ACI's 26th FDA Boot Camp

September 30-October 1, 2015

Part 1 –Patent Protection for Drugs and Biologics

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September 30, 2015
1:45 pm – 3:00 p.m.

Tweeting about this conference?

#ACIFDA

Outline

- Summary of the patenting process for drugs and biologics.
- Strategies for building patent protection drugs and biologics.
- Seeking extension of patent term for time spent in the drug approval process (Patent Term Extension, Supplemental Protection Certificates), and/or time spent obtaining a patent at the United States Patent Office (Patent Term Adjustment).
- 35 U.S.C. §271(e)(1) “safe harbor”
- Identifying the respective roles of the FDA and the PTO in the patenting of drugs and biological products.

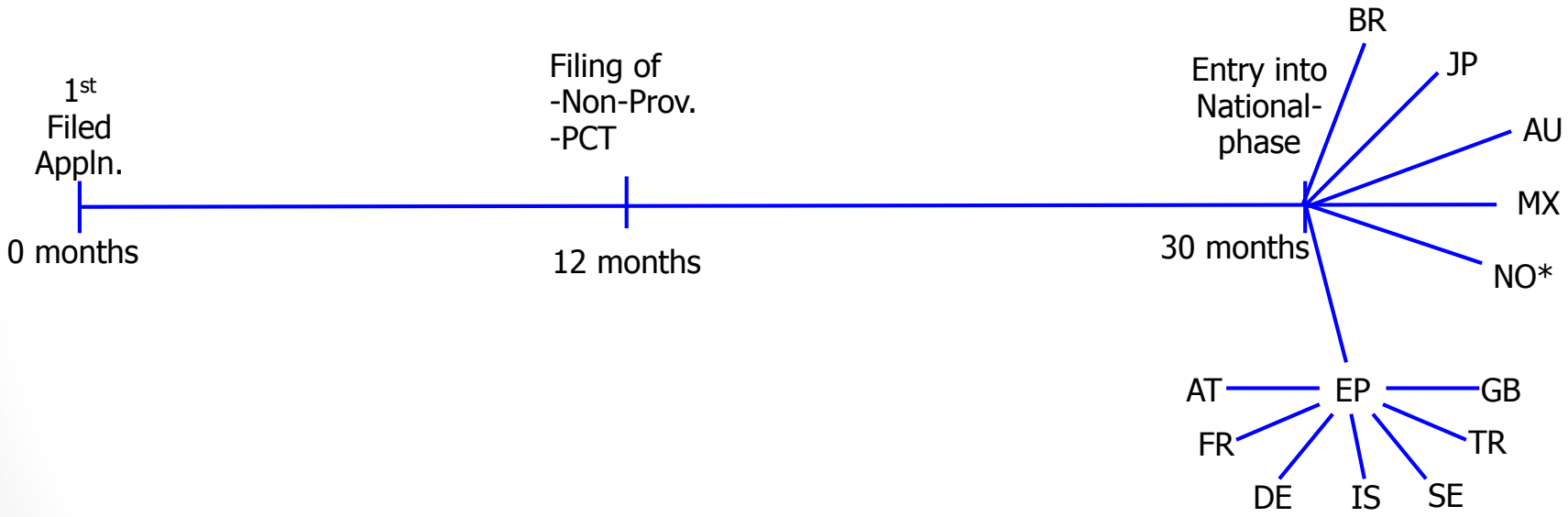
Pre-Filing

- Scientific research and discovery
- Evaluation of the discovery – patentability and freedom to operate
- Drafting of patent application

Types of Patent Applications

- **Provisional**
  - PTO Filing Fee $260
- **Non-provisional**
  - PTO Filing ($280), Search ($600) and Examination ($720) Fees: $1600
  - First filing
  - Continuing
    - Continuation,
    - Continuation-in-part,
    - Divisional
- Utility
- Plant
- Design

General Filing Timeline



*Norway is a member of the European Patent Convention for International Applications filed on or after January 1, 2008

Patentable Subject Matter

- 35 USC § 101 sets forth the four categories of **patentable subject matter** (MPEP § 2106):
  - **Process,**
  - **Machine,**
  - **Manufacture,** and
  - **Composition of matter**

- Judicially created **exceptions** to patentable subject matter: **(1)** laws of nature, **(2)** physical phenomena, and **(3)** abstract ideas

Patentable Subject Matter

Are biologics patentable?

***AMP v. USPTO/Myriad* 133 S.Ct. 2107 (2013)**

- **Issue**: Are human genes patentable?
- **Holding**: We merely hold that **genes and the information they encode are <u>not</u> patent eligible under §101 simply because they have been isolated from the surrounding genetic material**

Patentable Subject Matter

- ***Ariosa Diagnostics Inc. v. Sequenom Inc.*, 788 F.3d 1371 (Fed. Cir. 2015)**
  - Federal Circuit: Sequenom's patent for prenatal DNA tests invalid for claiming only natural phenomena.
    - DNA found in nature and the invention used conventional testing methods.
  - Federal Circuit said it was following Supreme Court guidance in *Mayo* and *Myriad* that natural phenomena cannot be patented unless the patent covers something "significantly more."

USPTO: Interim Guidelines

December 2014: "*2014 Interim Guidance on Patent Subject Matter Eligibility*"

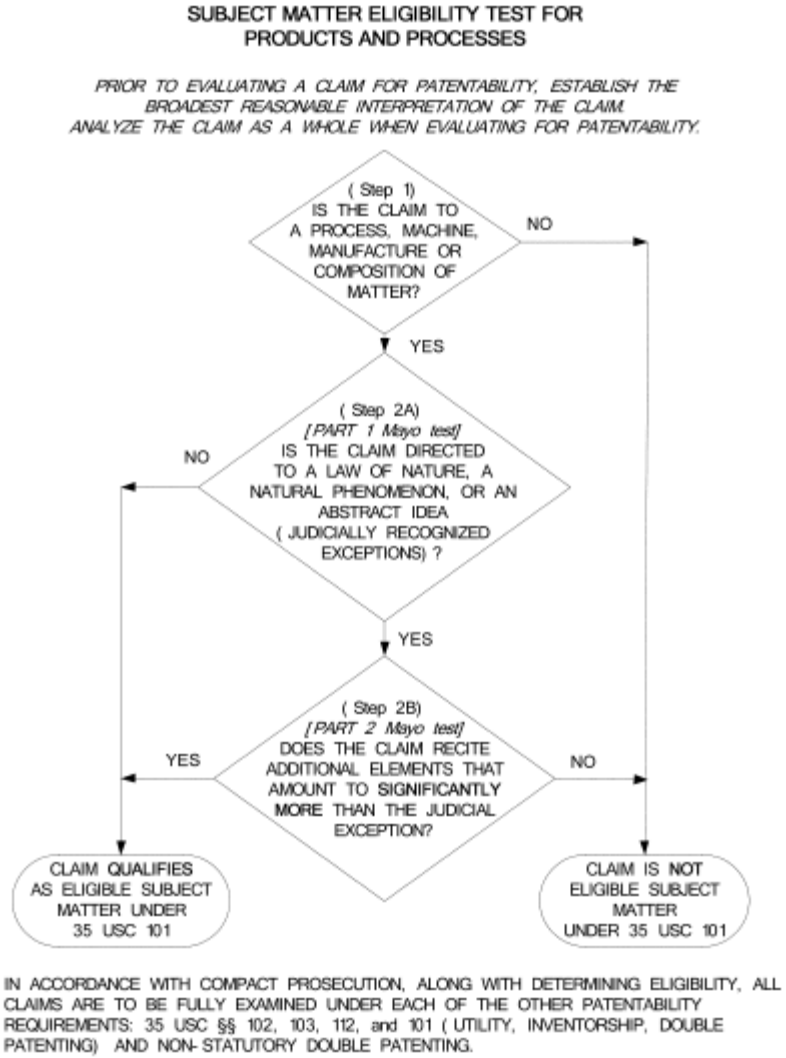
> "sets out the Office's interpretation of the subject matter eligibility requirements of 35 U.S.C. 101 in view of recent decisions by the Supreme Court and the U.S. Court of Appeals for the Federal Circuit (Federal Circuit),"

"Notable changes from prior guidance"

- "All claims (product and process) with a judicial exception (any type) are subject to the same steps."

- "Claims including a nature- based product are analyzed in Step 2A to identify whether the claim is directed to (recites) a 'product of nature' exception. This analysis compares the nature-based product in the claim to its naturally occurring counterpart to identify markedly different characteristics based on structure, function, and/or properties. The analysis proceeds to Step 2B only when the claim is directed to an exception (when no markedly different characteristics are shown)."

Patentable Subject Matter



SOURCE: USPTO Dec. 2014 Interim Guidelines

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USPTO: Two (ish)-Step Analysis

1. Is the claim to a process, machine, manufacture, or composition of matter?

2A. Is the claim directed to a law of nature, a natural phenomenon, or an abstract idea?

- Judicially-recognized exceptions
- *Mayo test Part 1*

2B. Does the claim recite additional elements that amount to significantly more than the judicial exception ?

- *Mayo test Part 2 (and Alice)*

USPTO's Analysis

- "directed to" appears to mean -- looks like, sounds like, smells like, or is somehow derived from or related to, a natural product, law, phenomenon .
- "markedly different" means from the "naturally occurring counterpart in its natural state." May be expressed by structure, function, and/or other properties.

USPTO's Analysis (cont'd)

- What does "significantly more" mean?
  - improvements to another technology or technical field
  - improvement to the functioning of the computer;
  - use of particular machine;
  - transformation or reduction of a particular article to a different state or thing;
  - specific limitation that is an inventive or unconventional step;
  - "other meaningful limitations beyond generally linking the use of the judicial exception to a particular technological environment."

