PHARMA & BIOTECH PATENTS

IN THE US

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FISH

FISH & RICHARDSON

Overview of Prosecution Issues

PART I

- **Maximize likelihood of infringement**
- **Maximize validity**
- **Patent-eligible subject matter**

Maximize likelihood of infringement

- Pursue claims that cover the product
  - Might seem obvious, but there are traps for the unwary
  - Don’t inadvertently exclude the specific form of the product from the claim
    - Salt form?
    - Specific stereoisomer, solvate, or polymorph?
    - Polypeptide claimed by sequence

Maximize likelihood of infringement

Problem: if the product is a salt form, don't simply claim "a compound of Formula I," where description of Formula I does not encompass a salt form.

Maximize likelihood of infringement

Problem: parsing the conjunctions…

Claim 1

Compound A, <u>or</u> a salt thereof, <u>or</u> a solvate thereof.

- Ambiguous as to whether "or a solvate thereof" modifies *both* "Compound A" *and* "a salt thereof" or only one of those two.
- If the approved drug is a *solvate of a salt* of Compound A, the claim may not be construed to cover the drug product

Maximize likelihood of infringement

Problem: wrong sequence…

Claim 2

A polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

- Does SEQ ID NO: 1 include a leader sequence that is absent from the final product?
- Does SEQ ID NO: 1 contain errors?

Maximize likelihood of infringement

- Pursue claims that are FDA “Orange Book” listable
  - **Composition of matter** claims
    - compounds (and their salts)
    - pharmaceutical compositions
    - solid forms (e.g., polymorphs)
    - formulations and dosage forms
    - kits
    - delivery device containing the drug
  - **Method** claims
    - treating a condition
    - administering drug
    - activating or inhibiting a particular biological mechanism

Maximize likelihood of infringement

- Pursue claims that will cover something ***stated*** on drug label
  - Method of administering the drug (e.g., IM injection, twice per day, with food, co-administer with a painkiller)
  - Characteristic of product containing the drug (e.g., pH, size of unit, extended release tablet)
  - Drug's action (e.g., method of inhibiting enzyme A, method of reducing level of protein X in plasma)
  - (Rare) Method of manufacturing, testing, or quality control

Maximize likelihood of infringement

- Also pursue claims to non-OB-listable subject matter – can augment infringement position
  - Process of preparing the drug or formulation
  - Key intermediates
  - Metabolites
  - Methods of treating non-approved diseases
  - Solid forms other than the approved product
  - Non-approved combination therapies
  - Any potential design-around possibilities

Maximize likelihood of infringement

- Consider pursuing different types of OB-listable claims in separate patents – results in more patents to list and more patents for generics to contend with

- Consider timing strategies that will result in as many OB-listable patents as possible before onset of Hatch-Waxman (H-W) litigation

Maximize validity

- Do a prior art search
  - Before drafting application: leads to cleaner prosecution history and lessens chances of invalidity
  - Search conducted after filing date: may still be useful for amending claims prior to examination
  - Periodic updates to the search: may reveal previously unpublished patent applications that are potentially invalidating

Maximize validity

- Build in narrower embodiments of varied scope as fallback positions
  - Provides support for narrowing amendments/new claims
  - Particularly helpful where state of prior art is unknown/unsearched

Maximize validity

- Pursue narrow claims that cover the product
  - Relying solely on broad claims to protect the product is risky
  - If the drug is a **neutral (non-salt) compound**, have at least one claim limited to that non-salt compound.
  - If the drug is a particular **stereoisomer**, have at least one claim limited to that isomer.
  - If the drug is a particular **polymorphic form**, have at least one claim limited to that specific form.

Maximize validity

- Pursue narrow claims that cover the approved method of treatment
  - Recite the specific disease in the narrow claim (e.g., “small cell lung cancer,” not “cancer”; “rheumatoid arthritis,” not “autoimmune disease”)
- Pursue narrow claims that cover the mechanism
  - Recite the specific mode of action (e.g., “inhibiting” or “reducing” or “increasing” as opposed to “modulating” or “changing” or “improving”)
  - If using relative term (e.g., “reducing”), specify comparator
  - Specify affected receptor or pathway, if known

Maximize validity

- If you have multiple priority dates, intervening art could be a problem
  - Keep track of which subject matter in the application has which priority date
  - Draft each claim with that information in mind
  - Any claim that needs the earlier priority date for patentability should not rely on disclosure added at the later priority date

Maximize validity

- Example

Priority application: Discloses treatment of eczema

Present application: Adds disclosure of treating psoriasis

The priority date of a claim drawn to "A method of treating eczema or psoriasis comprising…" would be the later filing date, so the claim is subject to intervening art.

Write separate claims for "eczema" and "psoriasis" to preserve correct priority date for each.

Maximize validity

- Anticipate (and fix) **inherent anticipation** problems
  - "Inherent anticipation" is where a prior art reference discloses only some of the claim limitations, but the missing limitations are *inherently* present in what was disclosed, so claim lacks novelty
    - They must *necessarily* be present—not just a possibility
    - Their presence in the prior art reference need not have been realized by anyone at the time
    - That they were present in the prior art reference can be proven with other references, not necessarily prior art

Maximize validity

- Certain types of claims especially vulnerable to **inherent anticipation** related to prior disclosures of the drug/use of the drug
  - Polymorphs or solid forms of known compounds
  - Metabolites of known prodrugs
  - Methods of treatment or prevention with known drugs

Maximize validity

- To avoid **inherent anticipation** problems, consider including claims drawn to:
  - Pharmaceutical formulations of the drug
  - Isolated or purified form of the drug
  - Method of using the drug in a therapeutically effective amount
  - Requiring a step of identifying a patient as having a particular condition and then treating that condition

Maximize validity

- **Inherent anticipation** hypothetical #1:
  - App1 discloses that Compound A was isolated as a crystalline solid, but gives no further details
  - Later-filed App2 discloses and claims a specific crystalline form of Compound A (Form I)
  - If the process of making Compound A disclosed in App1 necessarily produces a mixture of forms including Form I, the App2 claim may be inherently anticipated
  - Might help to limit App2 claim to “isolated” or “purified” Form I

Maximize validity

- **Inherent anticipation** hypothetical #2:
  - App1 discloses administration of A to treat a disease
  - Later-filed App2 discloses and claims B, a metabolite of A
  - If administration of A as disclosed in App1 inherently results in *in vivo* transformation to B, then App1 may inherently anticipate App2's claim to B
  - Limiting claims in App2 to "isolated" B or a pharmaceutical composition comprising B may help

    Schering Corp. v. Geneva Pharm., 339 F.3d 1373 (Fed. Cir. 2003)

Maximize validity

- Enablement issues
  - Specification should provide a full description of how to make and use at least the favored compound, and preferably several
  - Post-filing date evidence that it really does work as predicted can be submitted during prosecution, if challenged

Maximize validity

- Enablement issues
  - If there is a favored compound:
    - include a full description of its synthesis instead of relying on synthesis of a related compound
    - make sure any key reagents and conditions are fully described
    - make sure starting materials are commercially available or otherwise fully characterized in the literature
    - provide some evidence of characterization (e.g., MS or NMR)

Maximize validity

- Written description issues
  - Stereoisomer
    - Provide descriptive support (e.g., structures, formulas, and/or chemical names indicating stereochemistry) for all specific stereoisomers *regardless of whether they were isolated at the time of filing*
    - Where isomers were separated, provide details of the separation procedure as well as retention time, optical rotation, and other data characterizing the isomer – can provide a basis for claiming a specific isomer

Maximize validity

- Written description issues
  - Genus claimed by **function** requires description of either:
    - How the function relates to structure (so that one could predict all structures that will possess the function), or
    - Structures of a “representative number” of species (i.e., species across the entire scope of the claim)

Maximize validity

- Written description issues: case law
  - Cannot claim all cDNAs encoding all vertebrate homologs, based solely on disclosure of the sequence of one homolog

    UC v. Lilly, 119 F.3d 1559 (Fed Cir 1997)
  - Cannot claim all compounds that have a given function, based solely on disclosure of a screening assay that could be used to identify the compounds

    University of Rochester v. Searle, 358 F.3d 916 (Fed Cir 2004)

