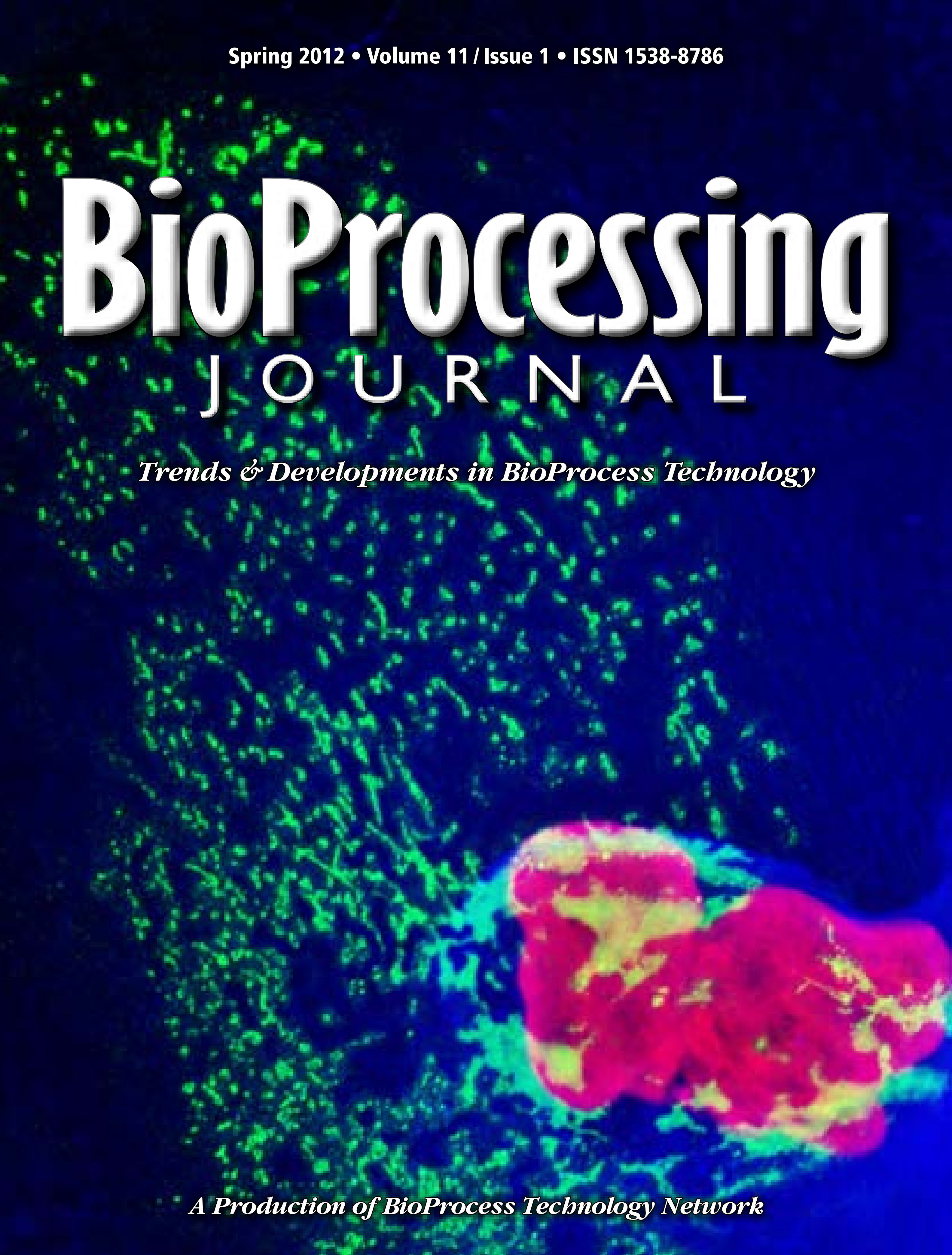
Spring 2012 • Volume 11 / Issue 1 • ISSN 1538-8786

BioProcessing JOURNAL

Trends & Developments in BioProcess Technology



A Production of BioProcess Technology Network

BioProcessing JOURNAL

TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Recent Statutes, Regulations, and Court Cases Affecting Intellectual Property Rights of Life Sciences Institutions:
Key Provisions of the Leahy-Smith America Invents Act and the Biologics Price Competition and Innovation Act

The Second of a Three-Part Series

Analysis of the BPCIA, the Pre-Approval Patent Resolution Process, Regulatory Exclusivity Periods, and Complementary Rules Affecting Patent Terms

By VERNE A. LUCKOW

The Patient Protection and Affordable Care Act (PPACA), which was passed in 2010, included the Biologics Price Competition and Innovation Act (BPCIA) authorizing the United States Food and Drug Administration (FDA) to establish an abbreviated regulatory approval pathway for complex macromolecules produced in living cells or organisms. The BPCIA implements many new provisions relating to the abbreviated review and approval of follow-on biopharmaceutical products. These include: (1) evaluating the biochemical properties of reference and follow-on macromolecules; (2) establishing procedures for the exchange of information between product sponsors, regulatory agencies, and the federal court system; and (3) establishing periods of regulatory exclusivity which complement patent rights typically awarded to the sponsor of a reference molecule. Important aspects of the BPCIA, particularly issues relating to the exchange of information between product sponsors and the establishment of periods of regulatory exclusivity protecting a novel or follow-on macromolecule are discussed in this article. This is the second in a series of three articles describing key provisions of the Leahy-Smith America Invents Act (AIA) and the BPCIA that affect intellectual property rights of academic and corporate institutions having an interest in the life sciences.

Introduction

Two recently-enacted statutes will fundamentally alter the business strategies and investment patterns of many institutions involved in projects relating to the life sciences for many years. The AIA of 2011 provides a transition from a "First-to-Invent" (FTI) system to a "First-Inventor-to-File" (FITF) patent system and significantly alters United States Patent and Trademark Office (PTO) policies relating to the filing, prosecution, and review of patents.[1] The BPCIA, which was included in the PPACA of 2010, established an abbreviated regulatory approval pathway through the FDA for macromolecules (*e.g.*, biologics) produced in living cells or organisms.[2] Three major issues are addressed in the BPCIA:

- Authorizing the FDA to establish formal guidelines for evaluating the similarity, bioequivalence, and immunogenicity of reference and follow-on macromolecules, commonly called follow-on biologics (FOBs);
- Establishing procedures for the sponsor of a reference macromolecule and the sponsor of an FOB to use in exchanging patent and regulatory information between each other, the FDA, and federal court systems; and
- Establishing periods of data and market exclusivity for reference macromolecules, regardless of patent protection, that reflect more complex methods

ABOUT THE AUTHOR

Verne A. Luckow, PhD, JD is a registered patent attorney who concentrates his practice on patent and regulatory matters for academic and corporate institutions and research foundations having interests in the life sciences.