USPTO's Analysis (cont'd)

- USPTO Webpage relating to Patentable Subject Matter
  - http://www.uspto.gov/patent/laws-and-regulations/examination-policy/2014-interim-guidance-subject-matter-eligibility-0
  - "July 2015 Update: Subject Matter Eligibility" issued in response to the public comment on the 2014 Interim Patent Eligibility Guidance.
    - http://www.uspto.gov/sites/default/files/documents/ieg-july-2015-update.pdf
    - Includes a new set of examples and discussion of various issues raised by the public comments.
    - Examples of Nature-Based Products (NBP), were issued December 16, 2014

Ineligible claim	Eligible claim
Example 5. *Mayo v. Prometheus* (U.S. Patent No. 6,355,623) Representative Claim: Claim 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immunemediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8x108 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8x108 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject. "The claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. Even though the laws of nature at issue are narrow laws that may have limited applications, the claim does not amount to significantly more than the natural law itself (Step 2B: NO). The claim is not eligible and should be rejected under 35 U.S.C. 101."	Example 1. *Diamond v. Chakrabarty* (U.S. Pat. No. 4,259,444) Representative Claim: A bacterium from the genus Pseudomonas containing therein at least two stable energy generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway. "The bacterium is new with markedly different characteristics from any found in nature, due to the additional plasmids and resultant capacity for degrading multiple hydrocarbon components of oil. These different functional and structural characteristics rise to the level of a marked difference, and accordingly the claimed bacterium is not a 'product of nature' exception.

Ineligible claim	Eligible claim
Example 2. *Association for Molecular Pathology v. Myriad Genetics, Inc.* (U.S. Patent No. 5,747,282) Representative Claims: Representative Claims: Claim 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2. Step 1: YES. The claims are directed to a statutory category, e.g., a composition of matter, and recite nature-based products (a DNA). Step 2A: YES. The claimed DNA is different, but not markedly different, from its naturally occurring counterpart (BRCA 1 gene), and thus is directed to a ‘‘product of nature’’ exception Step 2B: NO. Claim 1 does not include any additional features that could add significantly more to the exception. The claim is not eligible and should be rejected under 35 U.S.C. 101.	Example 2. *Association for Molecular Pathology v. Myriad Genetics, Inc.* (U.S. Patent No. 5,747,282) Representative Claims: Representative Claims: Claim 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. Claim 2: Step 1: YES. The claims are directed to a statutory category, e.g., a composition of matter, and recite nature-based products (a DNA). STEP 2A: NO. The claimed DNA has different structural characteristics than the naturally occurring BRCA1 Gene [that] are significant, e.g., they are enough to ensure that the claim is not improperly tying up the future use of the BRCA1 gene. Thus, they rise to the level of a marked difference, and the claimed DNA is not a ‘‘product of nature’’ exception. Thus, the claim is not directed to an exception. The claim is eligible.

Patenting Process

- Same process for all patentable subject matter, including drugs and biologics

- Patentability requirements include:
  - **utility** (35 USC § 101),
  - **novelty** (35 USC § 102),
  - **nonobviousness** (35 USC § 103),
  - **written description** (35 USC § 112), and
  - **enablement** (35 USC § 112)

Patenting Process

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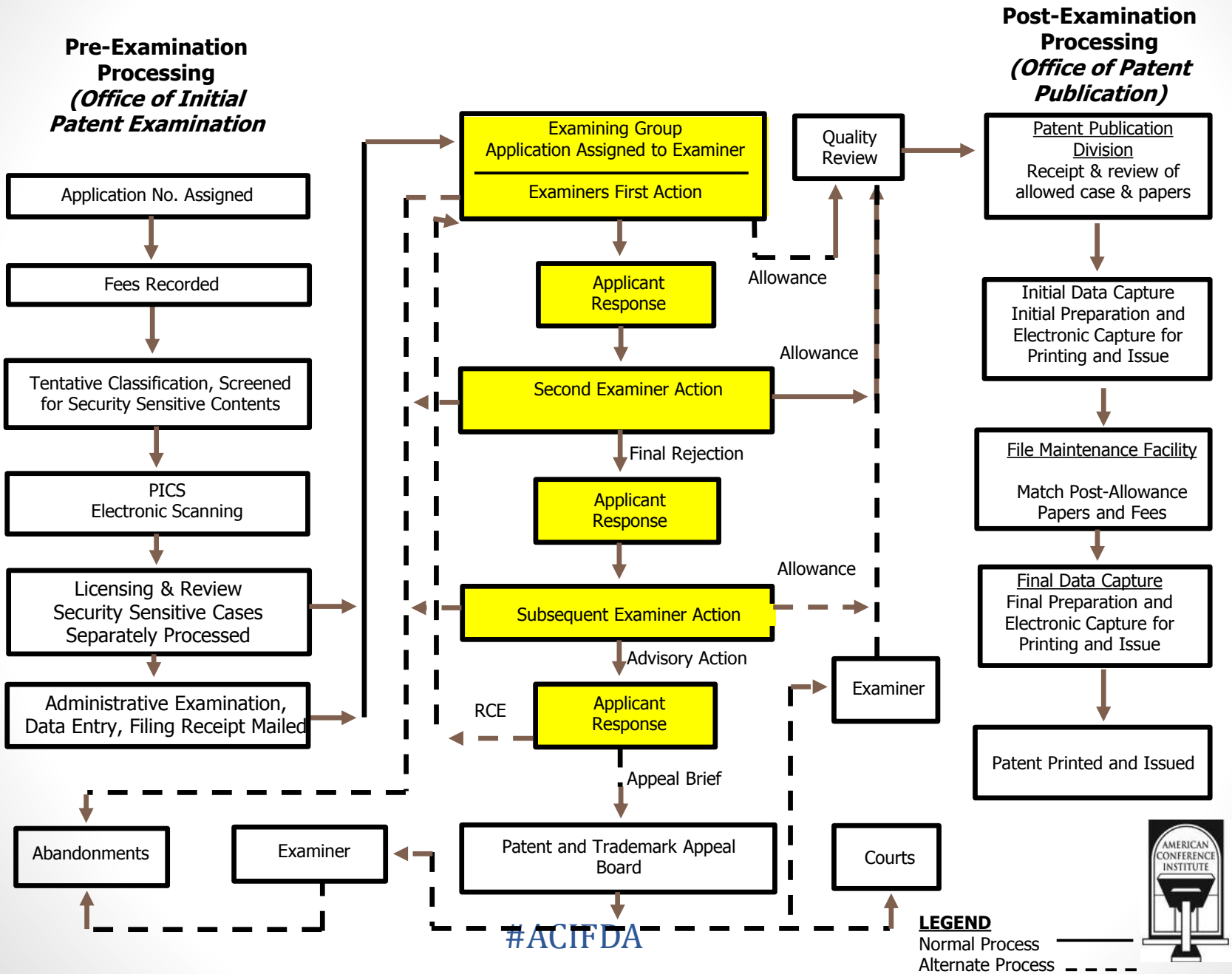
THE U.S. PATENT EXAMINATION PROCESS



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Strategies for Building Patent Protection

"There are few, if any, legal documents more difficult to craft, more fraught with pitfalls than patent applications[.]"

Circuit Judge Newman dissenting in Energizer Holdings, Inc. v. International Trade Commission, 2008 WL 1791980, *10 (Fed. Cir. April 21, 2008)(not published).

PREPARATION FOR DRAFTING

- Understand full scope of invention.
- Understand difference between invention and prior art.

- When preparing to draft the application, more is better.
  - Full and complete disclosure in an application is required to satisfy statutory enablement, written description, best mode requirements.
  - Consider all known and possible embodiments
  - Explore alternatives for each element of the invention.

- Disclosure to public – clarity and precision
  - Consider definition(s) of each and every claim terms.

DRAFTING OBJECTIVES

- Present claims of sufficient scope to read on the competition, yet just narrow enough to avoid the prior art.

