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*Comparing Hatch-Waxman Laws Regulating
Small Molecule Drugs with Existing and
**Proposed Laws Regulating the Approval of
Innovative and Follow-On Biologics***

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Topics To Be Discussed

- The interplay between rules regulating the term of a patent offered by the USPTO and those relating to data exclusivity offered by the FDA
 - Industry-independent rules relating to Patent Term Adjustments
 - Drug industry-specific rules relating to Patent Term Extensions
 - The interplay between PTAs and PTEs
- What are the current rules for small molecule drugs and novel biologics
- What is being proposed for follow-on biologics?
 - The debate over longer data exclusivity periods
 - The debate over the meaning of biosimilarity and immunogenicity
- How a recent court case concerning PTAs impacts all industries, particularly the pharmaceutical and biotechnology industries

Economics of Food and Drug Production

- Companies must be able to get a return on the investment they make in developing a food or drug product
- Regulatory review procedures delay entry into the marketplace
- Variable and uncertain review periods play havoc with business plans
 - Time and resources needed for discovery and development
 - Time post-approval to recover sunk costs of R&D before you make a profit
 - How long can you make a profit before competitors enter the market

Milestones in the Regulation of Drugs

- Before 1984, the FDA required full clinical trials before approval of a small molecule drug
- In 1984, Hatch-Waxman legislation was passed that introduced incentives to produce low-cost versions of many compounds
 - Abbreviated approval process (ANDA) where generic companies could reference clinical trial data of innovator company
 - Activities that reasonably relate to the submission of data for review by the FDA do not constitute patent infringement
 - Innovator companies could have their patents extended to account for FDA review delays taking into account periods before and after a patent has issued.

What about large molecules?

- The FDA has argued that while it does have the statutory authority to regulate innovative biological drugs, it does not have the statutory authority to regulate the approval of “follow-on” biological drugs (FOBs).
- Many companies want to introduce low cost versions of innovative biologics when their patents expire
- Global market for biologics estimated at \$50 billion in 2005, \$105 billion in 2010, or >50% of all expenditures, and increasing
- Many of the top selling biologics are coming off patent in the next few years

So what's the big deal?

- \$\$\$\$ - BILLION\$ in revenue
- \$ for the innovator at stake
- \$ for the follow-on manufacturer
- \$ for the government and insurance companies paying the bills for all of the health care products and services
 - i.e., YOU AND ME

For Drug Discovery and Development, Congress Provides Incentives

- Governments want to promote discovery and development of novel compounds to treat unmet medical needs, but at the same time, lower cost of medical treatment, particularly for old compounds
- What incentives are offered?
- Before 1984, all pharma companies had to run full clinical trials before a drug was approved by the FDA
- In 1984, major legislation was passed, often called the Hatch Waxman Act, which offered provisions that would reduce the cost of drugs by allowing manufacturers of generic drugs to reference clinical trial data of an innovator company when preparing an Abbreviated New Drug Application (ANDA)
- For the generic companies, referencing clinical trial data saves \$\$\$\$

Incentives Offered to Generic and Innovator Companies

- Generic companies
 - Referencing innovator clinical trial data saves big \$\$\$
 - Safe harbor provision prevents an innovator from suing a generic company, as long as generic's activities are reasonably related to submission of information to the FDA
- Innovator companies
 - Get their patents extended to take into account the long and variable periods of review needed by the FDA to ensure effectiveness and safety of new drugs

Statutes designed to compensate patent owners for delays before the patent office and other regulatory agencies

- Patent Term Adjustments (PTA)
 - Provided for under 35 USC 154(b)
 - Industry-independent
- Patent Term Extensions (PTE)
 - Provided for under 35 USC 156
 - Linked to long periods of review by agencies (such as the FDA)
 - Around drug 400 patents extended
 - The list is available on the USPTO website
 - But, these are very valuable patents!!!

Simplified Patent Extension Rule

- Innovator company can have an exclusive period of period of between 5 and 14 years to market a new drug, taking into account variable periods of FDA review before and after a patent has issued.