The Intellectual Property Law Office of Verne A. Luckow, LLC
PO Box 288, Chesterfield, MO 63006 | Email: VLuckow@LuckowIPLaw.com

needed to discover, characterize, and manufacture macromolecules compared to small chemicals, and periods of market exclusivity for the first sponsor to file and have an FOB application approved by the FDA.

The AIA and the BPCIA are both very complex statutes, authorizing implementation of many new PTO- and FDA-specific regulations relating to the granting of specific patent rights, or the review and approval of a product for human or animal use, respectively. Several provisions, such as those relating to patent term extensions and the length of regulatory exclusivity periods involve procedures requiring review by both agencies.

This article addresses the information exchange and regulatory exclusivity issues noted above, and briefly compares pre-approval procedures authorized under the BPCIA to procedures used under rules established under the Hatch-Waxman Act (HWA) relating to small molecules.[3] Patent prosecution and litigation strategies that are likely to be used by the sponsors of reference and follow-on macromolecules are discussed in the next section. Issues relating to regulatory exclusivity periods and the term of a patent protecting a reference molecule, along with recent court cases relating to patent term adjustments (PTA) and extensions that are often of high interest to many biotechnology and pharmaceutical institutions, will be discussed in subsequent sections. Key provisions of the AIA were reviewed in the first article in this series.[4] Regulatory issues relating to the biochemical characterization of macromolecules will be discussed in the third article in this series, which should be clarified by the FDA in draft BPCIA guidance documents released for public review on February 9, 2012.[5]

Pre-Approval Procedures for the Exchange of Patent and Regulatory Information Between the Reference Product and the FOB Sponsors, the FDA, and Federal Court Systems

The BPCIA provides a complex pre-approval process for the resolution of patent disputes between the sponsors of reference macromolecules and the sponsors of FOB. This process, which is different in many respects from the pre-approval process for small molecules established under the HWA, is designed to reduce uncertainty over patent infringement issues and anti-competitive conduct before FDA approval of a follow-on macromolecule. As noted below, some provisions outlined in the BPCIA do not appear to provide a stable doctrinal framework for the resolution of patent disputes in an efficient, or timely, manner.

Under the BPCIA, submission of an application is recognized as an act of patent infringement. Procedures relating to the exchange of information between the 42 USC § 262(k) applicant (the FOB Sponsor, or FOBS, for short) and the sponsor of the reference product (RPS) are complex and different in many ways from the procedures used under the Hatch-Waxman rules relating to small molecules. Under the BPCIA, lists containing the names of reference products, and the patents considered by the RPS to claim those products, are not published. The FOBS must provide its complete application to the RPS with its own list of relevant patents concerning the product itself, methods of use, and methods of making, or process, patents. This is different from the Hatch-Waxman rules, where the relevant product and method of use, but not process patents, are published in the FDA's Orange Book listing of approved drug products.[6] A multi-step exchange of documents then begins, with tight deadlines and strict confidentiality requirements, designed to lead to an agreement concerning the list of relevant patents to be litigated in court. In the second phase, the RPS brings an action against the FOBS for infringement with respect to each patent on the list. The BPCIA was designed to quickly resolve these disputes in court or through settlement agreements, using procedures that provide incentives for both parties, and strong penalties for those who do not comply with confidentiality and timeliness requirements. Czaban *et al.* described these procedures as "The Kabuki theater of biologics patent litigation."[7]

Confidentiality Requirements and Penalty Provisions Under the BPCIA

The BPCIA has strict provisions relating to the confidentiality of documents submitted to the FDA and the exchange of documents between the FOBS, the RPS, and their representatives, under 42 USC §§ 262(l) (B)–(H). Violations are construed as causing the FOBS irreparable harm, subject to immediate injunctive relief as appropriate and necessary by the court hearing the dispute between the parties. The application, and any other information which is provided to the RPS by the FOBS, is considered confidential. The RPS is allowed to have one attorney as in-house counsel, and one or more attorneys as outside counsel, to be recipients of confidential information from the FOBS, provided that such attorneys do not engage, formally or informally, in patent prosecution that is relevant or related to the reference product. A representative of the owner of a patent exclusively licensed to an RPS with respect to the reference product, and who has retained a right to assert the patent or participate in litigation concerning the patent, may be provided the confidential information, provided that the representative informs the RPS and the FOBS of his or her agreement to be subject to the confidentiality provisions set forth in the BPCIA.

There are also restrictions on the secondary disclosure and use of confidential information. A recipient is not allowed to disclose confidential information to any other person or entity, including the RPS' employees, outside scientific consultants, or other outside counsel retained by the RPS, without the prior written consent of the FOBS. The confidential information is the property of the FOBS, and the RPS and its outside counsel may not use it for any other purposes, except for the sole and exclusive purpose of determining, with respect to each patent assigned to (or exclusively licensed by) the RPS, whether a claim of patent infringement could reasonably be asserted if the FOBS engaged in the manufacture, use, offering for sale, sale, or importation into the United States of the biological product specified in the application. No confidential information shall be included in any publicly-available complaint or other pleading, although a court hearing a patent infringement suit may redesignate the confidentiality status of information under the terms of a protective order.

The First Phase Leading to Agreement on a List of Relevant Patents to be Litigated in Court

The BPCIA outlines a complex procedure, which is summarized in Table 1 below, for the exchange of documents between the applicant (FOBS) and the RPS, upon acceptance of the application by the FDA. The tight deadlines are designed to ensure that a reasonable list of patents to litigate or license is established within a 215-day period after the FOBS is notified that its application was accepted by the FDA.

TABLE 1. Phase I—Establishing a list of relevant patents.