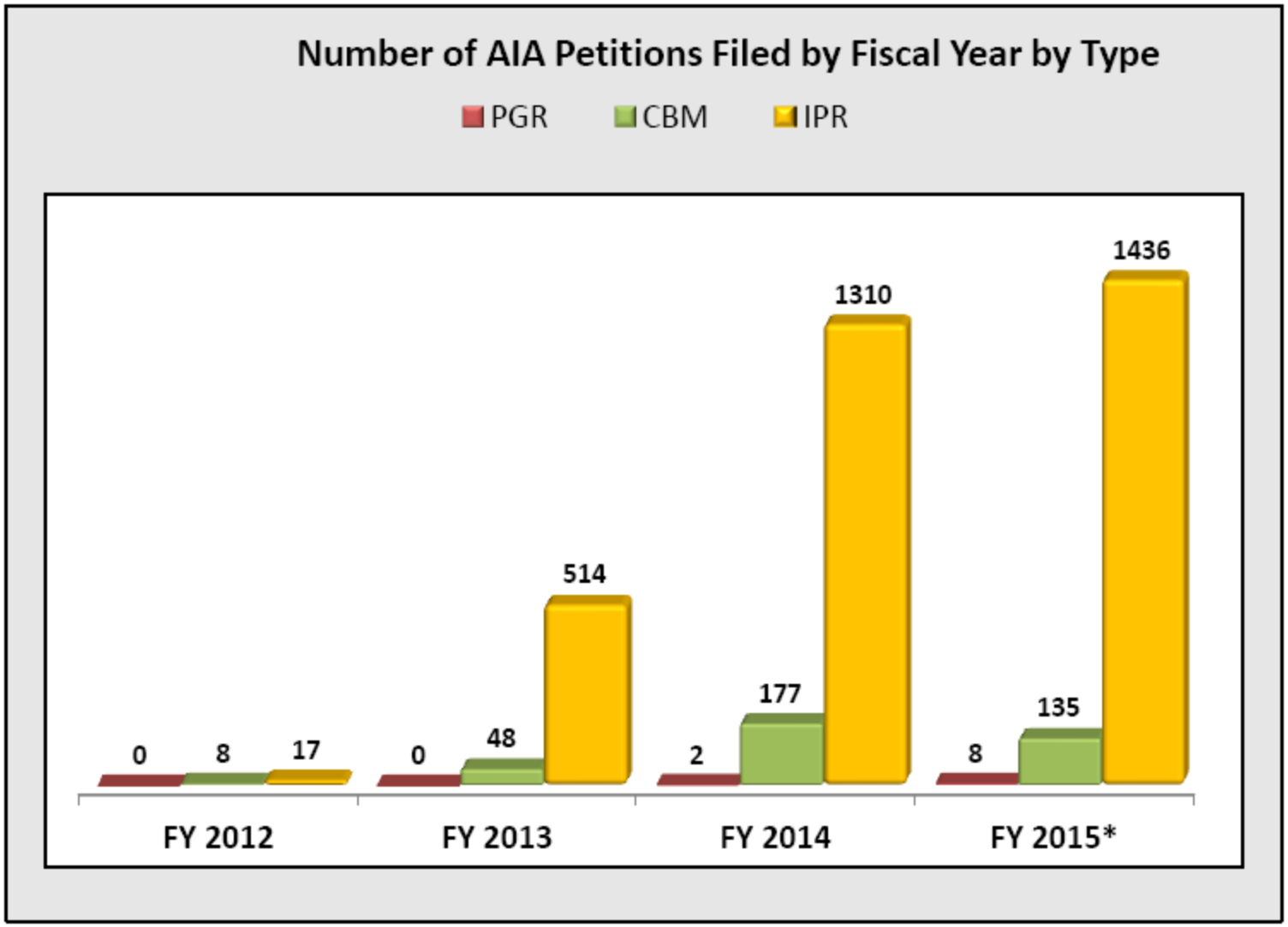
- Fully describe the inventor's conception and provide support for the desired claim construction and in compliance with the requirements of §112.

- Strong, enforceable claims that will withstand challenges both in litigation and in AIA post- grant proceedings.

SCOPE OF CLAIMS

- Claim subject matter narrowly enough to avoid art and prove literal infringement.
- Claim subject matter broadly enough to avoid design-arounds.

Preparing for IPR/PGR Attacks



*Data current as of: 7/31/2015

[http://www.uspto.gov/sites/default/files/documents/2015-07-31%20PTAB.PDF]

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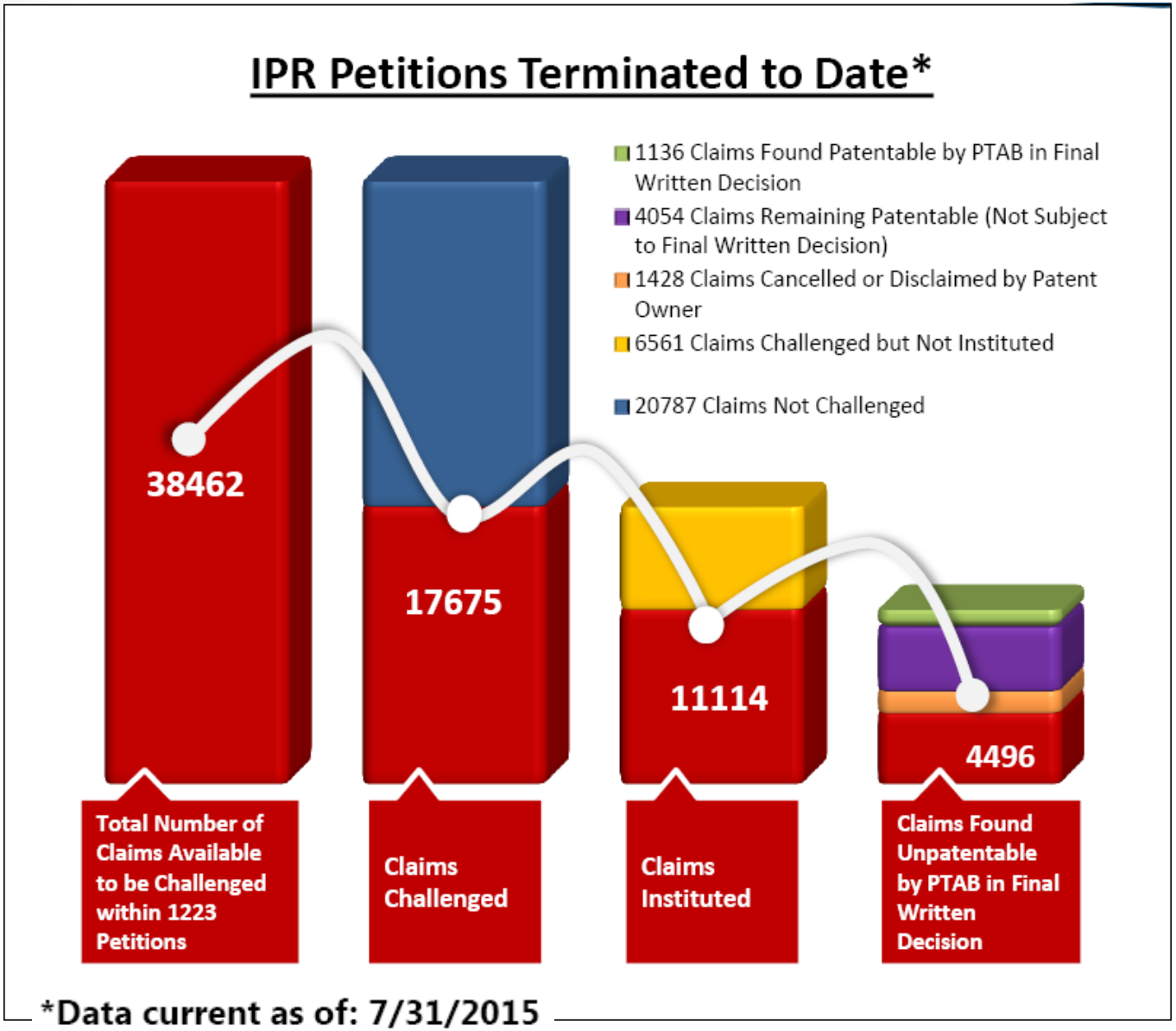
ISSUE	PGR/IPR	DISTRICT COURT
Burden of proof	Preponderance of the evidence	Clear and convincing evidence
Presumption of Validity?	No	Yes
Claim construction	Broadest reasonable construction	*Philips/Markman* framework: analyze claims, specification, and prosecution history to determine how claims would be understood by one of ordinary skill in the art
Decision maker	Patent Trial and Appeal Board (APJs)	District court judge or jury



[http://www.uspto.gov/sites/default/files/documents/061815_aia_stat_graph.pdf]

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Considerations for Countering IPR/PGR Attacks

- Lots of claims
- Lots of patents
- Continuation applications

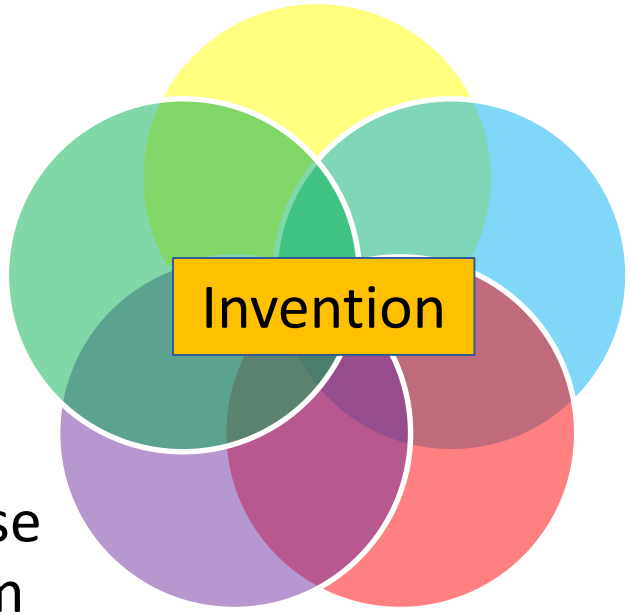
Considerations for Countering IPR/PGR Attacks (cont'd)

- Claim scope: broad enough to avoid close competitors (FTO) but narrow enough to avoid art (patentability).
  - Obtain claims directed to the FDA-approved drug substance/product and bioequivalents thereof.
  - Assure at least literal infringement (strongest position).

Considerations for Countering IPR/PGR Attacks (cont'd)

Process of making

Means-plus-function



Product-by-process

Method of use (downstream claims)

Compound and/or Composition

Considerations for Countering IPR/PGR Attacks (cont'd)

- Build into the patent application and prosecution a desired reasonable claim construction that will avoid unpatentability in PGR/IPR at PTAB
- Set forth strong patentability positions during drafting and prosecution.
- “More is more” for drafting and/or prosecution now???

Considerations for Countering IPR/PGR Attacks (cont'd)

→ Consider Substantive Declarations in Prosecution

Why? As of now, in the optional Patent Owner Preliminary Response (POPR) statement before institution of an IPR/PGR , the **Patent Owner cannot file new declarations**.*
But Patent Owner **can** rely on **public records,** e.g., declarations in prosecution history.

Patent Owner's goal is to avoid institution of an IPR/PGR.