Maximize validity

- Written description issues: case law
  - Cannot claim all possible ways to inhibit NFκB based solely on disclosure of NFκB and its interaction with its natural inhibitor, IκB

    Ariad v. Lilly, 598 F.3d 1336 (*en banc*) (Fed. Cir. 2010)

  - Cannot claim all antibodies that have a particular function, based solely on disclosure of a set of closely related antibodies with that function

    AbbVie v. Janssen, 759 F.3d 1285 (Fed. Cir. 2014)

Maximize validity

- Minimizing potential **written description** issues
  - Include a description of many structurally different compounds that fall within the claimed genus
  - Include theory of how drug's structure relates to its function, if known
    - X-ray crystallographic data
  - Include support for various degrees of claim scope, particularly narrower generic embodiments guided by the drug product and exemplified compounds

Patent-eligible subject matter

- Statute (35 USC 101) says that the following types of subject matter are eligible for patenting:
  - Composition of matter
  - Process
  - Machine
  - “Manufacture”

Patent-eligible subject matter

- Courts have imposed further limits, saying the following are ***not*** patent-eligible ("judicial exceptions", or "JE"):
  - Products of nature
    (*naturally occurring DNA; cloned sheep*)
  - Natural laws/phenomena of nature
    (*correlation between a biomarker and a disease*)
  - Abstract ideas
    (*algorithms; ways of doing business*)

Patent-eligible subject matter

A claim drawn to a JE is not patentable unless it also recites something amounting to “significantly more” than the JE

- Little guidance as to what could qualify as “significantly more”
- USPTO and courts are struggling to figure it out, with inconsistent outcomes
- USPTO issued guidelines in 2014 and 2016:

http://www.uspto.gov/patents/law/exam/interim_guidance_subject_matter_eligibility.jsp

Patent-eligible subject matter

Case law re patent eligibility of Life Sciences patents summarized on Fish & Richardson's *Mayo/Myriad* Life Sciences Tracker:

https://www.fr.com/mayo-myriad-tracker/

Patent-eligible subject matter

USPTO guidelines re “significantly more” for **product of nature**

- Features or steps that demonstrate the subject matter is “markedly different” from what exists in nature
- “Markedly different characteristics can be expressed as the product’s **structure, function, and/or other properties**, and will be evaluated based on what is recited in the claim on a case-by-case basis.”

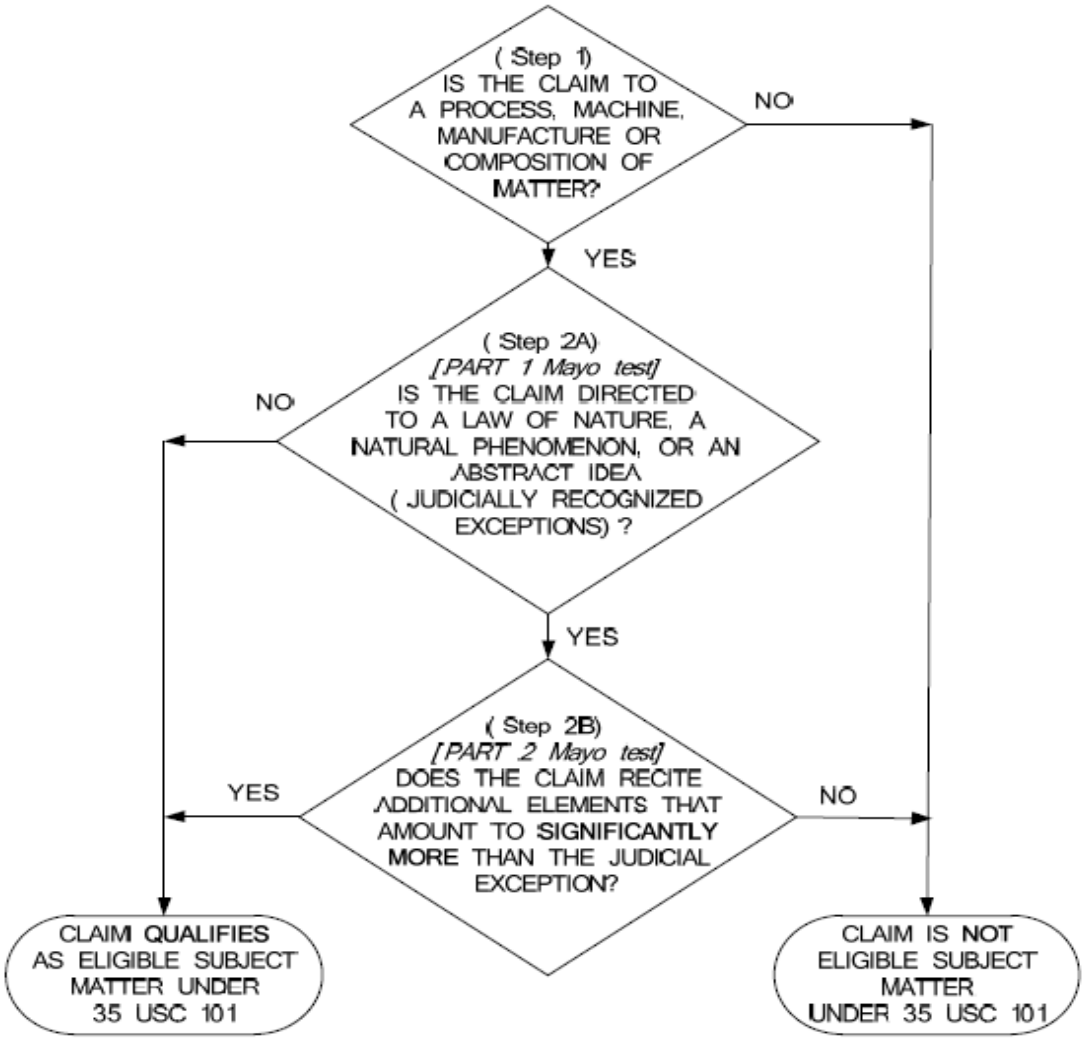
Patent-eligible subject matter

USPTO guidelines re “significantly more” for other JE’s

- Improvements to another technology or technological field.
- Applying the JE *with* or *by use of* a particular machine.
- Effecting a transformation or reduction of a particular article to a different state or thing.
- Specific limitation that is not well-understood, routine, or conventional in the field, or unconventional steps that confine the claim to a particular useful application.

Patent-eligible subject matter

USPTO guidelines



Overview of Prosecution Issues

PART II

- **Obviousness-type double patenting**
- **Prosecution history estoppel**
- **Inequitable conduct and duty of disclosure**
- **Lengthening patent term**
- **Other important quirks of US practice**

Obviousness-type Double Patenting (OTDP)

- OTDP is a ground of rejection when
  - A claim of an application (the rejected application) is an obvious variant of a claim of another application or patent (the “reference application/patent”), and
  - The rejected application and reference application/patent have overlapping inventorship or ownership
- Typically seen in parent/continuation pairs, but not limited to that situation
- The reference application need not be prior art against the other for OTDP to apply

Obviousness-type Double Patenting (OTDP)

- Under the “safe harbor” provision of 35 USC 121, an OTDP rejection cannot be made if one of the applications was filed as a divisional (not continuation) of the other as a result of a restriction requirement in the parent.

Obviousness-type Double Patenting (OTDP)

- OTDP rejection be overcome by argument, amendment, or filing a Terminal Disclaimer (TD)
  - To qualify for a TD, the two applications/patents must be commonly owned—i.e., by exactly the same entity or set of entities

Obviousness-type Double Patenting (OTDP)

- In a TD, the owner agrees that
  - A patent issuing on the rejected application will expire no later than the date the reference application/ patent expires, and
  - If a patent issuing on the rejected application ever ceases being commonly owned with the reference application/patent, it will be **unenforceable** until such time as common ownership is restored.