Action Required by FDA, FOBS, and/or RPS	Statute Reference
• The FDA notifies the FOBS that the application has been accepted for review.	42 USC § 262(l)(2)
• Within 20 days, the FOBS:	
(a) *shall provide* the RPS with a copy of the application, and other info describing processes used to make the RP; and	42 USC § 262(l)(2)(A)
(b) *may provide* other info requested by or on behalf of RPS.	42 USC § 262(l)(2)(B)
• Within 60 days, the RPS or its exclusive licensor:	
(i) *shall provide* to the FOBS a list of patents where a claim of patent infringement could reasonably be asserted against RPS; and	42 USC § 262(l)(3)(A)(i)
(ii) *shall provide* to the FOBS a list of patents that RPS is willing to license to the FOBS.	42 USC § 262(l)(3)(A)(ii)
• Within 60 days, the FOBS:	
(i) *may provide* to the RPS, a list of patents which the FOBS believes a claim of patent infringement could reasonably be asserted by the RPS (if a person not licensed by the RPS made, used, offered to sell, sold, or imported the RP);	42 USC § 262(l)(3)(B)(i)
(ii) *shall provide* to the RPS, with respect to each patent listed by the RPS:	
(I) a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of the FOBS that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product that is the subject of the subsection (k) application; or	42 USC § 262(l)(3)(B)(ii)(I)
(II) a statement that the FOBS does not intend to begin commercial marketing of the biological product before the date that such patent expires; and	42 USC § 262(l)(3)(B)(ii)(II)
(iii) *shall provide* to the RPS a response regarding each patent identified by the RPS under ¶ (A)(ii).	42 USC § 262(l)(3)(B)(iii)
• Within 60 days after receipt of the list and statement, the RPS *shall provide* to the FOBS a detailed statement that describes, with respect to each patent described in subparagraph (B)(ii)(I), on a claim by claim basis, the factual and legal basis of the opinion of the RPS that such patent will be infringed by the commercial marketing of the biological product that is the subject of the 42 USC § 262 (k) application and a response to the statement concerning validity and enforceability provided under ¶(B)(ii)(I).	42 USC § 262(l)(3)(C)
• Upon receipt of the detailed statement, the RPS and the FOBS *shall engage* in good faith negotiations to agree on which, if any, patents listed by the FOBS or the RPS shall be the subject of an action for patent infringement under ¶(6).	42 USC § 262(l)(4)(A)
• Within 15 days of beginning negotiations, if the FOBS and the RPS fail to agree on a final and complete list of patents, if any, the FOBS or the RPS *shall be the subject of an action* under the BPCIA for patent infringement.	42 USC § 262(l)(4)(B)

The Second Phase Concerning Resolution of Patent Infringement Issues in Court or By a License Agreement

In the second phase, the RPS brings an action against the FOBS for infringement with respect to each patent on the list, as summarized in Table 2 below.

Litigation Procedures and Limits on Declaratory Judgment Actions Under the BPCIA

The BPCIA imposes several limitations on the timing and nature of lawsuits involving the RPS and the FOBS, under 42 USC §§ 262(l)(8)(A)–(C). The FOBS is required to provide notice to the RPS not later than 180 days before the date of the first commercial marketing of the biological product licensed under 42 USC § 262(k). After receiving notice, and before the date of first commercial marketing, the RPS may seek a preliminary injunction prohibiting the FOBS from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that is: (i) included in the list provided by the RPS under ¶(3)(A) or in the list provided by the FOBS under ¶(3)(B); and (ii) not included, as applicable, on: (I) the list of patents described in ¶(4); or (II) the list of patents described in ¶(5)(B). The RPS and the FOBS are also required to reasonably cooperate to expedite discovery proceedings in connection with the preliminary injunction noted previously.

The BPCIA also places several limits on declaratory judgment actions. If the FOBS provides the application and information required under ¶(2)(A), neither the RPS nor the FOBS may, prior to the date notice is received under ¶(8)(A), bring any action under 28 USC § 2201, for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of ¶(8)(B), noted earlier. If the FOBS fails to complete an action required of the FOBS under ¶(3)(B)(ii), ¶(5), ¶(6)(C)(i), ¶(7), or ¶(8)(A), the RPS, but not the FOBS, may bring a declaratory judgment action for any patent included in the list described in ¶(3)(A), including as provided under ¶(7). If the FOBS fails to provide the application and information required under ¶(2)(A), the RPS, but not the FOBS, may bring a declaratory judgment action for any patent that claims the biological product or a use of the biological product.

It seems clear that the procedures leading to the various lists of patents and the lawsuits themselves will require a tremendous amount of analysis by the FOBS, the RPS, and their representatives. Complicating matters is the

TABLE 2. Phase II—resolving infringement issues.

Action Required by FDA, FOBS, and/or RPS	Statute Reference
• If there is no agreement on the number of patents on the list, the FOBS shall notify the RPS of the number of patents that it will provide to the RPS.	42 USC § 262(l)(5)(A)
• Within 5 days after notification, the FOBS and the RPS *shall simultaneously exchange*:	
(I) the list of patents that the FOBS believes should be the subject of an action for patent infringement; and	42 USC § 262(l)(5)(B)(i)(I)
(II) the list of patents that the RPS believes should be the subject of an action for patent infringement, which may not exceed the number specified by the FOBS, and if the FOBS lists none, the RPS may list 1.	42 USC § 262(l)(5)(B)(i)(II) 42 USC § 262(l)(5)(B)(ii)(I) 42 USC § 262(l)(5)(B)(ii)(II)
• If the FOBS and the RPS agree on the list of patents described in ¶(4), within 30 days of agreement, the FOBS *shall bring an action* for patent infringement with respect to each such patent.	42 USC § 262(l)(6)(A)
• If the FOBS and the RPS do not agree on the list of patents if the provisions of ¶(5) apply to the parties as described in ¶(4)(B), not later than 30 days after the exchange of lists under ¶(5)(B), the RPS *shall bring an action* for patent infringement with respect to each patent that is included on such lists.	42 USC § 262(l)(6)(B)
• Not later than 30 days after a complaint is served to the FOBS in an action for patent infringement, the FOBS *shall provide the FDA with notice* and a copy of such complaint, and the FDA *will publish a notice of a complaint* in the Federal Register.	42 USC § 262(l)(6)(C)(i)
• If a patent is issued or exclusively licensed to the RPS after the RPS has provided a list to the FOBS under ¶3(A), and the RPS reasonably believes that, due to the issuance of such patent, a claim of patent infringement could reasonably be asserted by the RPS:	42 USC § 262(l)(6)(C)(ii)
o Within 30 days the RPS *shall provide* to the FOBS a supplement to the list provided by the RPS under ¶(3)(A) that includes such patent;	42 USC § 262(l)(7)(A)
o not later than 30 days after such supplement is provided, the FOBS *shall provide* a statement to the RPS in accordance with ¶(3)(B), and such patent shall be subject to ¶(8).	42 USC § 262(l)(7)(B)

inclusion of process patents, requiring descriptions of the biochemical and immunological characteristics of the product under consideration, and whether the processes used by the FOBS fairly fall within the scope of patents owned by or licensed to the RPS. Many patents covering biological products that were issued over ten years ago have claims that are generally considered to be much broader in scope than what might be allowed under current guidelines for the examination of biotechnology inventions. While the "slow" trend may be towards claims having a narrower scope, there will be a great need for scientific and legal experts able to examine literature and parse claims to support or refute assertions that a biological product is within or outside the scope of a claim in one or more patents issued to the RPS over 15 years ago.