Consider declarations during prosecution to develop record – e.g., lack of inherency, objective evidence of nonobviousness.

**Proposed rules from USPTO include a revision allowing Patent Owner to support POPR with new testimony.*

Building Patent Protection (Cont'd)

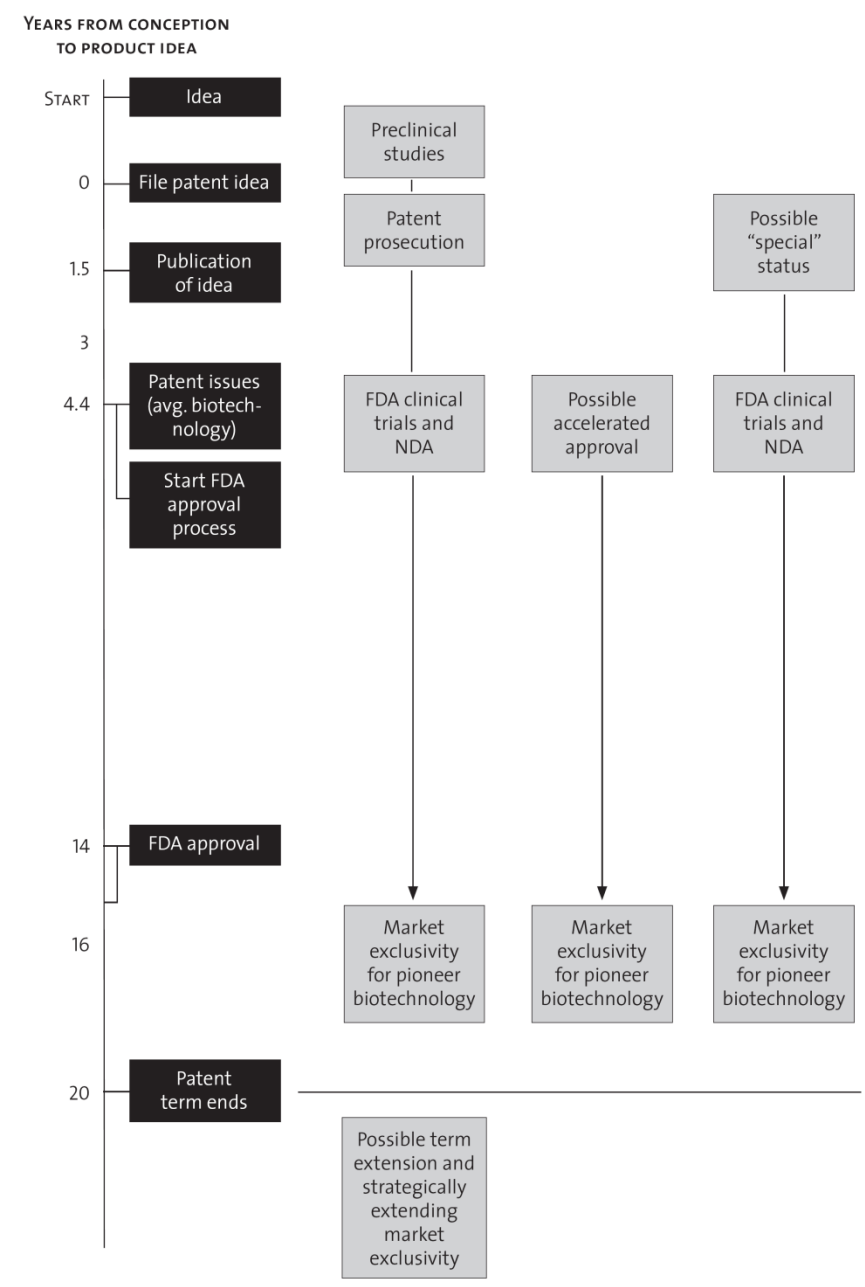
Timing Considerations:

patenting process
in view of
regulatory process

Patent During Pre-Approval Process

- Timing is important—patent application for a drug or biologic should be filed in advance of NDA/ANDA submission to **obtain a patent before FDA approval of the product.**

- Timing of patent issuance can be affected by one or more of the following:
  - Prioritized Examination
  - Extension(s) of time in responding to Office Actions.
  - Interview(s) with the Examiner



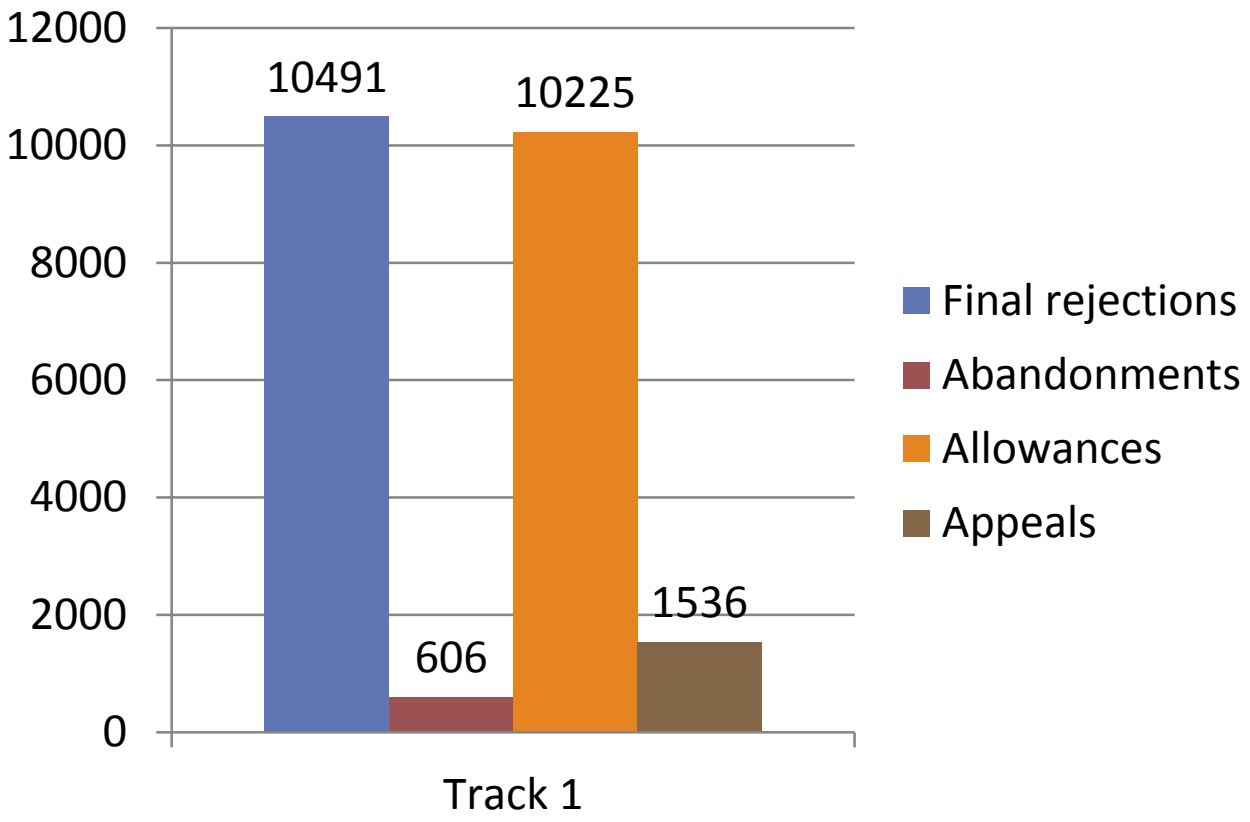
From Fernandez DS, J Huie and J Hsu. 2007. The Interface of Patents with the Regulatory Drug Approval Process and How Resulting Interplay Can Affect Market Entry. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.) MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. , page 967.

Prioritized Examination
SEC. 11(h) [125 STAT. 324]

- "Fast-track" examination – goal of "final disposition" in **12 months**.
  - **Eligibility**: does not apply to international applications, design applications, reissue applications, provisional applications, and reexamination proceedings.
    - US non-provisional and continuing applications are eligible (CON, DIV)
  - Must be "**complete**" (spec, claims, drawings, and oath/decl'n) and all fees paid upon filing
  - **Claim numbers:** only allowed 4 indept, 30 total, and no multiply dept
  - Request for prioritized examination **extra fee** ($4,000 large entity/$2000 small entity)
  - Only **1 RCE** allowed.
    - Lose "fast-track" status if file an extension of time or file an appeal

    76 Fed. Reg. 59,051 (2011)

PRIORITIZED EXAMINATION USPTO STATISTICS (as of August 2015)



49% of **terminations are allowances** (10225/20716)
Time from filing to petition grant: 1.3 months
Time from petition grant to first Office Action: 2.1 months
Time from petition grant to allowance: 5.1 months
Time from petition grant to final disposition: 6.5 months

Patent Term Extension

35 U.S.C. § 156

- 35 U.S.C. § 156 provides for patent term extensions for a patent that claims a product, a method of making a product, or a method of using a product that has been subject to premarket regulatory review before it is approved for commercial marketing in the United States.

- Extension = ½ (testing phase) + approval phase - any time applicant did not act with due diligence
  - Not to exceed 5 years from patent expiration, exclusive of any regulatory review period occurring before the patent issues §156(g)(6) or not to exceed 14 years from NDA approval § 156(c)(3), whichever comes first.

- Any PTE is for the entire patent, not individual claims.
  - *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291 (Fed. Cir. 2011).

Term Extension: Protection In Extended Term

- Depends on type of patent claim:
  - **Approved product -** rights during PTE limited to any use approved for the product that occurred before the expiration of the term of the patent.
  - **Method of making approved product –** rights during PTE limited to the method of manufacturing as used to make the approved product.
  - **Method of using approved product -** rights during PTE limited to any use claimed by the patent that has been approved for the product before the expiration of the term of the patent.