Intended and Unintended Consequences of Hatch Waxman Act

- Intended Consequences
 - Lowered cost of drugs for old compounds
 - Continued investment to fuel the discovery of new compounds
- Unintended Consequences
 - “Make hay” effect, where innovators raise prices to make the most of sales and marketing efforts at launch time and to reinvest in R&D efforts to speed time for to market for drugs in development
 - Blockbuster effect, where innovators focused research compounds to treat large populations of people, and eliminated or reduced efforts in less profitable areas
 - “No man’s land”, the period in which decisions are made to select a compound before it needs to proceed into development to guarantee commercial viability gets shorter, typically 1-4 years

What's the story for generic biologics?

- The FDA has stated that it has the authority to regulate the approval of innovative biologics, but does not have explicit authority to regulate the approval of generic or follow-on biologics (FOBs)
- Two big debates:
 - Concern over the activity and immunogenicity of compounds made by different processes (e.g., post-translational modifications produced by different host cells)
 - What should the data exclusivity period be for biologics that compensate the innovator for the long time to develop a suitable process, compared to chemical synthesis of small molecule drug?

Proposed Legislation Regulating Approval of FOBs

- Many proposals in Congress going back at least 5 years
- Until 2009, all previous bills died in committee
- Good chance now that something will pass, incorporated into major health care legislation
 - In late September, 2009, over 560 amendments were added to the conservative Baucus health care proposal, which are being sorted out in various representative and senate committees
- Four proposals in 2009, several similar, but two main camps concerning FOBs
 - Generic-friendly (Waxman)
 - Short data exclusivity periods (5-7 years)
 - Innovator-friendly (Eshoo)
 - Longer data exclusivity periods (12-14 years)

The Politicians...

Committee Chairman of the U.S. House Energy and Commerce Committee **Rep. Henry Waxman (D-CA) (C)** talks to **Rep. Anna Eshoo (D-CA) (L)** and other staff members prior to a mark up hearing on the healthcare bill July 30, 2009 on Capitol Hill in Washington, DC.

The committee has resumed its mark up hearing on the bill after reaching a deal with the "Blue Dog Democrats" to provide lower cost plans for small businesses. President Obama has predicted that the votes on the bill for both houses of the Congress would not happen until September, 2009.



(July 29, 2009 - Photo by Alex Wong/Getty Images North America)

Comparison of Hatch-Waxman (small molecule), Waxman (FOB), and Eshoo (FOB) laws

	Hatch Waxman (SM)	Waxman (FOB)	Eshoo (FOB)
Biosimilarity	N/A	<p>No clinically meaningful differences.</p> <p>Based on non-clinical, and non-duplicative clinical studies.</p>	<p>Highly similar to reference product.</p> <p>Requires animal, non-clinical, and clinical studies, and assessment of immunogenicity.</p> <p>FDA may waive requirements</p>

Comparison of Hatch-Waxman (small molecule), Waxman (FOB), and Eshoo (FOB) laws

	Hatch Waxman (SM)	Waxman (FOB)	Eshoo (FOB)
Innovator exclusivity	5 yr for NCE 3 yr supplemental indication or subpopulation 6 mo pediatric exclusivity	5 yr new biologic 3 yr supplemental indication or subpopulation, possible 6 mo extensions	Minimum of 12, but up to 14.5 years
Generic Exclusivity	180 days for first-to-file	180 days or less, depending on litigation for first product that is interchangeable	2 yr for first product that is interchangeable
Patent Listings	Orange Book	Innovator must provide list to generic, upon request	Innovator provides list after generic discloses product application

Comparison of Hatch-Waxman (small molecule), Waxman (FOB), and Eshoo (FOB) laws

	Hatch Waxman (SM)	Waxman (FOB)	Eshoo (FOB)
Stay of approval pending patent litigation	30 months	None	Not specified
Administrative matters	N/A	Provisions provided to prevent delays caused by filing citizen petitions	FDA must review and give guidance before making interchangeability determinations or waiving clinical tests for certain classes of molecules

Therefore, lots of room to debate

- Will new legislation adversely affect R&D towards biologics compared to small molecules?
- How will investing be impacted, where VC funds used heavily by biotech industries?
- How similar do molecules need to be?
- What about immunogenicity?
- Will everything be evaluated by the FDA on a case-by-case basis?
- How much will I need to spend to get my product approved?
- Am I better off, focusing on molecules that offer improved properties, and seeking approval as a new biologic rather than as an FOB?
- Since it took nearly 25 years for the boundaries of the Hatch Waxman rules to be defined by litigation, how long will it take for the new rules to be defined? How much will that cost?