Obviousness-type Double Patenting (OTDP)

- OTDP is a court-made doctrine intended to accomplish two goals:
  - Ensure that once a given patent expires, the public is free to practice that invention, including obvious variants claimed in other patents
  - Ensure that two different entities cannot separately sue a given party for infringement of two patents claiming essentially the same invention

Obviousness-type Double Patenting (OTDP)

- Before the GATT changes to US law in 1995, continuations often expired much later than their parents, so the effect of a TD on expiration date was often significant

- Now the primary effect is on applications that are awarded extra patent term via Patent Term Adjustment due to PTO delays, or applications from different families with different priority dates

Obviousness-type Double Patenting (OTDP)

- Recent Federal Circuit decisions like *Gilead Sciences, Inc. v. Natco Pharma Ltd*., 753 F.3d 1208 (Fed. Cir. 2014), are expanding the doctrine of OTDP to apply in more cases

- OTDP issues are difficult to avoid altogether, but there are strategies that can be used to minimize risk

Obviousness-type Double Patenting (OTDP)

- OTDP strategies
  - Best protection from OTDP is a restriction requirement in the first application of the family, so 35 USC 121 safe harbor applies
  - Prosecute applications in a family serially – having one application pending at a time minimizes the OTDP issues between family members
  - Pursue the most important claims in the first of a series of application family members. The first (earlier-filed) application will have the least risk of OTDP over other family members

Obviousness-type Double Patenting (OTDP)

- OTDP strategies
  - OTDP is also an issue for applications/patents in different families with similar subject matter (e.g., in the same research program)
  - Applications/patents related by subject matter but in different families should be prioritized and pursued in a manner that will limit OTDP risk to the more important applications

Obviousness-type Double Patenting (OTDP)

- OTDP strategies
  - Limit the number of subject matter-related applications that are ultimately filed
  - Delay prosecution in cases of lesser importance
  - Abandon applications with little value

Prosecution history estoppel

- Statements made during prosecution can be binding on patentee in subsequent litigation
  - Interpreting scope of claim terms
  - Interpreting what prior art says/means
  - Admitting that something qualifies as prior art
  - Examiner's statements, too—unless challenged by applicant during prosecution

Minimizing prosecution history estoppel

- Keep written record short
- Consider interviewing the case
- In written responses, try not to characterize the invention in words other than what is already of record

Minimizing prosecution history estoppel

- Avoid prophylactic arguments and inconsistent statements
- If a prior remark was not accurate, clear up the record
- If examiner misconstrues something or gives unhelpful "reasons for allowance," clear up the record

Inequitable conduct

- Action or inaction by applicant during prosecution that
  - was done with intent to mislead the examiner AND
  - was material to convincing the examiner to issue the patent (but for the misleading action/inaction, the patent would not have issued)

- If IC is proven in litigation, the patent is **unenforceable**
  - Related patents may also be infected and declared unenforceable

Inequitable conduct

- Examples
  - Failing to disclose material prior art known to a person involved in the prosecution
  - Failing to disclose contrary evidence known to applicant
  - Submitting a false or misleading declaration
  - Falsely claiming “small entity” status (and paying lower fees)
  - Possibly: failure to disclose the best mode in the specification as filed

Minimizing risk of inequitable conduct

- Duty of disclosure
  - Duty extends throughout prosecution until patent issues
  - Disclose all potentially material information in an information disclosure statement (IDS)
  - List all of applicant's applications/patents claiming related subject matter (for OTDP purposes)
  - Cross-cite relevant references from related applications (US and non-US)
  - If contradictory statements are made in other applications or publications, disclose them

Minimizing risk of inequitable conduct

- Duty of disclosure
  - For references discovered late in prosecution (e.g., after allowance), carefully review for pertinence and:
    - Cite if pertinent to patentability, of course
    - If decision is not to cite because it is immaterial, place a memo to that effect in file—this serves as evidence in later litigation

Minimizing risk of inequitable conduct

- Declarations under 37 CFR 1.131 and 1.132
  - Declarations are made under penalty of law and therefore are scrutinized in litigation for inconsistencies and potential falsehoods that could form the basis of an inequitable conduct charge
  - Filing declarations should be avoided if possible
  - When declarations are necessary:
    - take care to present arguments and data with accuracy, balance, and fairness
    - be certain declarant understands the importance of accuracy and that future deposition is likely

Lengthening patent term

- Two mechanisms
  - For claims drawn to pharmaceuticals, biologics, Class III medical devices, or methods of making or using same, Patent Term Extension (**PTE**) under 35 USC 156
  - For **all** types of claims, Patent Term Adjustment (**PTA**) under 35 USC 154(b)
  - A patent can qualify for both PTE and PTA

Lengthening patent term (PTE)

- Intent is to restore some patent term lost during clinical trials and FDA review of new product
- The extension applies solely to the **part** of the claim(s) that covers the FDA-approved drug or Class III device, process of manufacturing same, or FDA-approved use of same
- A given patent can be extended only once (even if it covers multiple products), and only for first commercial marketing of the product
- Only one patent can be extended for a given product

Lengthening patent term (PTE)

- Extension cannot exceed 5 years
- Total term remaining on the extended patent cannot exceed 14 years from date of FDA approval
- PTE application must be filed within 60 days following FDA approval
- Application requires detailed description of time spent on clinical trials and FDA review

Lengthening patent term (PTA)

- Intent is to restore patent term taken up by USPTO delays prior to issuance
- Applies to any patent filed on or after May 29, 2000
- Governed by 35 USC 154(b) and 37 CFR 1.702 – 1.705

Lengthening patent term (PTA)

PTA = (Days of PTO Delay) – (Days of Applicant Delay)

- If PTO delay > applicant delay, patent gets PTA added to term
- If PTO delay ≤ applicant delay, nothing happens (term is never reduced)

Lengthening patent term (PTA)

3 kinds of PTO Delay are added together to equal total PTO Delay, but any overlapping days counted only once

- "A Delay": failure of PTO to take certain actions within specified time frames
- "B Delay": failure of PTO to issue a patent within 3 years of filing (excluding time between RCE* filing and allowance)
- "C Delay": interference, appeal, or secrecy order

* RCE = Request for Continued Examination

Lengthening patent term (PTA)

<u>Applicant Delay</u>: period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution of the application

- Filing reply more than 3 months after Office action mailing date
- Supplemental replies
- Submitting IDS* at certain points during prosecution, unless the new references were first cited <30 days before in a related foreign case

* IDS = Information Disclosure Statement

Lengthening patent term (PTA)

Maximize PTA by taking advantage of any delays that do not subtract from PTA and avoiding delays that do subtract

- File replies just before or at the 3-month deadline
  - Do not take extensions of time beyond the 3 month date
  - ***Do*** take any extensions needed to get to the 3 month date (e.g., in replying to restriction requirement, which has a 2-month deadline, extend 1 month)
- Avoid need for supplemental replies to extent possible
  - Proofread initial reply before filing to correct errors/omissions
  - If supplemental reply is needed, file ASAP after initial reply

Lengthening patent term (PTA)

Maximize PTA by taking advantage of any delays that do not subtract from PTA and avoiding delays that do subtract

- Submit IDS's at any of the prescribed times
  - Within 3 months of application filing date
  - Before receipt of first OA
  - Before or with response to restriction requirement
  - With (not after) response to any non-final OA
  - With (not after) RCE
  - At other times if can certify under 1.704d that the new references were first cited in a related foreign prosecution <30 days before the IDS was filed

Lengthening patent term (PTA)

- PTO calculates days of PTA at issuance and prints on the face of the patent
- Incorrect PTA calculation can be challenged within 2 months of issuance
- Benefit of PTA is lost if terminal disclaimer was filed over patent that expires earlier

Other important quirks of US practice

A dependent claim can't cover anything not covered by the claim from which it depends.

1. A compound of Formula A.
2. A **salt** of the compound of claim 1. **(invalid)**

Pfizer, Inc. v. Ranbaxy Laboratories Ltd., 457 F.3d 1284 (Fed. Cir. 2006)

1. A polypeptide comprising SEQ ID NO:1.
2. A **DNA** encoding the polypeptide of claim 1. **(invalid)**

But a method claim <u>can</u> validly depend from a composition claim

3. A method of treating cancer by administering the compound of claim 1 to a patient in need thereof.

Other important quirks of US practice

Multiply dependent claims are disadvantageous in the US—both *weaker* and *more expensive* than a corresponding set of singly-dependent claims.