Limited Time To Apply for PTE

- Deadline for filing application for PTE: **non-extendible 60-day period from the date the product is approved** for commercial marketing.

- If the original term of the patent will expire before the product is approved for commercial marketing or use, **application for interim PTE** must be filed during the period beginning **6 months, and ending 15 days before the term is due to expire.**
  - Each subsequent application for interim extension must be filed during the period beginning sixty days before and ending thirty days before the expiration of the preceding interim extension.

- PTE available even where regulatory approval occurs after the expiration date of the original patent term.

Tips for Application For PTE

- **Start planning early in the product approval cycle. Avoid last-minute rush.**
  - File early to permit USPTO to review the application and identify any potentially fatal errors before the 60-day deadline expires.
  - And whether or not such early review occurs, file well before the non-extendible 60-day period.
  - Draft your PTE application as soon as FDA approval is obtained so you can see if you have any holes to fill.
  - Close communication with Regulatory group.

Tips for Application For PTE (cont'd)

- **Apply for PTE of all Orange Book-listable patents and later elect which patent will get the PTE.**
- Even though only one patent may be extended per regulatory review of a particular product, Patentee may file **multiple applications for PTE** based on different patents but the same regulatory approval of a product.
  - Preserve an opportunity to select an appropriate patent until the time that the Commissioner must grant a certificate of patent term extension.
  - Consider potential further development of approved product.
  - Hedge your bets against foreign litigation, AIA procedures of PGR/IPR, and possible use of Supplemental Examination.

PTE Eligibility

- Application for PTE must be **filed by the patent owner or its agent**.
- **Not precluded by terminal disclaimer**
  - *Merck & Co., Inc. v. Hi-Tech Pharmacal Co., Inc.*, 482 F.3d 1317 (Fed. Cir. 2007): "The terminal disclaimer is not ignored; the §156 patent term extension is **calculated from the terminal disclaimer expiration date**. The objectives of two separate policies are fulfilled."
- The **original term of the patent must not have expired** at the time the application for patent term extension is filed.
  - Keep the foot on the accelerator during regulatory review period.
- Term of the patent must **not have been previously extended under § 156**.
- For drug products containing a combination of active ingredients, it must be the **first approval for at least one active ingredient**.

Sample Patent Term Extension Notice

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 6,444,673, which claims the human drug product LUNESTA® (eszopiclone), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 760 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 760 days.

The period of extension has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of February 10, 2009, (74 Fed. Reg. 6636). Under 35 U.S.C. § 156(c):

Period of Extension	=	½ (Testing Phase) + Approval Phase
	=	½ (1,256 - 1,106) + 685
	=	760 days (2.1 years)

Since the regulatory review period began August 25, 1999, before the patent issued (September 3, 2002), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From August 25, 1999, to and including September 3, 2002, is 1,106 days; this period is subtracted for the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

- Patent granted Sept. 3, 2002
- NDA filed Jan. 31, 2003
- NDA approved Dec. 15, 2004
- PTE application Feb. 11, 2005
- Original expiration Jan. 16, 2012
- Term extension 760 days
- Extended term expiration Feb. 14, 2014

Sample Patent Term Extension Notice

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 4,738,974, which claims the human drug product NEXIUM® (esomeprazole magnesium), methods of use thereof and a pharmaceutical composition comprising NEXIUM® (esomeprazole magnesium), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 865 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 865 days.

The period of extension has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of February 28, 2002, (67 Fed. Reg. 9299). Under 35 U.S.C. § 156(c):

Period of Extension	=	½ (Testing Phase) + Approval Phase
	=	½ (838) + 446
	=	865 days (2.4 years)

Since the regulatory review period began, after the patent issued (April 19, 1988), the entire regulatory review period has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

Sample Request For Reconsideration Of Patent Term Extension

Reconsideration of the Notice of Final Determination dated March 27, 2007 with respect to U.S. Patent RE 37,314 and the product Crestor is respectfully requested. In particular, Applicant requests correction of the calculation of the Period of Extension, which should have resulted in an extended term of **1305 days** rather than 1304 days, giving an Expiration Date of Extension of **January 8, 2016**. It is respectfully submitted that this error arose from an erroneous rounding down (ignoring) of the one-half day in the 526½ days of the "½ (Testing Phase)" to 526 days when it was added to the 778 days of the "Approval Phase." As detailed further below, under the regulations (specifically 37 CFR § 1.775(d)(1)(iii)), half days are to be "ignored for purposes of subtraction" of one-half of the Testing Phase from the total regulatory review period, *i.e.*, 1,831 - 526 = **1305 days**. To be consistent with the calculation detailed in the regulations (and past practice of the US Patent and Trademark Office), the one-half day should have been rounded up to 527 days when added to the days of the Approval Phase, *i.e.*, 527 + 778 = **1305 days**, in the manner the calculation was carried out by the US Patent and Trademark Office.

Changing Information In The Orange Book

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 4,738,974 for a period of 865 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for

Third Party Has 180 Days After Publication Of Regulatory Review Period To Question Due Diligence Of PTE Applicant

Dear Director Dudas:

This is in regard to the patent term extension application for U.S. Patent No. 4,738,974 filed by AstraZeneca, LP, under 35 U.S.C. § 156. The patent claims Nexium (esomeprazole magnesium), new drug application (NDA) 21-153.

In the February 28, 2002, issue of the Federal Register (67 Fed. Reg. 9299), the Food and Drug Administration (FDA) published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before August 27, 2002, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired. FDA received one due diligence petition during the comment period. However, that petition has been withdrawn from consideration as confirmed by a telephone conversation, January 3, 2007, between Brian Pendleton, FDA, and Bruce D. Radin, Esq., Budd Larner, P.C. Therefore, FDA considers the regulatory review period determination to be final.

How Delay In Patent Issuance Costs PTE

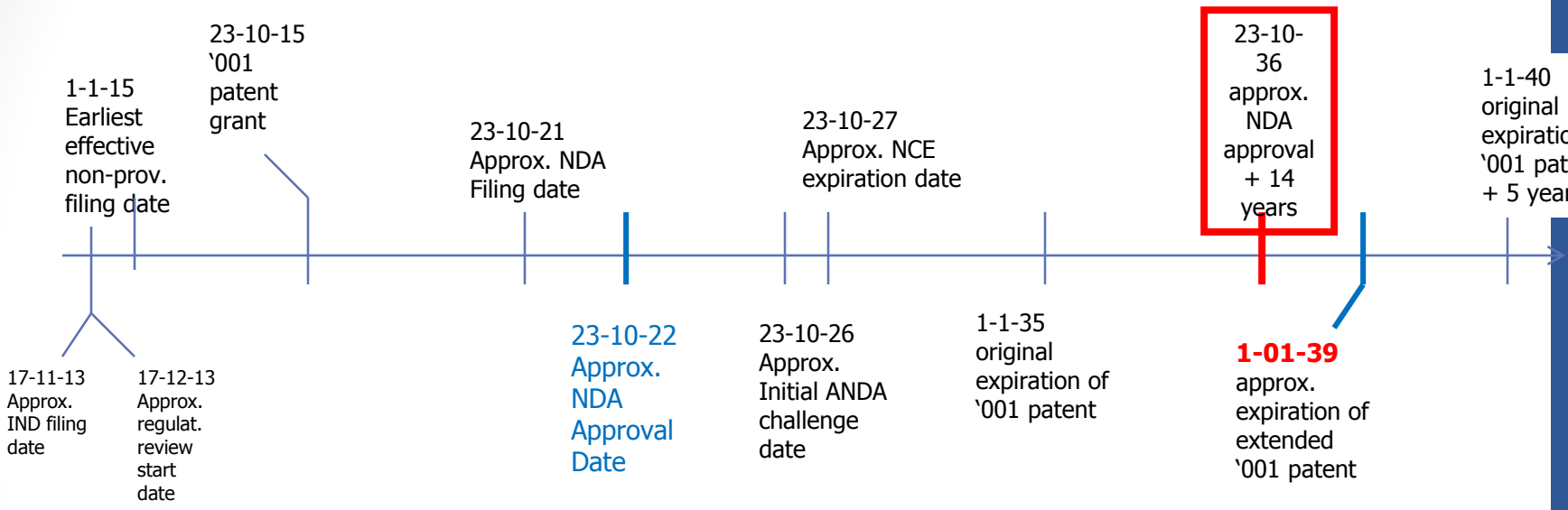
How to lose **900** days of PTE because of delayed issuance

- Scenario 1:
  - Day 0 - Regulatory review starts
  - Day 1 – Patent issues
  - Day 1000 – NDA filed
  - Day 1500 – FDA approval
    - Patent gets about 999/2 of PTE for the regulatory review to NDA period and all 500 days for the regulatory period from NDA to FDA approval, 500 + 500 = **1000** (subject to the 5/14 year caps)

- Scenario 2:
  - Same facts but patent issues on Day 998
  - Patent gets 2/2 of PTE for the regulatory review to NDA period and all 500 days for the regulatory period, from NDA to FDA approval, 1+500 = **501** (subject to the 5/14 year caps).