Provisions relating to violations of the confidentiality provisions, which are heavily weighed in favor of the FOBS, may need to be adjusted by statute, regulation, or court order, as well, to take into account inappropriate disclosure or use of RPS information that was received by the FOBS. Companies in the business of producing follow-on molecules are likely to be involved in filing many applications for such molecules, and it would be prudent to protect them as well, from unauthorized use of their information by an RPS or its outside counsel. Specific remedies for disclosure and use violations, or for failing to provide documents in a timely manner, are not provided in the BPCIA.

Establishing Periods of Regulatory Exclusivity for Reference and Follow-On Macromolecules That Complement Exclusivity Provisions Relating to Patent Terms

Regulatory exclusivity complements patent protection for the sponsors of innovative reference products and provides an advantage to the first sponsor to file an application for a generic or follow-on product compared to sponsors of applications filed at a later time. Exclusivity provides a benefit to the RPS when the remaining term of its patent is shorter than the effective length of its innovation exclusivity period at the time of approval. Lengthy preclinical research and clinical trials, which typically start after a patent is filed, may not be completed until well into the normal 20-year term of a utility patent claiming an active compound, methods of use, and methods of production. The RPS may also benefit from exclusivity provisions if a patent covering its reference molecule is challenged and found invalid or has its term reduced, before its normal expiration date.

The proper length of a new drug exclusivity period is considered to be the period, in aggregate, when the benefits from encouraging development of innovative reference molecules is equal to the costs of delaying competition by a sponsor of a generic version of a small molecule or an FOB.[8] The appropriate length of these periods is always subject to a vigorous debate, not only by the product sponsors, but also by politicians, economists, health care providers, insurance companies, and consumer advocates. During the debate leading up to the passage of the BPCIA, periods ranging from zero to 14 years were proposed, which have been summarized by Zuhn.[9] The sponsors of many innovative reference products favored a period that was much longer than the five-year period granted to the sponsor of a new chemical product under the HWA, asserting that more complex methods are needed to discover and characterize macromolecules produced on a large scale in living cells, compared to the synthetic methods used to produce small chemical molecules on a large scale. Macromolecules used as therapeutics may also stimulate the production of undesired antibodies, introducing another layer of complexity in preclinical research and clinical trials, compared to studies involving small molecules.

Congress eventually settled on a 12-year period of exclusivity for the RPS, beginning on the date of reference product approval, which runs concurrently with the term of patent protection for the product. During this period, the FDA will not approve any application for an FOB that uses data from the RPS. An application for an FOB cannot be submitted until four years after the reference product was approved. This leaves a long eight-year gap between the time an FOB application can first be filed, and when the 12-year exclusivity period ends. What is not clear, however, is whether the FOBS can incorporate and rely upon confidential data of the RPS when it prepares its FOB application for filing after the first four-year period, and what activities are permitted to occur during the eight-year gap period.

Data or Market Exclusivities, or Both Under the BPCIA?

There appears to be some confusion now over the apparent meaning of the exclusivity periods specified in the BPCIA, compared to those specified for the sponsors of new and generic drugs under the HWA. Generally, data exclusivity is considered to be the period in which the sponsor of a new, or reference, product has complete control over disclosure and use of the confidential information included in its application to the FDA for approval of a new product. Market exclusivity is generally considered to be the period in which the FDA will not approve an identical or similar drug to be sold within the United States, permitting the sponsor to be the sole source of that product. Market exclusivity can also be granted to the first sponsor to file a complete application for a generic (or follow-on) product, effectively limiting the source of the product to the reference sponsor and the first generic sponsor, compared to sponsors that file applications for a generic product after the first sponsor.

A data exclusivity period is usually shorter than, and fully contained within, a market exclusivity period, such that the sponsor of a generic product can incorporate and use the preclinical and clinical information provided in the application for a reference product in its application, which is filed after the expiration of the data exclusivity period. If the two periods are contiguous and of equal length, the generic sponsor cannot rely upon the data of the reference product sponsor, and introduction of the generic product is delayed beyond the expiration date of the two periods by the length of time it takes for the FDA to review and approve the application submitted by the generic product sponsor.

Unfortunately, many descriptions of data and market exclusivities often intermingle the meaning of the two terms, and several statutes and regulations are silent on that respect. Under the HWA, sponsors of new chemical entities are provided with a five-year period of new drug product exclusivity upon approval, which precludes approval of certain § 505(b)(2) applications under the Federal Food, Drug, and Cosmetic Act (FFDCA), and certain abbreviated new drug applications (ANDAs) under § 505(j) of the FFDCA.[10] No 505(b)(2) application or ANDA may be submitted during the five-year exclusivity period, but if they contain a certification of patent invalidity or non-infringement, they may be submitted after four years. A three-year "other significant changes" exclusivity is available for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations carried out by the sponsor that were essential to the approval of the application.[11] These include studies affecting the route of administration or composition, strength, or dosage of the active ingredients, but not bioavailability studies.

So, what is the nature of the four- and 12-year periods of exclusivity under the BPCIA? Advocates favoring the generic and follow-on product industry view the four-year period as a data exclusivity period contained within a 12-year market exclusivity period.[12] Others favoring the innovative product industry view the entire 12 years as a data exclusivity period, permitting the FOBS to use the confidential data of the RPS only after that period is over, but not prohibiting the FOBS to use other public data if it desires to file an application after only four years.[13] The latter view does not seem to be consistent with the four- and five-year submission prohibition periods (with and without certifications of patent invalidity or non-infringement) specified under the FFDCA for § 505(b)(2) and ANDA applications, noted previously. These provisions will certainly be challenged by at least one sponsor seeking clarification of the silent, or otherwise ambiguous, language in the BPCIA, despite assurances from some members of Congress that the legislative history favored one interpretation over another.[14] It is easy, however, for any member of Congress to have his or her comments on a proposed statute entered and archived in a historical legislative record.