- A claim that depends from 5 claims counts as 5 claims when determining excess claims fees, so there is no savings at all by drafting as multiply dependent instead of 5 separate singly dependent claims.
- An additional one-time charge (on top of the above multiplier) is applied if an application contains a multiply dependent claim.
- The separate singly-dependent claims are narrower and thus individually stronger than a multiply-dependent claim that attempts to cover the same scope in a single claim.

Other important quirks of US practice

Product-by-process claims are usually of little value in the US

- They are interpreted as *limited by the specified process* when assessing infringement, so will cover a competitor's product only if it was made by the specified process
- But they are interpreted as *not limited* by the specified process when assessing patentability/validity, so are anticipated or obvious in view of the same product made by any other process
- Their primary value is where the *only* way to describe the product is in terms of how it was prepared (e.g., an extract that is a complex and undefinable mixture)
- Far better to claim the product in terms of its structure, if possible

Other important quirks of US practice

Requirement to disclose "best mode" of practicing the invention

- Required by 35 USC 112 (along with enablement, written description, and definiteness)
- No longer a ground for invalidation, but still in the statute
- Possible ground for "inequitable conduct", which would mean the patent is unenforceable

Other important quirks of US practice

Mechanisms to speed up prosecution in the US

- Patent prosecution highway
- Petitions to make special
- Track 1
- Examiner interviews

Claiming Compositions of Matter

PART I

- Products of nature in general
- DNA
- Polypeptides
- Antigens/epitopes
- Antibodies

Products of nature in general

- Before 2013, we could claim “isolated” or “purified” products of nature

- Supreme Court *Myriad* decision changed the game

  Association for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013)

- Problem: distinguishing a product of nature without relying on “isolated” or “purified”

Products of nature in general

- How to do that depends on the context

- Discussed below (along with other patentability issues) for
  - DNA
  - Polypeptides
  - Antigens/epitopes
  - Antibodies
  - Small molecule drugs derived from nature
  - Extracts

DNA encoding a natural protein

- Prior to 2013, distinguished genomic DNA and naturally occurring mRNA with “isolated”

Claim 1

An isolated nucleic acid encoding Protein X.

- Now, “isolated” is insufficient for DNA
- No reason to think “isolated” works any better for mRNA
- Need a new strategy

DNA encoding a natural protein

- *Myriad* endorsed most cDNA claims

Claim 2

A cDNA comprising the nucleotide sequence of SEQ ID NO: 1.

[SEQ ID NO: 1 = a cDNA sequence]

- OK only if introns were removed in making the cDNA
- Can now omit “isolated” term
- Limited to <u>one</u> sequence. Strategies to broaden the scope?

DNA encoding a natural protein

- cDNA *plus degenerate variants*

Claim 3

DNA comprising the sequence of SEQ ID NO: 1 *[cDNA sequence]* or a degenerate variant thereof.

Claim 4

DNA comprising (a) cDNA encoding Protein X or (b) a degenerate variant of the cDNA.

Claim 5

DNA comprising an intronless sequence encoding Protein X.

DNA encoding a natural protein

- What if the cDNA is from an ***intronless*** gene?

Claim 6

DNA comprising a sequence encoding Protein X, wherein the sequence is operably linked to a heterologous expression control sequence.

Claim 7

A vector comprising a sequence encoding Protein X.

Claim 8

DNA comprising a sequence encoding a hybrid polypeptide comprising Protein X and a heterologous sequence.

Fragment of genomic DNA

- Specify presence of a label

Claim 9

A single stranded DNA oligonucleotide consisting of (a) a portion of SEQ ID NO: 5 *[a defined stretch of genomic or cDNA sequence]* or its complement at least 20 nucleotides in length, and (b) a detectable label.

Fragment of genomic DNA

- If the desired oligo is from cDNA and happens to span a splice site, it won't match genomic DNA:

Claim 10

A single stranded DNA comprising nucleotides 550-568 of SEQ ID NO: 6.

[SEQ ID NO: 6 is a cDNA sequence]

Fragment of genomic DNA

- If the desired oligo matches genomic DNA, something more is needed…

Claim 11

A single stranded DNA consisting of 18-30 nt of SEQ ID NO: 5 *[a stretch of genomic or cDNA sequence]* with a free hydroxyl at the 3' end of the DNA.

Claim 12

A solid substrate comprising a single-stranded DNA consisting of 18-30 nt of SEQ ID NO: 5.

Claim 13

A kit comprising a TAQ polymerase and a single stranded DNA consisting of 18-30 nt of SEQ ID NO: 5.

- *BUT PTO says a combination of naturally occurring substances is not patent-eligible*

DNA

Even if the subject-matter eligibility issue is solved (or doesn't exist in the first place because the claimed DNA is not identical to a naturally-occurring DNA), there are other claim-drafting issues to address.

§ 101	utility
§ 112, ¶ 1	written description
§ 112, ¶ 1	enablement
§ 102	anticipation
§ 103	obviousness

DNA

SCENARIO

- Novel cDNA (SEQ ID NO:1) encoding novel human protein (SEQ ID NO:2) that is a receptor for toenail growth factor (TNGF)

- Corresponding genomic DNA has introns, so cDNA (SEQ ID NO:1) is patent-eligible under *Myriad*

- Closest published prior art:
  - GenBank disclosure of *Drosophila* cDNA and protein with 30% sequence identity to SEQ ID NOs:1 and 2

DNA

Narrow end of spectrum:

Claim 14

A DNA, the nucleotide sequence of which consists of SEQ ID NO:1.

- no point in saying “isolated DNA” anymore
- “consists of” vs. “comprising”
- “DNA” vs. “nucleic acid” or “polynucleotide” (covering mRNA?)
- does not cover degenerate variants

Degenerate variants

Classic way to claim degenerate variants was in terms of *isolated* nt sequence *encoding a defined polypeptide sequence*; this is the type of claim invalidated in *Myriad* as reading on genomic DNA, so no longer works.

Instead, claim ***degenerate variants of cDNA*** directly

Claim 15

A DNA comprising the nucleotide sequence of SEQ ID NO:1 or a degenerate variant of SEQ ID NO:1.

- "DNA" vs. "nucleic acid/polynucleotide" (can't cover mRNA)

DNA homologs and mutants

- "A cDNA encoding a vertebrate TNGF receptor" fails WD requirement if only one example is disclosed

UC v. Lilly

- Other ways to cover homologs and mutants?

DNA homologs and mutants

Claim 16

A DNA comprising a sequence at least 95% identical to SEQ ID NO:1 and encoding a polypeptide that binds TNGF.

- Has to be written in terms of % identity to cDNA sequence (not polypeptide sequence), or will have a potential *Myriad* problem

DNA homologs and mutants

- algorithm and parameters
- choosing the %
- functional limitation
  - said to be necessary to satisfy utility and “how to use” enablement
  - something readily assayed
  - not “the activity of a TNGF receptor”

The Catch…

The Catch

If you include the functional limitation to satisfy what the PTO says is needed for utility/"how to use" enablement, your specification will then be newly scrutinized for WD and "how to make" enablement regarding functional variants.

- **consensus sequences**
  - *in prior art or in specification (e.g., alignment)*
  - *homologs with claimed function*
- **critical residues (may need to specify in claim)**
- **"representative number" of variants (e.g., deletion mutants, splice variants)**

DNA homologs and mutants

It might help to add to claim 16 a limitation specifying partial structure of the encoded polypeptide, e.g.:

…wherein the polypeptide comprises the sequence of SEQ ID NO:2 with 0-10 amino acid insertions, deletions, and/or substitutions.

…wherein the polypeptide comprises a sequence corresponding to residues 140-168 of SEQ ID NO:2.

…wherein the polypeptide comprises the extracellular domain of SEQ ID NO:2.

Other ways to cover the DNA

Claim 23

An expression vector comprising the DNA of claim 19 operably linked to an expression control sequence.

Claim 24

A cultured cell comprising the vector of claim 23.

Claim 25

A cultured cell comprising the DNA of claim 19 operably linked to an expression control sequence.

Claim 26

A method of making a polypeptide, the method comprising culturing the cell of claim 25 under conditions permitting expression of the DNA.