Recent Challenges to Patent Term Rules Could Dramatically Impact the Drug Industry

- Several statutes are designed to compensate patent owners for delays before the patent office and other regulatory agencies
 - Patent Term Adjustments
 - Patent Term Extensions

Patent Term Adjustments (PTA)

- Patent Term Adjustments are provided for under 35 U.S.C. 154(b)
- Designed to compensate patent owners and their licensees for delays (3 general types) during prosecution before the PTO
 - Delays attributable to the PTO
 - Delays attributable to the Applicant
 - Delays beyond the control of both the PTO and the Applicant
- Extremely complex formulas requiring a detailed analysis of the file history of a patent
 - Up to 75 calculations of various periods of delay
 - Not all periods easily ascertainable from electronic PTO records
 - PTO isn't even sure what all the Applicant Delay types are, but they will "know it when they see it"

Patent Term Extensions (PTE)

- Patent Term Extensions are provided for under 35 U.S.C. 156
- Designed to compensate a patent owner for delays due to periods of review by a regulatory agency (e.g., the FDA)
- General types of delay considered:
 - Periods of review by the regulatory agency before a patent issues
 - Periods of review by the regulatory agency after a patent issues
 - Periods of review by the PTO
- Moderately complex formula requiring documentation from the PTO and the regulatory agency noting the starting and ending dates of the relevant review periods and diligence of the applicant in responding to requests from the regulatory agency or the PTO

Disclaimers

- Terminal Disclaimers (TD)
 - Serve to truncate the term of a patent
 - Can be linked to the expiration date of an earlier related patent
 - Can be set to a specific date
 - Often used to overcome obvious-type double patenting rejections
- Statutory Disclaimers (SD)
 - Permit disclaiming one or more claims in a patent
 - Often used to overcome anti-trust issues

Comparing PTA, PTE, and TD

- PTAs lengthen the Normal Term (NT) of a patent
- Patents with a TD cannot be lengthened by PTA
- But, patents with a TD can be lengthened by a PTE

- A patent with a PTA can have a term lengthened further by a PTE

- Errors by the PTO in calculating a PTA can propagate and affect the terms of many related patents

What's the Big Deal?

- A recent court decision, *Wyeth v. Dudas*, in which the court held that the PTO:
 - had erred in interpreting the statute relating to the calculation of PTAs, and
 - improperly denied Wyeth a portion of the term of two of its patents