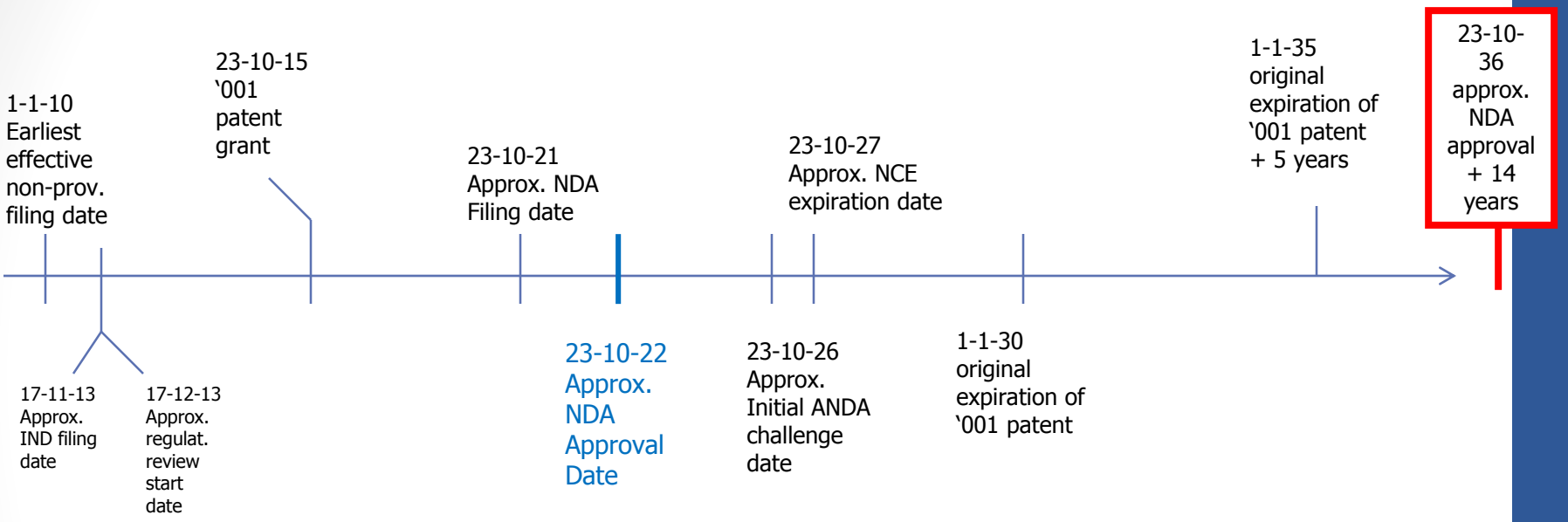
- Scenario 3:
  - Same facts but patent issues on Day 1400
  - Patent gets 0 of PTE for the regulatory review to NDA period , and only 100 days or so of PTE in the NDA approval time span, 0+100 = **100** (subject to the 5/14 year caps).

Sample PTE Timeline



Assume Prioritized Exam was used for the '001; issued in a little over 9 months
'001 extension approximately 1460 days; expires 1-01-39, as shown.
BUT subject to 14-year cap, 23-10-36, as shown which comes before 5-year cap!
Why?
Filing after regulatory period began, patent issued quickly.

Sample PTE Timeline (Not to Scale)



'001 extension approximately 1460 days to ~1-1-34, not shown.
BUT does not even hit 5-year cap, 1-1-35, which comes before 14-year cap!
Why?
Filed patent application before regulatory period began; patent did not issue quickly

Patent Term Adjustment

Patent Term Guarantee Act of 1999

35 U.S.C. § 154(b)

- Provides patent term adjustment (PTA) if certain USPTO actions take longer than decreed periods of time.
  - Guarantee of prompt USPTO responses ("A-Delays")
  - Guarantee of no more than 3-year application pendency ("B-Delays")
  - Guarantee of adjustment for delays due to interferences, secrecy orders, and appeals ("C-Delays")

A-Delays
Guarantee of Prompt USPTO Responses

A-Delays occur if the USPTO does not:

- Provide at least one notification within 14 months from filing date, e.g.:
  - Office Action, Restriction Requirement, Notice of Allowance
  - For national stage applications under 35 U.S.C. § 371, the 14-month clock starts at commencement of the national stage under § 371.

- Respond within 4 months for other actions, e.g.:
  - Respond to a reply, respond when an appeal is taken, act on a decision by PTAB, or issue a patent after issue fee paid

B-Delays
Guarantee of No More Than 3-Year Pendency

B-Delays occur if the USPTO does not issue a patent within 3 years of the actual filing date

But B-Delays do not include:

- time after request for continued examination (RCE) (*Exelixis* and *Novartis* cases)
- time consumed by an interference;
- time consumed by imposition of a secrecy order;
- time consumed by PTAB or Federal court review; and
- any delay at the request of the applicant.

C-Delays
Adjustments for Interferences and Appeals

C-Delays occur as a result of:

- Interference proceedings;
- Secrecy orders; and
- *Successful* appellate review.

- C-Delays accrue from the date jurisdiction passes to PTAB (Reply Brief received) until a final decision in favor of the applicant by the PTAB or a Federal court.

Subtract Applicant's Delays

- Reductions for applicant's failure to engage in reasonable efforts to conclude prosecution:
  - **time in excess of 3 months to reply to any action notice**;
  - submission of a reply having an omission;
  - submission of a supplemental reply;
  - submission of a preliminary amendment less than one-month before mailing of office action;
  - submission of an amendment after a decision by the PTAB;
  - submission of an amendment after a notice of allowance has been mailed;
  - suspension of action;
  - deferral of issuance;
  - abandonment or late payment of issue fees;
  - conversion of a provisional application

35 U.S.C. § 154(b)(2), 37 C.F.R. § 1.704

Calculating Patent Term Adjustment

- PTA is calculated by:
  - ***Adding*** any A-Delays + B-Delays + C-Delays;
  - ***Subtracting*** any overlap between A-Delays, B-Delays and C-Delays;
    - Overlap is calculated by counting delays occurring on the same calendar days. (*Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010))
  - ***Subtracting*** any Applicant Delays.

37 C.F.R. § 1.703(f)

PTA: Rule Changes

- **Jan. 9, 2015 -** 80 Fed. Reg. 1346 (Jan. 9, 2015), *Changes to Patent Term Adjustment in View of the Federal Circuit Decision in Novartis v. Lee*

- 37 CFR 1.703(b)(1) → time consumed by continued examination under 35 U.S.C. 132(b) does not include the time beginning on the date an RCE was filed and ending on the mailing date a notice of allowance (day of allowance, however, is excluded from B-Delay, contrary to *Novartis*)

- 37 CFR 1.704(c)(12) → reduction of PTA will occur if RCE filed after a notice of allowance (starting on date after the date of mailing of notice of allowance and ending on the filing date of the RCE).

RECENT FED. CIRCUIT PTA DECISIONS

- *Gilead Sciences, Inc. v. Lee*, 778 F.3d 1341 (Fed. Cir. 2015)
  - Restriction requirement issued November 18, 2009
  - Gilead responded on February 18, 2010
  - Gilead filed a supplemental IDS on April 16, 2010 (before Office Action).
  - USPTO assessed 57 days of applicant delay based on time between Gilead's initial reply to restriction requirement and filing supplemental IDS.
  - DC: Granted summary judgment in favor of USPTO.
  - FC: Affirmed.
    - "this court finds that a reasonable interpretation of the statute is that Congress intended to sanction not only applicant conduct or behavior that result in actual delay, but also those having the potential to result in delay irrespective of whether such delay actually occurred."

RECENT FED. CIRCUIT PTA DECISIONS

- *Mohsenzadeh v. Lee*, 790 F.3d 1377 (Fed. Cir. 2015)
  - Mohsenzadeh filed the original patent application on July 6, 2001.
  - USPTO issued restriction requirement on Sept. 21, 2006 - more than 5 years later (*A-delay*).
  - Patent issued June 2010 with PTA including 1476 days for delay in issuing restriction requirement.
  - Divisionals claiming other methods filed Jan. 8, 2010, issued without PTA. → Mohsenzadeh asked for PTA of 1476 days on each, because each claimed same priority date as the original application.
  - USPTO refused.
  - District court: SJ for USPTO
  - FC: Affirmed: A patent is only entitled to PTA for delay in the prosecution of the application from which the patent directly issued, not the application from which it derived priority.
    - Section 154(b)(1)(A) "an application" → limited to the original application.

35 U.S.C. 271(e)(1) Safe Harbor

Infringement Generally

- 35 U.S.C. 271(a)—the unauthorized use in the U.S. of a patented invention constitutes an act of infringement.
  - generally prohibits making, using, or testing of patented invention in preparing to enter the market upon expiration of a patent.

Exception—the "**Safe Harbor**" Provision of Hatch Waxman includes activities related to seeking FDA approval—**35 U.S.C. 271(e)(1).**

35 U.S.C. 271(e)(1) ("SAFE HARBOR")

- It shall **not** be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . **solely for uses reasonably related to the development and submission of information** under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Scope of Safe Harbor

Does 271(e)(1) just cover testing for ANDAs? Or does it cover other testing as well?

What types of activities does the "safe harbor" protect?

- Cover biologics?
- Protect "research tools" used in drug development?

Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005)

- **"Safe Harbor"** applies to use of a patented invention in testing **reasonably related to an FDA submission**, including INDs and NDAs—**even if not ultimately submitted** and even for drug candidates not ultimately developed.

- **Types of testing covered by "Safe Harbor:"**
  - To ID optimum drug candidates, including with rejected candidates
  - Preclinical studies – for safety and pharmacology, toxicology, pharmacokinetics, mechanism of action, potential efficacy issues

- **BUT** basic research to discover basic pharmacological properties - without intent to develop a particular drug or reasonable belief that it will yield desired effect-is not covered by the "Safe Harbor."