Other ways to cover the DNA

Routinely include the above types of claims when claiming cDNAs

- Same restriction group
- Not throwaway claims—can be very valuable
  - Can end up being the only valid claims if prior art inherently anticipates the DNA claims or if courts broadly apply the *Myriad* decision
  - "Method-of-making" claim can cover the polypeptide product under 35 USC §271(g)

Polypeptides

- Strategies to establish patent eligibility for a polypeptide that occurs in nature
  - Claiming “purified” probably won’t work
  - Claim *altered* aa sequence
  - Sufficiently different?
  - PTO: a *functional* difference makes the case stronger, but isn’t essential

Polypeptides

- *Hypothetical* natural product irrelevant
- BUT if later found in nature, claim presumably fails
- Claim covalently attached moieties (PEG, label, etc.)
- Claim in terms of “composition” to change the focus… (see next 5 claims)

Polypeptides

Claim 1: *pharmaceutical composition*

A sterile pharmaceutical composition suitable for intravenous administration, the composition comprising a polypeptide comprising SEQ ID NO:2 and a pharmaceutically acceptable diluent.

Claim 2: *formulation*

A composition comprising a polypeptide comprising SEQ ID NO:2, the composition being in solid form.

Claim 3: *specified 2nd ingredient*

A composition comprising (a) a polypeptide comprising SEQ ID NO:2 and (b) a calcium chelator.

Polypeptides

Claim 4: *lacking* a specified ingredient

A composition comprising a polypeptide comprising SEQ ID NO:2 and lacking any other human protein.

Claim 5: *lacking* a specified ingredient

A cell-free and serum-free composition comprising a polypeptide comprising SEQ ID NO:2.

Polypeptides

- Include a **process of manufacture** claim so you can rely on 35 USC § 271(g) to cover product itself
- Claim a cell transfected with a DNA encoding the polypeptide and expressing the polypeptide

Polypeptides

ISSUE:

Prior art disclosed several bands on SDS gel, one of which happens to have same MW as your polypeptide

- if your polypeptide was in that band, there is an **inherent anticipation** issue *even if prior art didn't point to the band*
- claim purified polypeptide ***free of SDS***
- claim purified polypeptide that possesses TNGF-binding activity
- claim purified polypeptide free of all other human proteins
- use same strategies as for distinguishing naturally occurring polypeptide

Antigens/epitopes

- Claiming a newly discovered **antigen or epitope** itself
  - Challenging if it is naturally occurring
  - See above strategies for claiming naturally occurring polypeptides
  - Specify that it is linked to an immunogenic molecule to enhance immune response
  - Specify that it is mixed with an adjuvant
  - Specify that it is bound to a solid substrate

Antigens/epitopes

- Broadly claiming **all Abs** that bind to the new antigen/epitope
  - Though disclosure of new antigen/epitope would **enable** generation of Abs, it is not sufficient **written description** support for broadly claiming all Abs

    Amgen v. Sanofi (Fed Cir 2018)
  - To claim all Abs that bind to it, need to disclose a "representative number of species" of Abs, or structural features common to all such Abs

Antigens/epitopes

- Could claim method of using the antigen/epitope to generate Abs
  - If claim is drafted with 271(g) infringement in mind, may be able to assert against one who imports, sells, or uses the Ab product

Antibodies

Patent-eligibility (product of nature?)

- If generated by hand of man, and natural counterpart is only hypothetical, should be OK
- Risk: *may later be found in nature*
- Include narrow claims to reduce that risk
  - Sequence-specific
  - Altered Fc region
  - Monoclonal
  - Humanized, chimeric, Fab, scFv
  - Covalently attached moieties (PEG etc.)

Antibodies

Written Description (WD) requirement

- Where antigen is novel and fully described, a broad antibody claim used to be easy to get, even if no antibodies had been generated.

Claim 1

An antibody that binds specifically to protein X.

- Recent Federal Circuit case changed that.

***Amgen v. Sanofi*, 872 F.3d 1367 (Fed Cir 2017)**

Antibodies

- Now, claiming an antibody solely by its function will fail the WD requirement unless the specification and/or prior art disclosed either:
  - structures of a “representative number of species” of the claimed antibody, or
  - a “structure/function correlation”
- The fact that the claimed antibodies would be easy to generate is not relevant to the WD requirement

Antibodies

- Where specification provides insufficient support for the broad claim, may be limited to claiming the antibody sequence(s) actually disclosed

- See next two claims…

Antibodies

Claim 2

An antibody comprising a heavy chain variable domain comprising SEQ ID NO: 2 and light chain variable domain comprising SEQ ID NO: 3.

Claim 3

An antibody comprising heavy chain CDRs1-3 respectively comprising SEQ ID NOs: 4-6 and light chain CDRs1-3 respectively comprising SEQ ID NOs: 7-9.

Antibodies

"Comprising" vs "consisting of"

- "Comprising" can be used to describe the antibody's sequence.
- Avoid "comprising" to describe the antigen's sequence.
- Instead use narrow description of antigen:

  "…specifically binds to Protein X" (where Protein X has a defined sequence)

  "…specifically binds to a polypeptide consisting of SEQ ID NO: 2"

  "An anti-Protein X antibody comprising SEQ ID NOs: …."

Antibodies

"**Specifically binds**" term is intended to ensure "binds" does not encompass non-specific stickiness

Antibodies

If you have sequence data from successive rounds of affinity maturation, could do consensus sequence claims:

Claim 4

An anti-IL-2 antibody that comprises VH CDR1-CDR3 and VL CDR1-CDR3, wherein the VH CDR1 comprises the sequence A-X-I-F-R-D-X-X-G-H (SEQ ID NO:14), wherein X is any amino acid, and the VH CDR2 comprises….

Antibodies

Deposit permits hybridoma-specific claims

Claim 5

An antibody produced by hybridoma ATCC H-1234.

Claim 6

An antibody identical to the antibody produced by hybridoma ATCC H-1234.

Claim 7

A cell of hybridoma ATCC H-1234.

Claiming Compositions of Matter

PART II

- Small molecules derived from nature
- Extracts
- Obviousness of pharmaceuticals
- Formulations that contain natural products
- Obviousness of formulations

Small Molecule Drugs Derived from Nature

- E.g., hormone, GABA, vitamin, lithium, NO gas
- Patent-eligibility strategies
  - Try “purified” and see what the courts say
  - Claim pharmaceutical composition
  - Claim composition containing additional ingredient
  - Claim dosage form (other than aqueous solution)
  - Claim method of manufacture and assert under 35 USC 271(g)

Small Molecule Drugs Derived from Nature

- Derivative of natural molecule (e.g., Taxol®)
  - Should be patent eligible if not identical to any natural molecule and “sufficiently different”
  - Unclear if, unlike situation with DNA, simply breaking 2 covalent bonds is sufficiently different
  - Adding moieties should help
  - Different function should help
  - See above strategies

Extracts

- Mixture extracted from natural source
  - Claim composition with defined percentages of various molecules (different from in nature)
  - Claim composition containing extract and specified other ingredient(s)
  - Claim dosage form
  - Claim method of manufacture and assert under 35 USC 271(g)

Obviousness of Pharmaceuticals

Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc., 520 F.3d 1358 (Fed. Cir. 2008)

Obviousness: *Ortho-McNeil*

- Compound (topiramate) originally prepared as intermediate in synthesis of new diabetes drugs
- Found to be useful for treating epilepsy
- Mylan said it would have been obvious to make it as an intermediate in synthesis of diabetes drug

Obviousness: *Ortho-McNeil*

- Fed Cir said **not obvious**
  - to select the starting compound
  - to follow the inventor's synthetic route
  - to stop at the intermediate and test for anticonvulsive activity
- Warned against hindsight reconstruction
- Pointed to objective indicia of nonobviousness

Obviousness of Pharmaceuticals

Eisai Co. Ltd. v. Dr. Reddy's Laboratories and Teva Pharmaceuticals USA, Inc., 533 F.3d 1353 (Fed. Cir. 2008)

Obviousness: *Eisai*

- Eisai's patent covering AcipHex® (rabeprazole) challenged by generics
- Issue: obviousness of modifying lead compound lansoprazole by replacing trifluoroethoxy with a methoxypropoxy
- Though structurally similar, no motivation, so **not obvious**
  - Trifluoroethoxy was responsible for lansoprazole's activity, so no reason to replace it

Obviousness: *Eisai*

- In the chemical arts, "*the potential solutions are less likely to be predictable*"

- Predictability is key to *prima facie* obviousness
  - for motivation to modify lead compound
  - for expectation of success

Obviousness: *Eisai*

- *Eisai* test
  - Begins with “reasoned identification of a [prior art] lead compound”—i.e., motivation to select the lead compound
  - Also need motivation to modify it in a particular way to achieve the claimed compound
    - This motivation requires expectation the new compound will have properties similar to the old: i.e., the substitution is predictable
  - Also need to show there was an expectation of success upon making modification (but already part of motivation prong?)