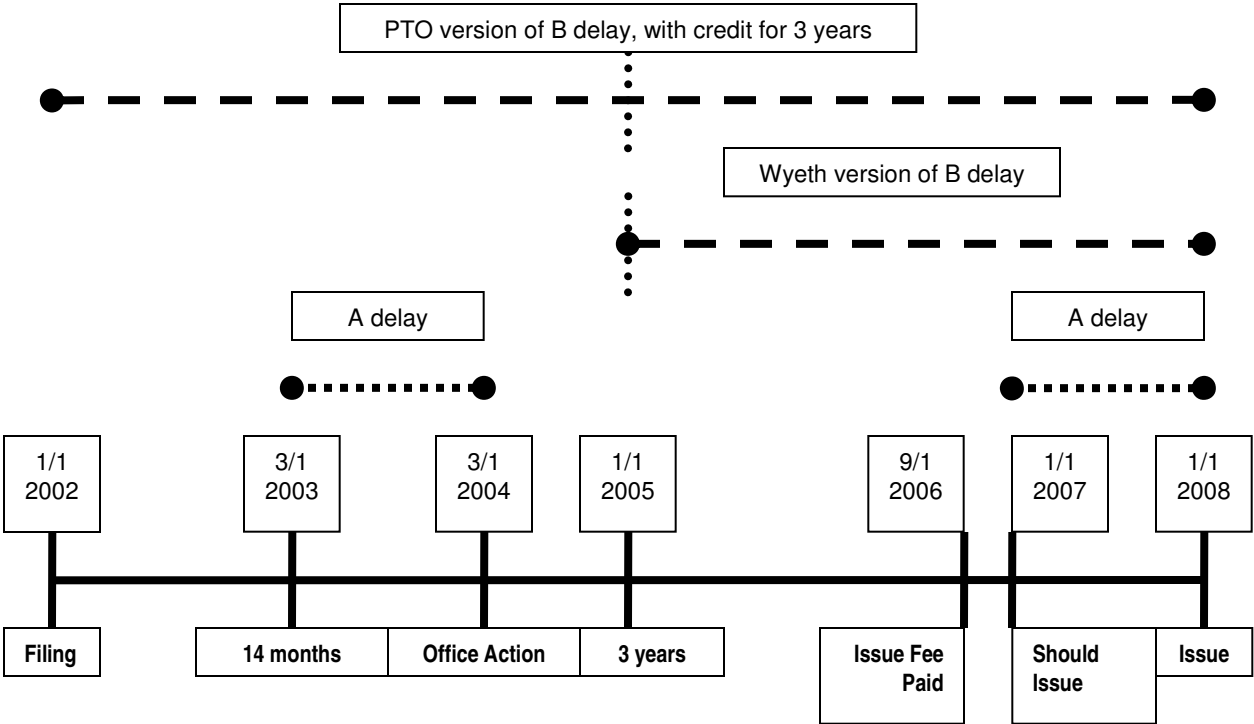
The Key Issue in Wyeth v. Dudas

- The court held that the PTO had improperly interpreted 35 U.S.C. 154(b) relating to a type of delay which provides a guarantee that the PTO will issue a patent within 3 years from its filing date (taking into account certain kinds of offsetting delays, particularly by the applicant)
- The issue revolved around interpretations of the statute when two or more general types of delays overlap.

General Types of Delay under 35 U.S.C. 154(b)

- A delays:
 - Guarantees the PTO will mail an official communication so many months after filing or when an applicant response is filed
 - 14 months for a first office action, 4 months to respond to a reply, 4 months to issue a patent after the issue fee is paid, 4 months to act on an application after a decision by the BPAI or a federal court
- B delays:
 - 3 year pendency guarantee
- C delays (three subtypes) relating to:
 - C₁ interference proceedings
 - C₂ secrecy orders
 - C₃ appeals to the BPAI or a federal court