Scope of Safe Harbor - Cases

- **Subject to Safe Harbor:**
  - **Medical devices, biologics and other items eligible for PTE and FDA-approval** (*Eli Lilly v. Medtronic, Inc.*, 496 U.S. 661 (1990))
  - ***In vitro, in vivo*, preclinical testing, and clinical studies (for IND, NDA, ANDA)** including use of some biologics as controls, e.g. peptides in *Merck v. Integra I,* 545 U.S. 193 (2005)
  - **Post-market approval testing <u>if</u> that testing might reasonably yield information that would be appropriate to include in a submission to the FDA,** e.g., post-approval testing required by FDA to be retained but not submitted as quality control for batches of generic product (*Momenta v. Sandoz, Inc.,* 686 F.3d 1348 (Fed. Cir. 2012), *cert. denied*, Jun 24, 2013)

Scope of Safe Harbor - Cases

- **Not Subject to Safe Harbor:**
  - **Non-FDA-regulated research tools,** e.g., aerosol-characterizing system used in the development of information for FDA submission but not itself subject to the FDA approval process in *Proveris Scientific Corp. v. Innovasystems, Inc*., 536 F.3d 1256 (Fed. Cir. 2008)
  - **Non-FDA-mandated post-approval studies,** e.g., post-approval activities of providing vaccines, advising on immunization schedules, and reporting adverse vaccine effects in conformity with FDA regulations in *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057 (Fed. Cir. 2011) cert. denied, 133 S. Ct. 973 (2013).
- **Open question: FDA-regulated research tools** (e.g., peptide research tools)

Roles of the FDA and PTO in Patenting of Drugs and Biologics

Role of FDA in Patenting Drugs & Biologics

FDA

- Not involved in patenting of drugs or biologics.
- Role in listing patents in FDA's Orange Book is purely ministerial.
- In applications for patent term extension, FDA assists the PTO in determining a product's eligibility for patent term extension and provides product's regulatory review period to the PTO.
- Would be responsible for resolving challenges to diligence in a regulatory review period determination.

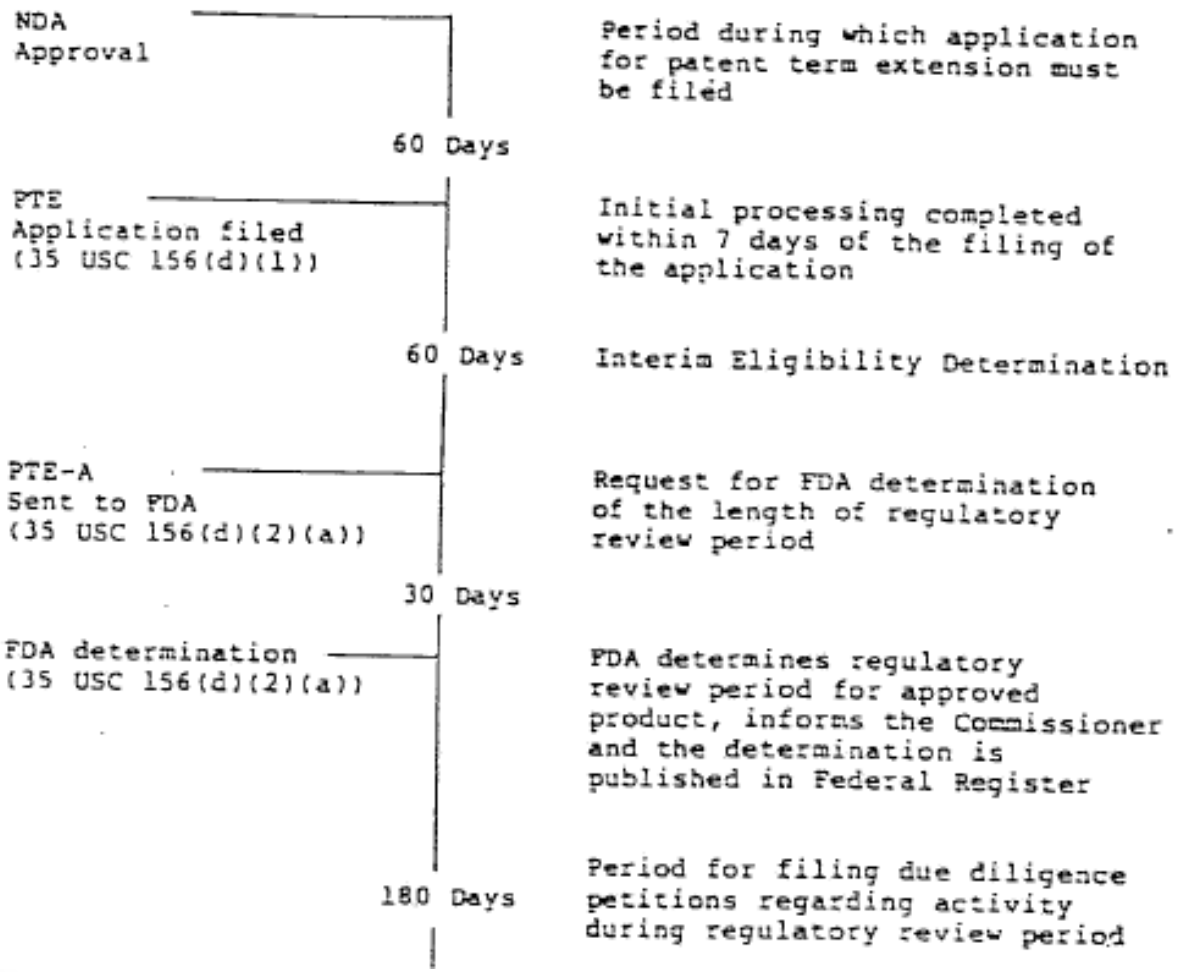
Role of PTO in Patenting Drugs & Biologics

Patent Office

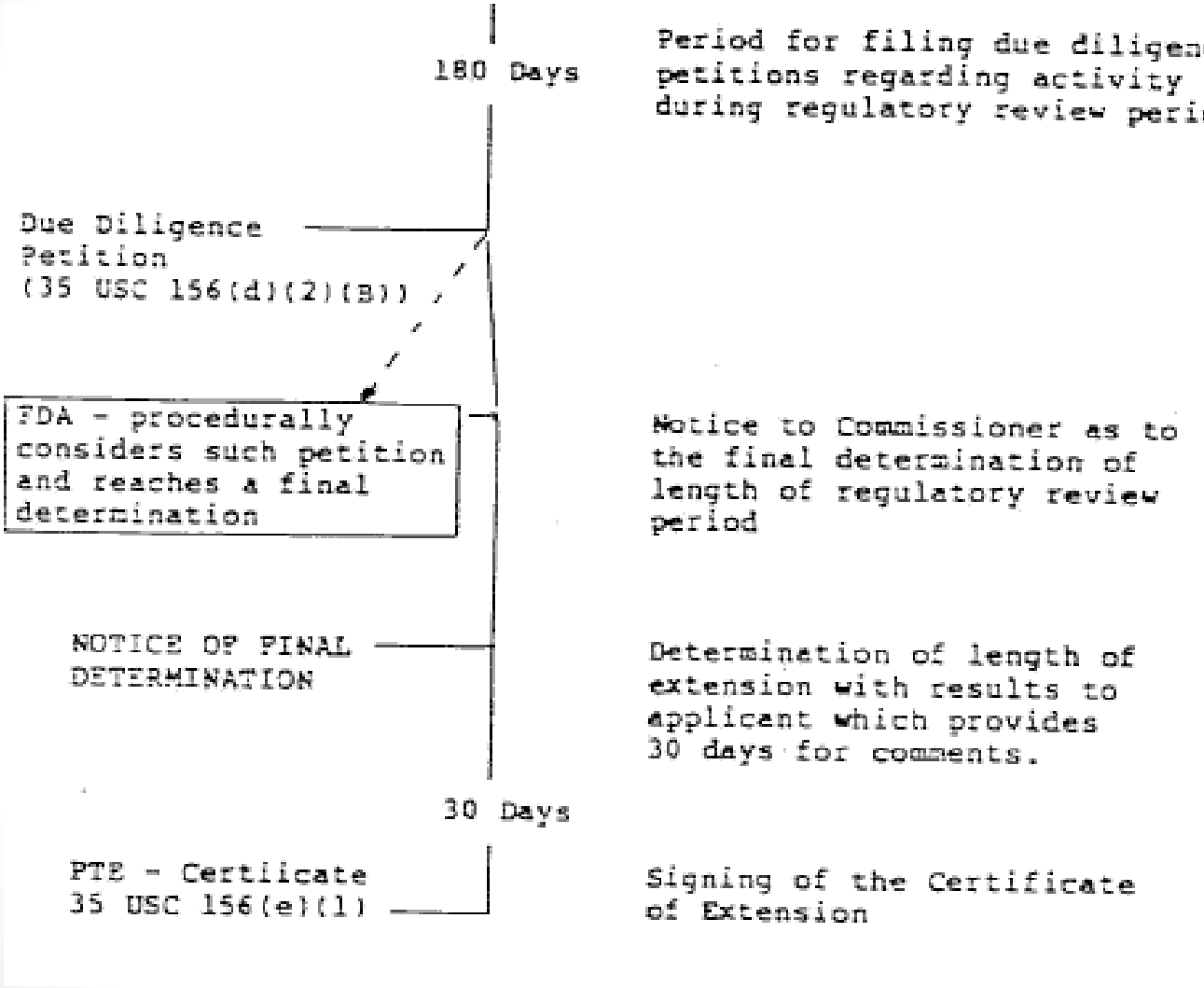
- Determines whether the patent application includes patentable claims (i.e., claims drawn to useful, novel, and nonobvious patentable subject matter that are fully supported and enabled by the specification).

- Responsible for determining the eligibility and period of patent term adjustment and extension.