Obviousness of Pharmaceuticals

The Procter & Gamble Company v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989 (Fed. Cir. 2009)

Obviousness: *P&G*

- Risedronate (3-pyr EHDP) **not obvious** in view of prior art 2-pyr EHDP

- Applied the *Eisai* test
  - Since bisphosphonates have unpredictable properties, no motivation to modify 2-pyr EHDP and no expectation of success
  - Also found surprising results
  - Declined to address whether there was a reason to select 2-pyr EHDP as “lead compound”

Obviousness of Pharmaceuticals

Daiichi Sankyo Company, Ltd., v. Matrix Laboratories, Ltd., Mylan Inc. et al., 619 F.3d 1346 (Fed. Cir. 2010)

Obviousness: *Daiichi*

- Olmesarta medoxomil (Benicar®, an angiotensin receptor blocker) **not obvious**
  - Not obvious to select the structurally closest prior art compound as the lead compound
    - Art *taught away* (better to have hydrophobic moiety at the 4' position)
    - Other prior art compounds were more potent and better studied, so more logical to select
  - Modifying the 4' and 5' positions of the lead would require hindsight

Obviousness of Pharmaceuticals

Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc. et al., 678 F.3d 1280 (Fed. Cir. 2012)

Obviousness: *Otsuka*

- Aripiprazole (Abilify®, an antipsychotic) **not obvious**
  - As in *Daiichi*, no motivation to select the structurally closest prior art compound as the lead compound
    - Two standard classes of antipsychotics on the market, so would have selected a lead compound within one of *those* classes, not one similar to aripiprazole
    - Defendant's lead compound *"a poster child for impermissible hindsight reasoning"*
    - *"As KSR made clear, predictability is a vital consideration in the obviousness analysis."*

Obviousness: *Otsuka*

- Defendant argued that, since inventor's development of aripiprazole "took only a few months," it would have been obvious to do.

- Court: *"The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art."*

Obviousness of Pharmaceuticals

Sanofi-Aventis v. Glenmark Pharmaceuticals, 748 F.3d 1354 (Fed. Cir. 2014)

Obviousness: *Sanofi*

- Tarka® [combo of 2 known drugs, trandolapril (ACE inhibitor) + verapamil HCl (calcium antagonist)]

- Claim: trandolapril + any calcium antagonist in amount effective for treating hypertension **not obvious**

Obviousness: *Sanofi*

- Glenmark argued:
  - Obvious to try every combination of every known ACE inhibitor and calcium antagonist
  - Because inventors tried trandolapril, must have been obvious to try that one
  - Because obvious to try, unexpected results are irrelevant

Obviousness: *Sanofi*

- Fed Cir disagreed
  - Not “obvious to try” when “prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful”
  - Prior art favored single-ring ACE inhibitors, not double-ring like trandolapril
  - Fact that inventors tried double-ringed inhibitors does not mean it was obvious to try them
  - Unexpected properties are relevant

Obviousness of Pharmaceuticals

Bristol-Myers Squibb v. Teva, 752 F.3d 967 (Fed. Cir. 2017)

Obviousness: *BMS*

- Entecavir (Baraclude®, an HBV antiviral nucleoside derivative) **obvious**

- Court agreed with Teva that it was obvious to select prior art 2'-CDG compound as "lead"

  - 2'-CDG known to be effective against herpes virus and HBV

  - Prior art as of filing date identified 2'-CDG as "exciting lead compound" with low toxicity

  - Its toxicity was discovered only *after* filing date, so not pertinent to obviousness analysis

Obviousness: *BMS*

- Obvious to alter 2'-CDG's carbocyclic ring to end up with entecavir
  - Other labs were altering that ring to make antivirals
  - Methylene at 2' or 5' position is obvious choice to try
  - Prior art put methylene at 5' position of similar compound and found increased antiviral potency—so expectation of success
- Unexpected results insufficient to overcome *prima facie* obviousness

Formulations: *Natural Products*

- ***Problem***: Drug A is a product of nature (isolated from a plant), so PTO says not patent-eligible.

How to get a composition claim for A?

Formulations: *Natural Products*

- Claim composition of purified A, if structurally or functionally different from A in nature
- Claim a crystalline or other solid form of A
- Claim composition comprising **both A and second ingredient B**

See 2 examples of A + B…

Formulations: *Natural Products*

Example 1:

- B is an artificial anti-oxidant, a compound with no natural counterpart
- So A+B combination does not occur in nature
- Per PTO Guidelines, can argue either
  - A+B is “markedly different” from A alone, or
  - Claim limited to A+B clearly does not attempt to “tie up” all uses of A

Formulations: *Natural Products*

Example 2:

- B is HSA, a naturally-occurring human protein

- A+B *combo* is "markedly different" from anything in nature
  - Different structure: A and B never occur together
  - Different properties of A: A aggregates less when in the presence of B (just a "natural phenomenon"?)
  - *Funk Brothers* Supreme Court case is contrary law

Formulations: *Obviousness*

- Hard to establish nonobviousness of formulation comprising a known drug
- Usually all ingredients are standard and concentrations are within known ranges

Formulations: *Obviousness*

- Argue:
  - Pick-and-choose from prior art lists of excipients is not the standard
  - Need actual reason in the art—not something made up by examiner
  - Newly discovered problem can be the invention
  - Teaching-away
  - Objective indicia such as surprising results, long-felt need, commercial success

Formulations: *Obviousness*

Leo Pharmaceutical Products v. Rea,
726 F.3d 1346 (Fed. Cir. 2013)

- Claimed **storage-stable** composition of 2 known drugs in particular solvent
- BPAI: obvious to pick and choose
- Fed Cir reversed: **not obvious**
  - BPAI made up a hypothetical motivation not found in the art
  - Prior art did not recognize the problem that was the real motivation
  - Possible approaches to solving the problem were not known or finite
  - Solution was not predictable

Formulations: *Obviousness*

InSite Vision v. Sandoz,
783 F.3d 853 (Fed. Cir. 2015)

- Sandoz argued obvious to substitute azithromycin for erythromycin in an ophthalmic formulation

- Court: **not obvious** because art teaches that azithromyicin is
  - Less potent than other classes
  - High MW and charged, so cannot penetrate ocular tissue
  - Poorly water-soluble

Formulations: *Obviousness*

Senju v. Lupin,
780 F.3d 1337 (Fed. Cir. 2015)

- Ophthalmic formulation of gatifloxacin and 0.01 w/v% EDTA is **obvious** because art teaches:
  - other quinolone compositions use 0.01 w/v% EDTA
  - gatifloxacin is an improved quinolone
  - evidence of 27-40% increase in corneal permeability with 0.01 w/v% EDTA was product of routine optimization and not unexpected

Formulations: *Obviousness*

Momenta v. BMS,
IPR2015-01537 (PTAB 2016)

- Aqueous solution of a known protein was **not obvious**
  - Prior art said it is difficult to make a stable solution of proteins and unpredictable whether it is possible with any given protein

Formulations: *Obviousness*

- **Not obvious:**
  - ***In re Omeprazole Patent Litigation***, 536 F.3d 1361 (Fed. Cir. 2008)
  - ***Unigene Labs v. Apotex***, 655 F.3d 1352 (Fed. Cir. 2011)
  - ***In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation***, 676 F.3d 1063 (Fed. Cir. 2012)
  - ***Alcon v. Apotex***, 687 F.3d 1362 (Fed. Cir. 2012)
  - ***Leo Pharmaceutical Products v. Rea***, 726 F.3d 1346 (Fed. Cir. 2013)
  - ***InSite Vision v. Sandoz***, 783 F.3d 853 (Fed. Cir. 2015)
  - ***Cumberland Pharms. v. Mylan***, 846 F.3d 1213 (Fed. Cir. 2017)
  - ***Momenta v. BMS***, IPR2015-01537 (PTAB 2016)