Overlapping Delays Considered in *Wyeth v. Dudas*



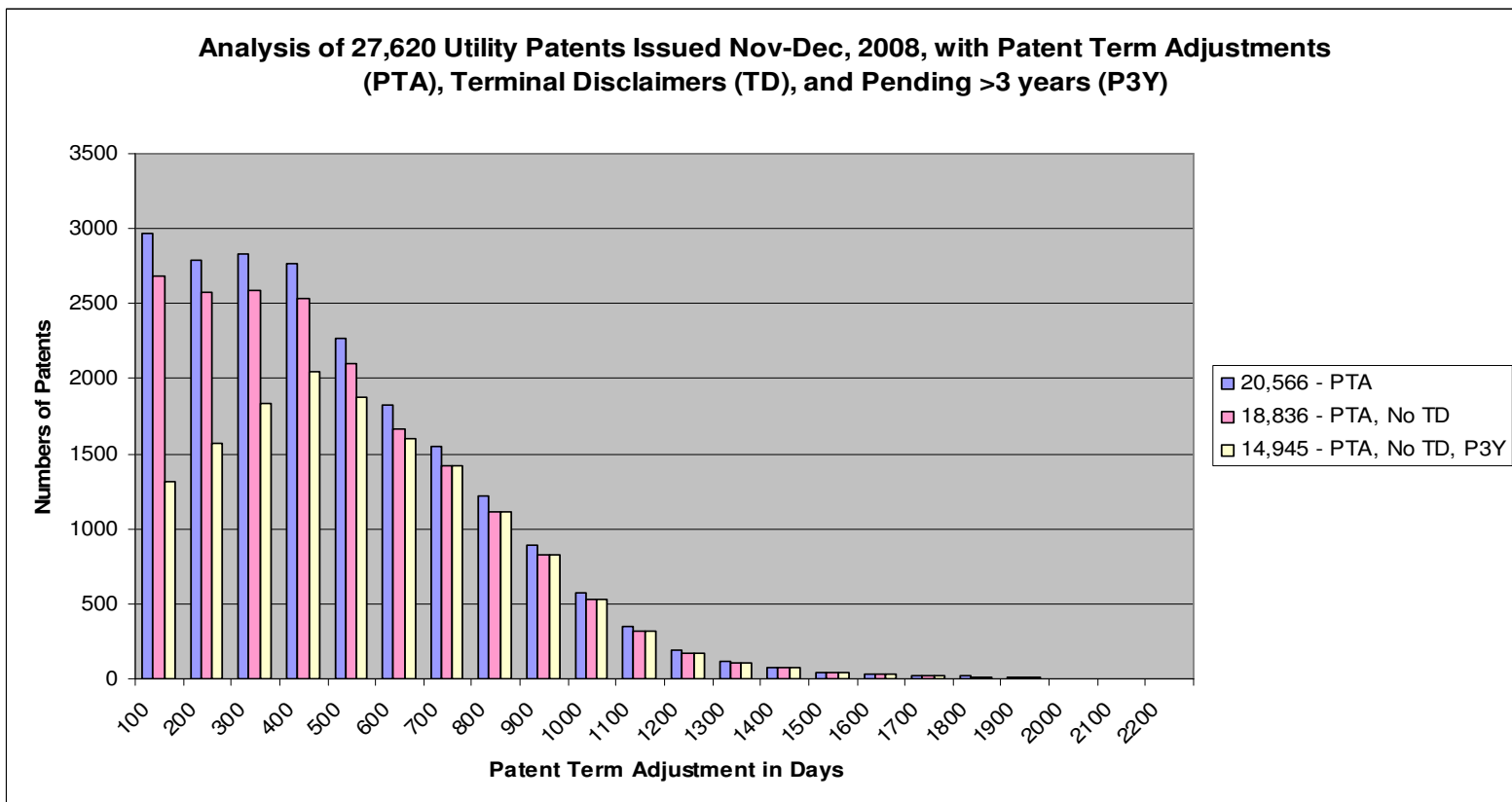
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A Large Majority of Patents in Many Industries Are Affected by Wyeth v Dudas, if upheld (*)

Table 1
Analysis of 27,620 Utility Patents issued November-December, 2008 for
Patent Term Adjustments (PTA) and Terminal Disclaimers (TD)