PTE Application Processing



PTE Application Processing (cont'd)



BPCIA

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BIOLOGICS PRICE COMPETITION AND INNOVATION ACT ("BPCIA")

- In effect since March 2010.
- Involves a complicated and time consuming pathway to challenge patents covering an approved biologic.
- Permits a biosimilar applicant to rely in part on the approved license of a reference product.
- Multi-step "patent dance" procedures include:

Step 1 – Transmission of Biosimilar Application
Step 2 – Reference Product Sponsor's Para. 3(A) Patent List
Step 3 – Biosimilar Applicant's Para. 3(B) Patent List
Step 4 – Reference Product Sponsor's Response
Step 5 – Patent Resolution Negotiations
Step 6 – Patent Resolution If No Agreement and
Step 7 – Filing of the Patent Infringement Action.

FDA Purple Book

- Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations
  - Date biological product was licensed;
  - Whether FDA evaluated biological product for reference product exclusivity;
  - Whether licensed biological product determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product).
    - Listed under reference product to which biosimilarity/ interchangeability demonstrated.
    - Reference product exclusivity expiry date.
- Separate lists for those biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

BPCIA Rationale and Result

- Desire by companies planning to market a biosimilar to resolve patent issues early.

- Companies that do not intend to go the biosimilar route but do plan to produce a "me too" or copycat product (e.g., companies that want a full 12-years of market exclusivity) may also desire the increased certainty provided by early resolution of patent issues.

- Drug products (large or small molecule) do not infringe patents while undergoing regulatory approval (§271(e)(1)) – so no standing to challenge patents in court before approval.

- Results in company having to go through the entire approval process before it can address the uncertainty associated with patent challenges, unless the biosimilar company goes for unpatentability in IPR/PGR or skips biosimilar regime and goes with its own BLA.

First BPCIA Biosimilar Filings

- Sandoz filed biosimilar application with FDA for Zarxio, Sandoz's biosimiar version of Amgen's Neupogen.
- Apotex filed biosimilar application with FDA for versions of Amgen Inc.'s biologics Neupogen and Neulasta.
- Hospira filed one for an epoetin zeta version of Amgen's Epogen and J&J's Procrit, both of which use epoetin alfa.
- Celltrion filed one for Johnson & Johnson's Remicade (infliximab)
  - Celltrion also filed a declaratory judgment action rather than invoke the patent-exchange provisions of the BPCIA.
    - *Celltrion, Inc. v. Kennedy Trust for Rheumatology Research*, 14 Civ. 2256 (SDNY Dec. 1, 2014)
      - District Court dismissed: "The BPCIA purposefully keys its dispute resolution procedures to the occurrence of certain events on the path to FDA approval. Celltrion has failed to show why this carefully crafted and well-timed procedure should be avoided here."

SANDOZ BPCIA FILING

May 2014

Sandoz filed aBLA

July 2014

FDA accepted Sandoz application; Sandoz notified Amgen and communicated that

it had "opted not to provide Amgen with Sandoz's biosimilar application within 20 days of the FDA's notification of acceptance" (no disclosure of its aBLA or product manufacturing information to Amgen)

March 6, 2015

FDA approved Sandoz aBLA for all approved uses of Neupogen.

Notified Amgen again of commercial marketing plan for Zarxio.

BPCIA Process Separate From FDA

- March 27, 2015: FDA denied Amgen's petition that the agency require biosimilar applicants to certify they will participate in the information exchanges specified in the BPCIA.
    - "Section 351(1) describes procedures for information exchanges and the resolution of certain patent rights between the biosimilar applicant and the reference product sponsor. These procedures are parallel to, but separate from, the FDA review process. The BPCI Act generally does not describe any FDA involvement in monitoring or enforcing the information exchange by creating a certification process or otherwise."

First BPCIA Federal Circuit Decision

- *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015) (LOURIE, Newman, Chen)
  - Reference product sponsor (Amgen) sued biologics license applicant (Sandoz) alleging violations of state laws and BPCIA, conversion, and patent infringement.
  - Amgen: Sandoz failed to disclose the required information under § 262(l)(2)(A) and gave premature, ineffective, notice of commercial marketing under § 262(l)(8)(A) before FDA approval of its biosimilar product.
    - Also filed motion for a preliminary injunction to enjoin Sandoz from launching Zarxio after FDA approval.
  - Sandoz: motion for declaratory judgment that it correctly interpreted the BPCIA, and that Amgen's patent was invalid and not infringed.
  - In February 2015, through discovery, Amgen obtained access to Sandoz's biosimilar application.

First BPCIA Federal Circuit Decision

- *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015) (LOURIE, Newman, Chen)
  - DC: Judgment in favor of Sandoz on BPCIA issues.
    - No. 14–cv–04741, 2015 WL 1264756 (N.D.Cal. Mar. 19, 2015).
    - Judge granted declaratory judgment to Sandoz.
      - Permissible under BPCIA to not to disclose aBLA and the manufacturing information to the RPS, subject only to the consequences outlined in BPCIA.
      - Refusal alone does not offer a basis for the RPS to obtain injunctive relief, restitution, or damages against the applicant.
      - Applicant may give notice of commercial marketing under § 262(l)(8)(A) before FDA approval.
      - Sandoz did not violate the BPCIA or act unlawfully.
      - Denied Amgen's motion for a preliminary injunction.

First BPCIA Federal Circuit Decision

- *Amgen Inc. v. Sandoz Inc.* (con't)
  - FC:
    - Vacated declaratory judgment and directed the district court to enter judgment consistent with Federal Circuit's interpretation of the BPCIA.
    - Federal Circuit affirmed that applicant did not violate the BPCIA by failing to disclose its application and manufacturing information to Amgen by the statutory deadline, but Sandoz may only give effective notice of commercial marketing after the FDA has licensed its product.

First BPCIA Federal Circuit Decision: Applicant May Choose To Not Disclose

- *Amgen Inc. v. Sandoz Inc.* (con't)
  - FC:
    - "under the plain language of paragraph (l)(1)(B)(i), when an applicant chooses the abbreviated pathway for regulatory approval of its biosimilar product, it is required to disclose its aBLA and manufacturing information to the RPS no later than 20 days after the FDA's notification of acceptance, but not when the 'when' criterion is not met."
    - "However, the 'shall' provision in paragraph (l)(2)(A) cannot be read in isolation. In other provisions, the BPCIA explicitly contemplates that a subsection (k) applicant might fail to disclose the required information by the statutory deadline. It specifically sets forth the consequence for such failure: the RPS may bring an infringement action under 42 U.S.C. § 262(*l*) (9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii). Those latter provisions indicate that "shall" in paragraph (l)(2)(A) does not mean 'must.' And the BPCIA has no other provision that grants a procedural right to compel compliance with the disclosure requirement of paragraph (l)(2)(A)."

First BPCIA Federal Circuit Decision: Applicant May Choose To Not Disclose

- *Amgen Inc. v. Sandoz Inc.* (con't)
  - FC:
    - "…the BPCIA does not specify any non-patent-based remedies for a failure to comply with paragraph (l)(2)(A). Once the RPS brings an infringement suit under those two provisions, it can access the required information through discovery."
    - "…we ultimately conclude that when a subsection (k) applicant fails the disclosure requirement, 42 U.S.C. § 262(/)(9)(C) and 35 U.S.C. § 271(e) expressly provide the only remedies as those being based on a claim of patent infringement. Because Sandoz took a path expressly contemplated by the BPCIA, it did not violate the BPCIA by not disclosing its aBLA and the manufacturing information by the statutory deadline."

First BPCIA Federal Circuit Decision: NOTICE only after FDA approval

- *Amgen Inc. v. Sandoz Inc.* (con't)
  - FC:
    - "under paragraph (l)(8)(A), a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product. The district court thus erred in holding that a notice of commercial marketing under paragraph (l)(8)(A) may effectively be given before the biological product is licensed, and we therefore reverse its conclusion relating to its interpretation of § 262(l)(8)(A) and the date when Sandoz may market its product.
    - "Sandoz's notice in July 2014, the day after the FDA accepted its application for review, was premature and ineffective. However, the FDA approved Sandoz's aBLA on March 6, 2015, and Sandoz gave a 'further' notice of commercial marketing on that day. …That notice in March 2015 thus serves as the operative and effective notice of commercial marketing in this case."
    - A question exists, however, concerning whether the "shall" provision in paragraph (l)(8)(A) is mandatory. We conclude that it is."

First BPCIA Federal Circuit Decision: NOTICE only after FDA approval

- *Amgen Inc. v. Sandoz Inc.* (con't)
  - FC:
    - "because Sandoz did not provide the required information to Amgen under paragraph (l)(2)(A), Amgen was unable to compile a patent list …"
    - "nothing in subsection (l) excuses the applicant from its obligation to give notice of commercial marketing to the RPS after it has chosen not to comply with paragraph (l)(2)(A). The purpose of paragraph (l)(8)(A) is clear: requiring notice of commercial marketing be given to allow the RPS a period of time to assess and act upon its patent rights."
    - "We therefore conclude that, where, as here, a subsection (k) applicant completely fails to provide its aBLA and the required manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (l (8)(A) is mandatory. Sandoz therefore may not market Zarxio before 180 days from March 6, 2015, *i.e.,* September 2, 2015.

BPCIA PROVISIONS

•42 U.S.C. §262(l)(2)(A): Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application....

•42 U.S.C. §262(l)(9)(C): If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action …for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.

•35 U.S.C. §271(e)(2)(C)(ii)as amended by the BPCIA, provides that:
•It shall be an act of infringement to submit ... if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act....

•42 U.S.C. §262(l)(8)(A): "[t]he subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)."

Thank you!

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