Orphan Drug and Pediatric Exclusivity Periods under BPCIA

The HWA and the BPCIA both have exclusivity provisions that offer incentives to sponsor developing products that treat rare medical conditions, *i.e.*, orphan drug, and for completing clinical studies in children. An orphan drug designation, which provides a seven-year exclusivity period, is offered to the sponsor of a product that can be used to treat a disease where the prevalence is less than 200,000 persons in the United States.[15] A pediatric designation, which is a six-month extension to a patent covering a product, is offered if the FDA determines that: (1) information relating to the use of a new product in the pediatric population may produce health benefits in that population; (2) the FDA makes a written request for pediatric studies (which shall include a timeframe for completing such studies); (3) the applicant agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe; and (4) the reports thereof are submitted and accepted in accordance with section 505A(d)(3) of the FFDCA [21 USCS § 355a(d)(3)]. The six-month pediatric extension can be appended to the seven-year orphan drug exclusivity period, as noted below.

Section (h) of the BPCIA specifies that if a reference product, as defined in section 351 of the Public Health Service Act (42 USC § 262) which has been designated under section 526 of the FFDCA (21 USC § 360bb) for a rare disease or condition, is a biological product for which approval is sought for the use in treating of such disease or condition under § 351(k) as being biosimilar to, or interchangeable with, such reference product, it may be licensed by the FDA only after the expiration for such reference product of the later of: (1) the seven-year period described in § 527(a) of the FFDCA (21 USC § 360cc(a)); and (2) the 12-year period described in § 351(k)(7).

Under 42 USC §§ 262(m)(2)(A) and (3)(A) of the BPCIA, relating to the market exclusivity for new and already marketed biological products, respectively, if pediatric studies are carried out and the reports accepted, the periods referred to in 42 USC § 262 (k)(7) are deemed to be four years and six months, rather than four years, and 12 years and six months, rather than 12 years. Under 42 USC §§ 262(m)(2)(B) and (3)(B) of the BPCIA, relating to the market exclusivity for new and already marketed biological products, respectively, if pediatric studies are carried out and the reports accepted, and the product has an orphan drug designation, the period of exclusivity is deemed to be seven years and six months rather than seven years under section 527(a) of the FFDCA [21 USCS § 360cc(a)].

Under 42 USC § 262(m)(4), the FDA shall not extend a pediatric or orphan product exclusivity period referred to in ¶¶ (2)(A), (2)(B), (3)(A), or (3)(B), if the determination under section 505A(d)(3) [21 USCS § 355a(d)(3)] is made later than nine months prior to the expiration of such period. The pediatric extensions described here, are clearly described in the BPCIA as market exclusivity periods offered to the sponsor of a reference product.

Statutes, Regulations, and Court Cases Relating to Patent Term Adjustments and Patent Term Extensions

There are a variety of complex interrelationships between provisions of the FDA statutes relating to regulatory exclusivity periods under the BPCIA and the HWA, noted above, and several provisions of the patent statutes which modify the term of a patent (designated here as "patent term modifications"). The term of a patent can be truncated through a terminal disclaimer (TD) under 35 USC § 253, or lengthened by a patent term adjustment under 35 USC § 154(b), a patent term extension (PTE) under 35 USC § 156, or by both a PTA and a PTE, depending on the nature of the product claimed in the patent. Understanding these modifications and various "tacking rules," noted below, is key to the development of successful business strategies for the production and sale of reference and generic or follow-on molecules.

PTAs Under 35 USC § 154(b)

Patent term adjustments (PTAs) were designed by Congress to compensate patent owners for delays from the date an application is filed through the date a patent is granted, taking into account delays attributable to both the PTO and the applicant.[16] Adjustment guarantees are provided in view of three general types of PTO delays recognized under 35 USC § 154(b):

- "A" delays provide a day-for-day extension for every day that issuance of a patent is delayed by failure of the PTO to comply with various statutory deadlines.
- "B" delays provide a day-for-day extension for every day greater than three years and one day after the filing date of an application that it takes for the application to issue as a patent, regardless of whether the delay is the fault of the PTO. Periods attributable to certain types of applicant delays are excluded.
- "C" delays, which are rare, relate to certain periods involving interferences, secrecy orders, and appeals.

The statute also specifies that, to the extent that periods of A, B, or C delay overlap, the period of any positive adjustment shall not exceed the actual number of days the issuance was delayed. The sum of the A, B, and C delays, minus any double-counting adjustments (as a result of overlaps), must also be offset by periods of delay attributable to the applicant's failure (by act or failure to act) to engage in reasonable efforts to conclude prosecution of the application (Applicant Delay [AD]). The statutes and regulations relating to PTAs are remarkably complex, requiring an evaluation of dozens of delay periods recorded in the electronic and paper file histories of an application and related patent documents, which are not always linked so as to facilitate retrieval of key event dates.

This was a sleepy area of patent law until 2007, when Wyeth challenged the PTO's interpretation of the statute in a scenario where the B delay (the three-year pendency guarantee) overlapped two periods of the A delay, the first, a year-long period ending before the date that is three years plus one day after the filing date, and the second, a year-long period, starting after that date, and ending before the patent issued at year six.[17] Wyeth argued that the delay only overlapped with the second A-delay period and that the proper PTA was four years, one for the first A-delay, and three for the B-delay period.[18] The PTO interpreted the statute as meaning that the B-delay overlapped both A-delays for years one through six, and the applicant was entitled only to the longer of the B-delay (with a credit only for periods where the application was pending beyond three years) and the A-delay, but never A-delay plus B-delay, resulting in a PTA of only three years.[19]

A year later, the Federal District Court (Wyeth v. Dudas, 580 F. Supp 2d 138 (DDC. 2008) ruled against the PTO, which later appealed. The U.S. Court of Appeals for Federal Circuit (CAFC) affirmed the lower court ruling on Jan 7, 2010, noting that the language of 35 USC § 154(b) "is clear, unambiguous, and intolerant of the PTO's suggested interpretation" of the meaning of the word "overlapping." (Wyeth v. Kappos, 591 F.3d at 1372). On Jan 26, 2010, the PTO posted a notice on its website indicating that it was not going to challenge the decision of the CAFC, and a formal notice regarding interim procedures to request a recalculation of a PTA to comply with Wyeth v. Kappos was published on Feb 1, 2010.[20] Patents issuing on or after Mar 2, 2010 would have a PTA calculated according to the ruling in Wyeth v. Kappos.