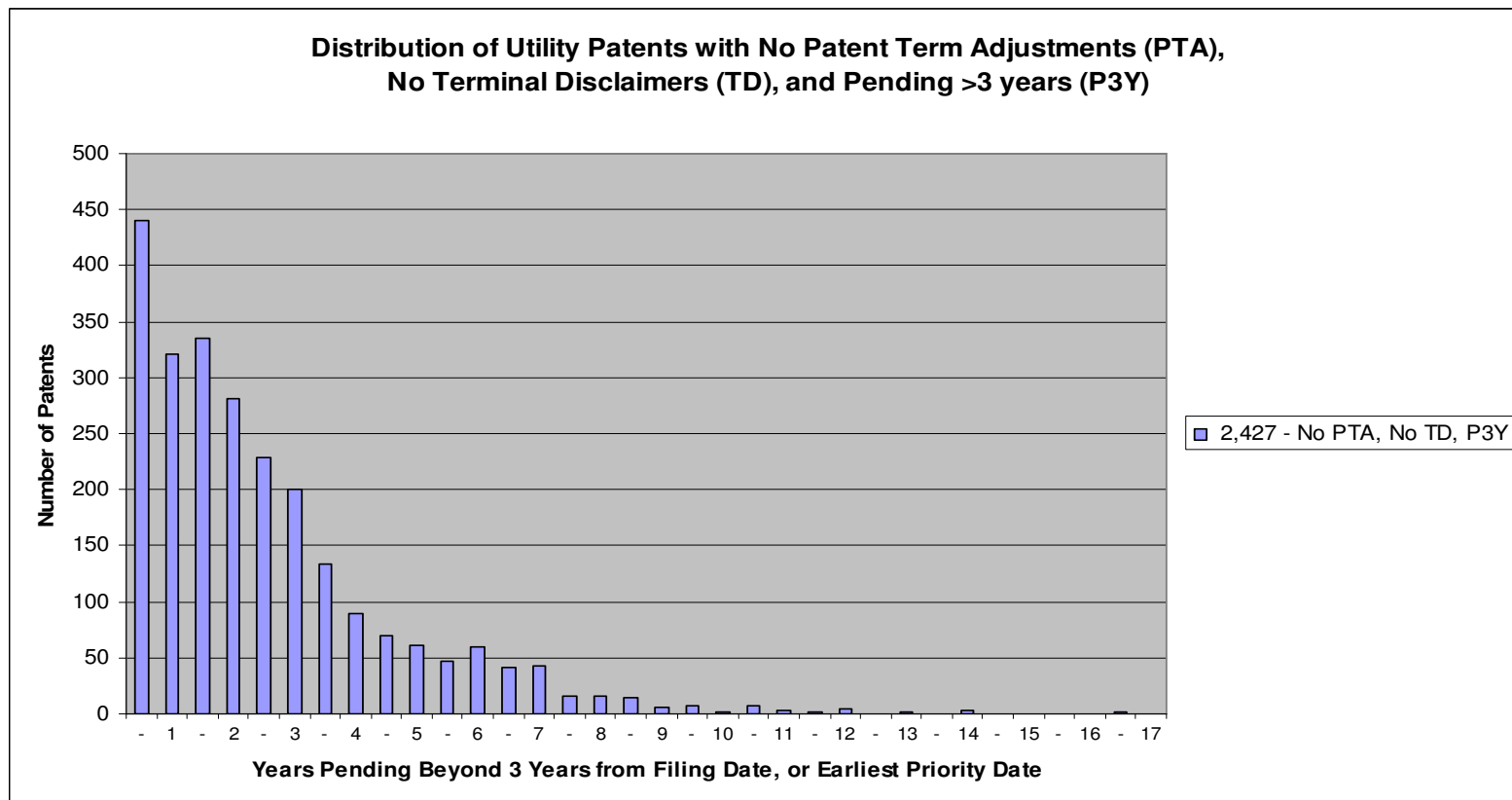
	Pending any number of years			Pending >3 yrs (P3Y)				
	PTA listed	PTA listed, No TD	TD	P3Y	P3Y PTA listed, No TD	P3Y No PTA listed	P3Y No TD	P3Y, No PTA listed, No TD
PTA	+	+	±	±	+	-	±	-
TD	±	-	+	±	-	±	-	-
%	74.46%	68.20%	10.76%	69.53%	54.11%	10.51%	62.90%	8.79%

Distribution of patents with PTA, +/- TD, or P3Y (*)



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Patents pending >3 years, but no PTA or TD listed, might be eligible for longer PTA (*)



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So what's next?

- You need to evaluate your portfolio for recently-issued patents
- For patents which issued less than 2 months ago, you can file a petition with the PTO to request reconsideration of the calculation of a PTA
- For patents which issued between 2 months ago and 180 days ago, you can file a case in a Federal District Court against the PTO commissioner to request reconsideration of the calculation of a PTA
- For patents which issued over 180 days ago, you are out of luck, unless...
 - The Appeals Court hearing the appeal filed by the PTO in *Wyeth v. Dudas* rules that the District Court was correct and that the PTO must offer applicants a grace period back to a specific date, to request reconsideration of the calculation of a PTA

Broad Impact of *Wyeth v Dudas* on the Provisions of Various Patent Licensing Agreements

- Provisions linked to the Expiration Date of one or more patents in a portfolio
 - Expiration date of the agreement may be tied to the expiration date of the last patent in a licensed portfolio
 - Upfront payments, milestone payments, and royalty rates are usually tied to the perceived value of a patent, which is linked to its expiration date

What else to you need to do?