- **Obvious:**
  - ***Alza v. Mylan***, 464 F.3d 1286 (Fed. Cir. 2006)
  - ***McNeil v. Perrigo***, 443 F. Supp.2d 492 (S.D.N.Y. 2007), *aff'd* by Fed. Cir. in 2008 without published decision
  - ***Bayer Schering v. Barr***, 575 F.3d 1341 (Fed. Cir. 2009)
  - ***Tyco v. Mutual***, 642 F.3d 1370 (Fed. Cir. 2011)
  - ***Galderma Laboratories v. Tolmar***, 737 F.3d 731 (Fed. Cir. 2013)
  - ***Senju v. Lupin***, 780 F.3d 1337 (Fed. Cir. 2015)
  - ***Novartis v. Torrent Pharms.***, 853 F.3d 1316 (Fed. Cir. 2017)
  - ***Bayer Pharma v. Watson***, 874 F.3d 1316 (Fed. Cir. 2017)

Claiming Processes and Methods of Treatment

- **Claiming manufacturing processes**
- **Using process claims to cover the product**
- **Claiming methods of treatment**
- **Patenting the label**

Manufacturing Processes: *Patent-eligibility*

- Generally not an issue for this category of claims
- Claim should not encompass a naturally occurring process, e.g.:
  - **Bad**: A method of making albumin comprising expressing a nucleic acid encoding albumin.
  - **Good**: A method of making albumin comprising expressing a **cDNA** encoding albumin.
  - **Good**: An ***in vitro*** method of making albumin comprising **culturing a cell** expressing a nucleic acid encoding albumin.

Using US Process Claims to Cover Products

- **35 USC 271(g)** is part of the US statute defining what constitutes infringement

- Turns a **process of making** claim into a claim that essentially covers a product, *even if the product itself is unpatentable*

Using US Process Claims to Cover Products

- This gives the savvy patentee:
  - A perfectly legal “end-run” around the product-of-nature problem for a patent-ineligible product
  - A way to extend patent life for a known product
  - A way to cover the valuable end product, even where the invention pertains only to an intermediate
  - (But only if the process is patentable and is what competitors would actually use)

Using US Process Claims to Cover Products

The 271(g) statute:

Whoever without authority **imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer**, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after –

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product

Using US Process Claims to Cover Products

- If a product was made by the claimed process anywhere in the world, the process claim can be asserted against anyone who:
  - **Imports** the product into the US
  - **Offers to sell or sells** the product in the US
  - **Uses** the product in the US

Using US Process Claims to Cover Products

- Limits on what products will qualify
  - Must be a manufactured, physical article

    Bayer v. Housey, 340 F. 3d 1367 (Fed. Cir. 2003)

    Momenta v. Teva, 809 F. 3d 610 (Fed. Cir. 2015)
  - Cannot have been "materially changed" by subsequent processes

    Lilly v. American Cyanamid, 82 F. 3d 1568 (Fed. Cir. 1996)

    Amgen v. Hoffmann-LaRoche, 580 F. 3d 1340 (Fed. Cir. 2009)
  - Cannot be a "trivial and nonessential component of another product"

Using US Process Claims to Cover Products

- How to draft a process claim for 271(g)
  - Claimed **process** must be patentable, even if resulting **product** is not itself patentable
  - Refer in the preamble to “manufacturing” or “making” the end product that will be imported/sold
  - Be sure the immediate product of the last step of the claimed method is exactly what will be imported/sold in the US, with no further “material changes” needed

Using US Process Claims to Cover Products

- How to draft a process claim for 271(g)
  - If the invention is a process of preparing an **intermediate**:
    - The preamble should refer to “making” or “manufacturing” the ultimate composition to be imported/sold
    - The claimed process should include not only the steps of preparing the intermediate, but also any steps that will be needed to end up with the ultimate composition.
  - Not intuitive to add steps not needed for patentability, but may be needed to qualify for 271(g)

Using US Process Claims to Cover Products

- How to draft a process claim for 271(g)
  - If the invention is essentially a **quality control** technique (such as in *Momenta*):
    - Refer to it as a process of manufacturing the product
    - Include a step or steps that broadly reflect how the product is actually made, followed by the steps of the QC technique, and ending with the ultimate product.
  - Again, not intuitive to add those extra steps if not needed for patentability

Methods of Treatment

US law generally permits claiming methods of treatment directly (but not EP-style “use in treating”)

Claim 1

A method of treatment comprising administering compound X to a subject who has cancer.

Methods of Treatment

- Patent-eligibility during prosecution
  - Not usually an issue
  - Can be an issue if the claim actually *recites* a "natural law," e.g., a mechanism of action

1. A method of treating cancer, the method comprising administering Drug D to a subject in need of treatment for cancer, **wherein the Drug D antagonizes Receptor R in the subject**.

2. A method of **antagonizing Receptor R**, the method comprising administering to a subject an amount of Drug D **sufficient to antagonize Receptor R** in the subject.

3. A method of **antagonizing Receptor R**, the method comprising contacting a Receptor R-expressing cell with Drug D.

Methods of Treatment

- Patent-eligibility in litigation
  - May hinge on whether courts decide that a method of treatment is just an attempt to patent a "natural law"
  - Supreme Court has implied that ***methods of using drugs*** are patent-eligible:

"***Unlike**, say, a typical patent on a new drug **or a new way of using an existing drug**, the [Prometheus] patent claims do not confine their reach to particular applications of those laws."* *(Mayo v. Prometheus,* 132 S. Ct. 1289, 1302 (2012))

Methods of Treatment

- Inherent anticipation
  - Issue crops up where drug is known in the art for other purposes
  - Pay attention to how drug was used in the art
    - Overlapping patient populations?
    - Did claimed new effect *inherently* happen in prior patients?

Methods of Treatment

- Ways to fix the inherent anticipation problem:
  - Add language such as:
    - "**identifying** a patient in need of treatment for…"
    - "administering the compound to a patient **in recognized need for** said treatment…"

Methods of Treatment

- Or add a step:
  - Pre-treatment
    - diagnosing or measuring something
    - identifying a patient as being in a limited patient population
  - During treatment
    - co-treatment with a second agent
    - novel dosage form or regimen
    - monitoring effect and adjusting dosage appropriately
  - Post-treatment
    - noticing or monitoring for an effect
    - following up with a different treatment

Methods of Treatment

- Or add *negative* limitation:
  - Excluding prior patient population
  - Excluding dosage used in prior art
  - Excluding particular formulation or route of administration used in prior art

Methods of Treatment

- Enablement issues
  - Claims are presumed to be enabled
  - Assertions in the specification are presumed to be true
  - Burden is on the examiner to provide evidence the claimed methods would not work
  - Generic skepticism not enough (e.g., gene therapy “never works”)

Methods of Treatment

- When examiner has met that burden, then burden shifts to applicant to rebut with evidence supporting enablement
  - *In vivo / in vitro* experiments

    In re Brana, 51 F.3d 1560 (Fed Cir 1995)
  - Homology to compounds with known efficacy
  - Enablement evidence can be generated post-filing, but should be of record before patent issues

    In re '318 Patent Infringement Litigation, 583 F.3d 1317 (Fed Cir 2009)

    But see, *Eli Lilly v. Actavis,* 2011 WL 3235718 (Fed Cir 2011) (non precedential)

Methods of Treatment

- *Scope of enablement* issues
  - Where only one or a few embodiments are shown to work, and others are unpredictable
    - treatment of any type of cancer
    - compound broadly defined
  - Supplement record with evidence, new or from prior art

Methods of Treatment

- Written description issues
  - Where drug or treatment is described in claim primarily in functional terms
  - Need to show either **representative number of species** or **structure/function correlation** was disclosed in specification or the art

University of Rochester v. Searle, 358 F.3d 916 (Fed. Cir. 2004)

Ariad v. Lilly, 560 F.3d 1366 (*en banc*) (Fed. Cir. 2009)