To better understand the economic and legal implications of the two court decisions concerning the calculation of PTAs, the author began collecting and analyzing court cases that were filed against the Director of the PTO, where the plaintiffs were seeking to have the District Court reconsider the PTA calculated by the PTO of their recently-issued patents. Better knowledge of the factors affecting the length of delay periods would facilitate the development of business strategies that minimize applicant delays, maximizing the terms of patents. Court cases identifying patents needing longer PTAs would also provide early notice to the public, including investors and competitors, of technologies considered to have particular value to the applicant.

To illustrate the extraordinary complexity of these statutes and regulations, Luckow and Balsarotti (2010) recently published a statistical analysis of 179 court complaints filed from September 2007 through July 2010, in which applicants sought longer patent term adjustments for 225 patents.[21] The pace of filings decreased through 2011, however, with only 18 new complaints, bringing the total to 197 cases, encompassing 253 patents.[22] Although patent term adjustments under 35 USC § 154(b) were intended to be industry-independent, there was a strong bias in these cases towards pharmaceutical and biotechnology institutions seeking to have the PTO reconsider the characterization of events during prosecution that were used to calculate a PTA. Applicant and PTO errors were common, often relating to counting errors due to the mischaracterization of events that occur at the beginning or end of specific delay periods. Asymmetries were also noted in the treatment of delay periods encountered in the prosecution of national phase applications based on earlier-filed international applications, compared to applications which take priority only to earlier-filed U.S. applications.

The median difference between the requested PTA and that originally granted by the PTO was 301 days.[23] The minimum difference was minus 75 days (where the PTA granted for one patent was too large), the maximum difference was 1754 days, and the mean difference was 330 days.[24] In one case, an applicant sought a PTA that was longer than that granted by the PTO by a single day.[25] The willingness of academic and corporate institutions to challenge PTA calculations in expensive court proceedings is strong evidence of strategic business plans that balance the risk and reward of facing challenges that would reduce the term of a patent, and its perceived value.

Some of the applicants did not appreciate the complexity of the statutes and regulations relating to PTAs, and neglected to recognize events which contribute to applicant delay under 35 USC § 154(b) and the corresponding regulations under 37 CFR §§ 1.703 and 1.704. The top ten patent owners having the largest applicant delays had their PTAs reduced by 384 days (1.05 years) to 612 days (1.68 years), easily reducing the perceived value of their patents by hundreds of millions of dollars.[26]

The clear lesson from this analysis is that inventors, patent practitioners, and their sponsors all need to recognize delay events and to respond to office actions or other requests for information in a timely manner to support the development of practices which maximize PTAs. Understanding the complex calculations behind PTAs and expiration dates is key to the development of successful scientific, legal, and business strategies involving licensing and ownership of patented technologies.

PTEs Under 35 USC § 156

Institutions having strong interests in pharmaceutical, biotechnology, or medical device products often face hurdles that erode the value of core technologies and new products due to requirements for review by regulatory agencies that delay entry to the marketplace. To compensate for such delays, 35 USC § 156 (implemented as part of the HWA enacted in 1984 to make it easier for generic manufacturers to obtain FDA approval to market their drugs) provides opportunities to extend the term of a patent, subject to many limitations with respect to the nature of the claims, and earlier approvals of related products, processes, or methods of use.[27] Patent term extensions authorized under 35 USC § 156 are limited to patents involving human or animal drugs, food or color additives, and medical devices. The patent must claim a product, a method of using a product, or a method of manufacturing a product.[28] If it is a product, it can be the active ingredient of a new drug product, which is a new drug, antibiotic drug, human biological product, or it can be any medical device, food additive, or color additive.[29]

35 USC § 156 also provides limitations that require that: (1) the term of the patent has never been extended under this provision; (2) a compliant application is submitted by the owner of the patent or its agent; (3) the product

has been subject to a regulatory review period before its marketing or use; (4) applications are filed within 60 days of the marketing approval being given; and (5) the application for extension is submitted before the term of the patent has expired.[30]

Unlike PTAs offered under 35 USC § 154, PTEs under 35 USC § 156 are limited not only in duration, but also in scope. Patents may be extended only if the permission for commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use under the relevant provisions of law relating to the regulatory review process.[31] Additional limitations relate to whether the product is manufactured by a process that primarily uses recombinant DNA technology and whether the first commercial marketing or use after the regulatory period is the first commercial marketing or use for the product.[32]

If a patent claims new animal drugs or veterinary biological products, it may be extended if: (1) the products have not been covered by the claims in any other patent that has been extended; (2) permission was granted for commercial marketing or use in non-food-producing and food-producing animals; (3) it was not extended on the basis of review for use in non-food-producing animals; and (4) the permission for commercial marketing or use of the drug or product after the regulatory period for use in food-producing animals is the first permitted commercial marketing or use of the product for administration to a food-producing animal.[33]

Interim term extensions are provided under 35 USC § 156(e)(2) for patents covering drug products and medical devices that are delayed due to regulatory review.[34] Interim extensions provide an applicant with an extension of patent term during the processing of the application. An applicant can request an interim extension for a period of up to one year. If an interim extension is granted and the eligibility is later determined to be in error, the interim extension is vacated. Multiple requests are permitted.

Calculating PTEs Under 35 USC § 156

The formulas for calculating a PTE granted under 35 USC § 156 are fairly complex, depending on the type of product being evaluated and the procedures used by the FDA to review the product. 35 USC § 156 (c), in slightly abbreviated form, states that:

> The term of a patent eligible for extension under §(a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, except that:
>
> (1) each period of the regulatory review period shall be reduced by any period determined under §(d)(2)(B) during which the applicant for the patent extension did not act with due diligence during such period of the regulatory review period;
>
> (2) after any reduction required by ¶(1), the period of extension shall include only one-half of the time remaining in the periods described in ¶¶(1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of §(g);
>
> (3) if the period remaining in the term of a patent after the date of the approval of the approved product under the provision of law under which such regulatory review occurred, when added to the regulatory review period as revised under ¶¶(1) and (2), exceeds 14 years, the period of extension shall be reduced so that the total of both such periods does not exceed 14 years; and
>
> (4) in no event shall more than one patent be extended under §(e)(i) for the same regulatory review period for any product.