- Consider the impact of *Wyeth v. Dudas* on:
 - All of the patents that are related or linked to the expiration date of a patent having an incorrectly calculated PTA
 - The strategic value of all related patents in your portfolio
 - Business plans that rely on the expiration dates of your patents or your competitors
 - Licensing agreements which may have terms tied to the expiration date, *and the value*, of one or more patents having an error in the determination of its PTA

Conclusions

- FDA and PTO regulations are complex, requiring careful preparation of documents that are reviewed by regulatory officials and patent examiners according to procedures that take years to complete.
- The rules for calculating patent expiration dates, taking into account patent term adjustments, extensions, and disclaimers are very complex
- Knowledge of the expiration date is critical for allocating resources, by the innovator, and by the generic manufacturer to meet business goals
- Minimizing delays by the applicant increases \$\$\$ in the bank
- The debate over similarity and immunogenicity of biologics will take decades to resolve, not only for the creation of FDA guidance documents, but also in the courts

Questions?

- **Contact info** – VLuckow@PatPro.Com
- **Firm website** – www.PatPro.Com
- (*) **Original data on numbers of patents affected by the Federal District Court ruling in Wyeth v. Dudas was first published as “Opportunities for Longer Patent Term Adjustments”, Browne, RE, Romza-Kutz, D, Luckow, VA, and Browne, RE, Jr, on January 15, 2009.**
- **This paper is now available upon request from V.A. Luckow**

Overlapping Agency Authority = Complexity

- FDA and PTO regulations are complex, requiring careful preparation of documents that are reviewed by regulatory officials and patent examiners according to procedures that often take years to complete.
- Despite attempts by Congress to fairly compensate inventors or assignees for delays which occur during periods of review by the FDA or the PTO, products regulated by both agencies may be subject to overlapping periods of data (market) exclusivity, and patent exclusivity, the normal term of which may be adjusted, extended, or disclaimed.
- Predictable, fixed terms of exclusivity, have given way to variable overlapping terms, determined by the starting and ending dates of dozens of review periods, which may a single time, more than once, or rarely before a regulatory agency.
- Variable periods, reviewer discretion, and complex multi-agency rules, all invite challenges, by innovators seeking to prolong the right to exclude others from selling their products, and by generic manufacturers, seeking to sell competing products, that fuel healthy competition in the market.
- Striking the right balance, to avoid industry- or size-specific regulations, is not an easy task.

Challenges to Patent Term Rules Affect Business Strategies

- Recent challenges to the interpretation of PTO rules that affect the term of a patent, if upheld, plus proposed new rules affecting the regulation of biopharmaceutical and small molecule products, if implemented, will dramatically alter the procedures needed to discover, develop, approve, and market these products.
- Many business strategies, reflected in research and development plans, license agreements, and litigation, depend on a clear understanding of all the issues affecting the regulatory approval process *and* the term of a patent, to facilitate decision-making by executives seeking to protect their products in competitive business environments around the world.

Data Exclusivity Provisions Offered by the FDA Affect Business Strategies and Are Highly Litigated

- There is currently a lot of debate in Congress over the provisions in proposed bills regulating the length of various data exclusivity provisions that are designed to protect an innovative biopharmaceuticals “reference compounds” from competition by manufacturers offering “follow-on biologics”.
- While a 12 year period of data exclusivity is currently favored, many of the proposed laws leave much to be desired with respect to the definition of key terms, such as identity, functional similarity, and immunogenicity, and the extent to which the FDA has control regulating the approval of biopharmaceuticals on a case-by-case basis.
- Areas likely to be litigated, between manufacturers and the FDA, and between innovator and follow-on manufacturers, will be briefly discussed, along with strategies for minimizing delays, and maximizing data exclusivity and patent term protections, that add value to companies seeking to bring products to market that meet unmet medical *and economic* needs in today’s challenging global economy.