From these provisions, it's clear that several layers of cross-referenced FDA statutes need to be incorporated to determine the relevant start and stop dates used in the calculations to determine the relevant regulatory review periods for each category of products being considered. A more complex scheme is revealed when that is done, and a key provision under 35 USC § 156(g)(6) is also applied. This provision states that the period of extension for most products determined on the basis of the regulatory review period determined under any such paragraph, may not exceed "five (5)" years.[35] The complex nature of these formulas, requiring information from both the PTO and the FDA, is well beyond the scope of this article. More detailed information is available in public presentations by representatives from the PTO[36], and in a recent publication by the author.[37]

Tacking Rules Involving Terminal Disclaimers, PTAs, and PTEs

Several "tacking rules" also apply to the patent modifications described above, complicating matters further. A patent having a terminal disclaimer, linking expiration of a patent to the expiration of an earlier, related, commonly-owned patent filed under 35 USC § 253 to overcome an obvious-type double patenting rejection during prosecution, is not eligible for a PTA which extends beyond the term of the disclaimed patent, as provided for under 35 USC § 154(b).[38] A pharmaceutical patent having a terminal disclaimer, however, can be extended under 35 USC § 156, to reflect delays due to periods of regulatory exclusivity before and after a patent is granted.[39] Pharmaceutical patents eligible for PTAs under 35 USC § 154(b), are also eligible for PTEs under 35 USC § 156.[40]

Ultimately, applicant delays directly and dramatically affect the term and perceived value of a patent. In many cases, however, the applicant delays considered by the FDA and PTO under 35 USC § 156 are zero compared to the applicant delays considered by the PTO that occur during prosecution under 35 USC § 154(b), and the review period is often complete before the issuance of a patent, limiting the PTE to five years. That makes applicant delays used in the calculations of patent term adjustments all the more undesirable, in view of the tacking rules noted above, when developing business and legal strategies to maximize patent terms for regulated pharmaceutical and biotechnology products.

Assessing Interagency Obligations to Facilitate Marketing Approval for Patented and Off-Patent Products

When PTAs and PTEs are considered together with complementary periods of data and marketing exclusivity granted by the FDA, particularly for innovative reference molecules, strategies to optimize patent terms and exclusivity periods get more complex. The terms of patents claiming a drug product, methods of use, and methods of production, plus the length of regulatory exclusivity periods are key factors affecting the profitability of a molecule produced by an RPS. The expiration date of a patent and the end of an exclusivity period are also key factors affecting the ability of the sponsor of a generic or follow-on molecule to launch and capture a share of the market established by the RPS. If the end of the exclusivity period is before the expiration date of a relevant patent covering the molecule, its method of use, or methods of production, then the FOBS will have to wait until the expiration of the patent to market its FOB. While these relationships are fairly well-understood for statutes and regulations concerning small chemicals, the only thing perfectly clear after reading the BPCIA is that regulations interpreting and implementing provisions of statutes relating to macromolecules, will certainly be more complex.

Conclusions

The BPCIA is a complex statute that will take years for the FDA, the PTO, product sponsors, health care providers, and consumers to fully understand and appreciate. While some provisions of the BPCIA are similar to well-established schemes used to regulate the abbreviated review and approval of small molecule drug products under the HWA, many are different, requiring creative new strategies by the sponsors of reference molecules and the sponsors of FOBs. Litigation concerning the characterization of reference and candidate molecules, periods of regulatory exclusivity, the exchange of patent and regulatory information, and the infringement of patent rights between the sponsor of a reference molecule and the sponsor of an FOB, will most certainly take years to shape and resolve questions relating to the authority of the FDA and the PTO to interpret statutes and issue regulations, and the rights and responsibilities of parties seeking approval of drug products under this statute.

Provisions of the BPCIA that relate to definitions of similarity, bioequivalence, and immunogenicity of reference and candidate macromolecules should soon be released by the FDA, which are critical to the development of technical, legal, and business strategies of many institutions. Guidelines that are ambiguous or delayed will help only well-financed companies that have the ability to comply with all the proposed requirements, and have the ability to wait out the long delays expected for approval of new products under these regulations.

Institutions that understand the relationships between PTAs, PTEs, and regulatory review periods, and can implement strategies that minimize periods of applicant delay, will have patents covering products with longer terms and complementary exclusionary periods that offer enhanced legal protection and business value in competitive environments around the world. All of these relationships, from the time a molecule is conceived, to a time well beyond its protected period of exclusivity, should be considered, to optimize profits from the sale of a product. Competitors seeking to produce a generic molecule or an FOB can benefit, if they are successful in challenging the validity of a patent covering the reference molecule and its eligibility for, or length of, a PTA, a PTE, or a regulatory exclusivity period. Product sponsors, regulatory agencies, and the federal courts all benefit when statutes, regulations, and court decisions concerning affordable biopharmaceutical products are clearly-written, timely-published, and fairly-enforced. The public deserves no less.

REFERENCES (Part II of the Series)

[1] Leahy-Smith America Invents Act (AIA), commonly known as the "Patent Reform Act" of 2011 (Pub.L. 112-29, H.R. 1249), signed on September 16, 2011, available at http://www.govtrack.us/congress/billtext.xpd?bill=h112-1249.
[2] Biologics Price Competition and Innovation Act (BPCIA) of 2009, incorporated into the Patient Protection and Affordable Care Act (PPACA), Public Law No: 111–148, signed on March 23, 2010, available at http://www.govtrack.us/congress/bill.xpd?bill=h111-3590.
[3] Drug Price Competition and Patent Term Restoration Act of 1984, PL 98-417, 98 Stat 1585 (the "Hatch-Waxman Act", Title II of which is codified in part, at 35 USC § 156).
[4] Luckow, VA (2011) Recent Statutes, Regulations, and Court Cases Affecting Intellectual Property Rights of Life Sciences Institutions: Key Provisions of the Leahy-Smith America Invents Act (AIA) and the Biologics Price Competition and Innovation Act (BPCIA), Part I, Analysis of the Leahy-Smith America Invents Act. *BioProcessing Journal*, 10(2): 4-9. (Posted online December 22, 2011.) http://www.bioprocessingjournal.com/bioprocessingjournal.com/index.php?option=com_content&view=category&layout=blog&id=41&Itemid=81.
[5] Luckow, VA (2012) Recent Statutes, Regulations, and Court Cases Affecting Intellectual Property Rights of Life Sciences Institutions: Key Provisions of the Leahy-Smith America Invents Act (AIA) and the Biologics Price Competition and Innovation Act (BPCIA), Part III, FDA Guidelines Concerning the Characterization of Reference and Follow-On Macromolecules. *BioProcessing Journal*, 11(2): (In press).
[6] Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations*, available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
[7] Czaban JN, Hessler KA, and Dowd, MJ. (2010) *Pharmaceutical Law and Industry Report*, 8: 698, 05/28/2010.
[8] Tzeng L. (2010) Follow-On-Biologics, Data Exclusivity and the FDA. *Berkeley Technology Law Journal*, 25: 135-158.
[9] Zuhn, D. (2009) Follow-on Biologics Data Exclusivity Debate Scorecard – Part I. http://www.patentdocs.org/2009/10/followon-biologics-data-exclusivity-scorecard-part-i.html.
[10] Development & Approval Process, Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity. Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm, last visited 2011-01-16.
[11] *Id.* See Q&A #1 and #6 for more details on "other significant changes" exclusivity.
[12] Karst KR. (2011) Tussle over BPCIA "Market" Versus "Data" Exclusivity Continues; This Time the Generic Supporters Chime In. FDA Law Blog (Jan 21, 2011), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/01/tussle-over-bpcia-market-versus-data-exclusivity-continues-this-time-the-generics-side-chimes-in.html.
[13] Mundy A. (2011) Firms push for Biotech Generics. The Wall Street Journal (Jan 26, 2011), http://online.wsj.com/article/SB10001424052748704013604576104413760150024.html.
[14] Carroll J. (2011) Data vs. market "exclusivity" in blockbuster scrap over biosimilars. (Jan. 26, 2011), Available at http://www.fiercebiotech.com/story/data-vs-market-exclusivity-blockbuster-scrap-over-biosimilars/2011-01-26.
[15] Orphan Drug Act (PL 97-414), signed on January 4, 1983, as amended. Excerpts available at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm.
[16] 35 USC § 154(b); 37 CFR § 1.703(a). The PTA provisions apply to utility and plant applications filed on or after May 29, 2000. American Inventors Protection Act of 1999, Pub L No. 106-113, 113 Stat. 1536.
[17] Wyeth v. Kappos, 591 F.3d at 1368.
[18] *Id.*
[19] The PTO took the view that if an application is entitled to an adjustment under the three-year pendency provision of 35 USC § 154(b)(2)(B), the entire period during which the application was pending before the office (except for periods excluded under 35 USC § 154(b)(1)(B)(i) – (iii)), and not just the entire period beginning three years after the actual filing date of the application, is the relevant period under 35 USC § 154(b)(1)(B) in determining whether periods of delay "overlap" under 35 USC § 154(b)(2)(A). Under this interpretation, for any administrative delay under 35 USC § 154(b)(1)(A), the applicant gets credit for the longer of A delay or B delay, but never A delay plus B delay. See 69 Fed Reg 21,704 (April 22, 2004), and "Explanation of 37 CFR 1.703(f) and of the United States Patent and Trademark Office Interpretation of 35 USC 154(b)(2)(A)" 69 Fed Reg 34,283 (June 21, 2004) for more details.
[20] 75 Fed Reg 5043, http://www.uspto.gov/patents/announce/pta_wyeth.pdf.
[21] Luckow VA, Balsarotti SC. (2010) Statistical Analysis of Federal District Court Cases Seeking Longer Patent Term Adjustments in the Wake of Wyeth v. Kappos. *J Marshall Rev Intell Prop L* 10(1): 1-94, available at http://www.jmripl.com.
[22] Luckow VA, unpublished data.
[23] Luckow and Balsarotti at 8, Table 1. (See reference [21].)
[24] *Id.*
[25] See, for example, the file history for US 7,713,969, assigned to ArQule Inc, available on Public PAIR, http://portal.uspto.gov/external/portal/pair.
[26] Luckow and Balsarotti at 33, Table 6. (See reference [21].)
[27] Drug Price Competition and Patent Term Restoration Act of 1984, PL 98-417, 98 Stat 1585 (the "Hatch-Waxman Act", Title II of which is codified, in part, at 35 USC § 156).
[28] 35 USC § 156(a).
[29] A product defined under 35 USC § 156(f) is: a drug product, which is the active ingredient of: a new drug, antibiotic drug, or human biological product (as those terms are used in the federal Food, Drug, and Cosmetic Act and the Public Health Service Act); or new animal drug or veterinary biological product (as those terms are used in the federal Food, Drug, and Cosmetic Act and the Virus-Serum-Toxin Act), which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site-specific genetic manipulation techniques, including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient; or any medical device, food additive, or color additive subject to regulation under the federal Food, Drug, and Cosmetic Act.
[30] 35 USC § 156(a)(1)-(4).
[31] 35 USC § 156(a)(5)(A).
[32] 35 USC § 156(a)(5)(B).
[33] 35 USC § 156(a)(5)(C).
[34] 35 USC § 156(e)(2); 37 CFR. § 1.760; MPEP § 27550.1.
[35] See, generally, 35 USC § 156(g)(6)(A)-(C), defining the term "regulatory review period" for different types of products approved before and after the enactment of this section, where the period of extension is generally 5 years for most human products, and 2-3 years for animal drug or veterinary biological products.
[36] See, for example, Till, MC. (2011) Life Sciences Lawyer's Guide to PTA and PTE, available at http://www.uspto.gov/patents/law/exam/presentation/pta_pte_27jan2011.ppt, publicly posted 2011-03-09, and Ferriter KL. (2007) Patent Term Adjustments and Extensions, available at http://www.uspto.gov/web/offices/dcom/olia/conf_gipa2007nov5/agenda/day2e/jordanPTEandPTA.ppt, for presentations with simplified examples given by PTO representatives.
[37] Luckow VA. (2011) Complex Interactions Between FDA and PTO Regulations Affecting Exclusivity Periods and the Patent Term of Biopharmaceutical Drug Products, p. 151-181, 395-405. In *Inside the Minds: Recent Developments in Food and Drug Law 2012, Leading Lawyers on Dealing with Increased Enforcement, Keeping Up-To-Date with FDA Requirements, and Developing Compliance Practices.* Aspatore Books, a Thomson Reuters business. [www.west.thomson.com/aspatore, November 14, 2011].
[38] 37 CFR § 1.703(g).
[39] See, *e.g.*, King Pharm., Inc. v. Teva Pharm. USA, Inc., 409 F. Supp. 2d 609, 611 (DNJ 2006); Merck & Co. v. Hi-Tech Pharmacal Co., 482 F.3d 1317, 1318 (Fed Cir 2007).
[40] 35 USC § 156 (2006).