Methods of Treatment

- Divided infringement issues
  - To have direct or induced infringement, there must be a **direct infringer**
  - Where a claim has multiple steps carried out by different parties, there may be **no direct infringer**
    - Answer depends on many factors
  - Situations where this can arise:
    - Doctor and diagnostic lab
    - Two different doctors
    - Doctor and patient

Methods of Treatment

- Important recent divided infringement case:

  Eli Lilly v. Teva Pharms., 845 F.3d 1357 (Fed. Cir. 2017)

  - Claim: Method of administering 3 drugs, where **patient** self-administers 1st drug and **doctor** administers the other 2

  - Court said the doctor is a direct infringer

    - Doctor requires patient to administer 1st drug as a precondition to treatment with other 2, so doctor is direct infringer, with the patient acting under her control

    - Teva's label says to administer all 3 drugs, so Teva **induced** the direct infringement

Patenting the Label

- New patentable invention relating to a new or altered use of a drug already on the market—often based on negative news
- Label amended to recite the new invention
- Ideally, new patent is Orange Book (OB) listed
- New patent expires later, so extends period of exclusivity--***unless generic can carve it out--***

Patenting the Label

- What *doesn't* work:
  - Patent on second indication that can be carved out ("skinny" label)
  - Patent relating to safety or efficacy *of a carved-out indication* (and not of the indication remaining on the skinny label)
  - Patent claiming a method that can be omitted on generic's label without affecting safety/efficacy of the drug
  - Patent claiming a method that is infringed only when conducting activities that are safe-harbored under 35 USC 271(e)(1)

Patenting the Label

- What *does* work:
  - Patent on newly discovered **safety** or **efficacy** information that relates to the drug itself and/or to all approved indications
  - Patent on process specified on the label and used **post-approval** during commercial production of the drug, even if the method generates information that is routinely reported to FDA post-approval

Momenta v. Teva, 809 F.3d 610 (Fed. Cir. 2015)

Patenting the Label: Example #1 (safety)

- Drug X is approved for treatment of stomach cancer
- **New discovery:** Drug X increases the risk of stroke in patients who have blood marker ABC, but not in patients lacking ABC
- Warning added to label applies to all indications, so can't be carved out

Patenting the Label: Example #1 (safety)

Claim:

A method of treatment comprising

identifying a patient as having stomach cancer;

determining that the patient does not have blood marker ABC; and

treating the patient with Drug X.

Patenting the Label: Example #2 (efficacy)

- Drug Y is marketed for treatment of several autoimmune diseases.
- **New discovery**: Drug Y is significantly less efficacious if patient currently has influenza
- FDA says a contraindication re influenza must be added to the label
- Contraindication applies to all label indications, so can't be carved out

Patenting the Label: Example #2 (efficacy)

Claim:

A method of treatment comprising

identifying a patient as having an autoimmune condition that is treatable with Drug Y;

determining that the patient has an influenza infection;

monitoring the patient to determine when the influenza infection has ended;

withholding treatment with Drug Y until the influenza infection has ended, and then administering Drug Y to the patient.

Claiming Diagnostics & Personalized Medicine

- **Personalized medicine inventions**
- **Companion diagnostics**

Personalized Medicine

- Treatment customized for individual patient
- Usually based on biomarkers found to predict efficacy or safety issues
  - Mutations
  - Gene expression levels
  - Blood biochemistry

Personalized Medicine

- Claim-drafting challenges:
  - Limiting to patent-eligible subject matter (“law of nature”)
  - Avoiding inherent anticipation
  - Avoiding reliance on content of communicated information for novelty/nonobviousness
  - Ensuring that all steps would be carried out by a single entity or, if a combination of entities, the combination qualifies as a legally sufficient direct infringer
  - Ensuring enablement/written description for broad claims

Personalized Medicine

SCENARIO #1

Known: open reading frame of gene X (SEQ ID NO:1)

Novel: **G → A** SNP (Single Nucleotide Polymorphism) at position 245, associated with adverse response to Drug D, a Protease P inhibitor

Personalized Medicine

Claim 1

A method comprising assaying a sample of nucleic acid from a human subject to determine the identity of the nucleotide at position 245 of the open reading frame of gene X in the sample.

- broad claim covers any technique
- no mention of Drug D or identity of nucleotide or any diagnostic conclusion

*****PROBLEM WITH THIS CLAIM?*****

INHERENTLY ANTICIPATED

by prior art sequencing of gene X cDNA or genomic DNA

Personalized Medicine

- Would not help to say:

“determining whether the nucleotide is a G or an A”

Personalized Medicine

- Limit who “subject” can be: e.g.,

  “**a subject in need of a Protease P inhibitor**”

  - If SNP turns out to have broader applicability, this could be unfortunately narrow

Personalized Medicine

- Limit to presence of SNP: e.g.,

  "**determining that the nucleotide at position 245 of the ORF of gene X in the sample is an A.**"

  - Could mean that damages are restricted to rare case where SNP is found to be present in the subject

Personalized Medicine

- Or add further method step (as in claims 2-4) to avoid inherent anticipation

*(Claims 2-4 are intended to address the **inherent anticipation** issue, ignoring for now all other patentability issues)*

Personalized Medicine

Claim 2

A method for evaluating whether to treat a human subject with Drug D, the method comprising:

(a) assaying a sample of nucleic acid from the subject to determine the identity of the nucleotide at position 245 of the open reading frame of gene X in the sample; and

(b) determining that the subject should not undergo therapy with Drug D if the nucleotide is A, and that the subject may undergo therapy with Drug D if the nucleotide is not A.

- Specific to **Drug D** **and the determination to be made**

Personalized Medicine

Claim 3

A method of treatment comprising:

(a) assaying a sample of nucleic acid from a subject to determine the identity of the nucleotide at position 245 of the open reading frame of gene X in the sample; and

(b) administering a protease P inhibitor to the subject if the nucleotide present at position 245 is associated with tolerance to the protease P inhibitor.

- Method of treatment rather than diagnosis *per se*
- Problem: when "**if**" clause of step (b) does not apply, claim is inherently anticipated. Claim 4 is a narrower fix.

Personalized Medicine

Claim 4

A method of treatment comprising:

(a) assaying a sample of nucleic acid from a subject to determine the identity of the nucleotide at position 245 of the open reading frame of gene X in the sample, thereby determining that the nucleotide is not an A; and

(b) administering a protease P inhibitor to the subject.

- Specifies "**is not an A**" and "**administering**"

Personalized Medicine

SCENARIO #2

Known: Expression levels of Genes A, B, C, D, E in blood cells can vary in different people, including cancer patients, for unknown reasons

Novel: A particular pattern of expression of Genes A-E in blood cells of a cancer patient ("expression pattern X") predicts responsiveness to immunotherapy.

Personalized Medicine

Claim 5

A method comprising:

determining that a cancer patient's blood sample expresses Genes A-E according to expression pattern X; and

determining that the patient's cancer is likely to respond to immunotherapy.

Personalized Medicine

- Patent-eligible subject matter issues:
  - All steps are “mental” steps
  - No “transformation”
    - changing first “determining” step to “assaying” makes it a transformation
  - An attempt to “preempt” all applications of a “natural law”? (*Mayo v. Prometheus*)
    - Even “assaying” (claim 6) may not help if assay is “conventional”

Personalized Medicine

Claim 6

A method comprising:

assaying a blood sample from a cancer patient to determine whether the sample expresses Genes A-E according to expression pattern X,

wherein expressing Genes A-E according to expression pattern X indicates that the patient's cancer will be responsive to immunotherapy.

Personalized Medicine

- Anticipation/obviousness issues ("wherein" clause describes inherent fact)
- Patent-eligible subject matter issue (claim 6 modeled on the doomed Prometheus claim in *Mayo*)
  - "Wherein" clause merely describes a natural law
  - Claim arguably preempts all applications of the natural law
  - "Assaying" step, though transformative, may not be enough if "conventional"

Personalized Medicine

Claim 7

A method comprising:

receiving from a medical caregiver a blood sample of a cancer patient;

assaying the sample to determine whether the sample expresses Genes A-E according to expression pattern X; and

informing the medical caregiver that the patient's cancer is likely to be responsive to immunotherapy.

Personalized Medicine

- Content of "informing" step ignored when determining anticipation/obviousness, unless informing step "interrelates" with the other steps

  King Pharmaceuticals v. Eon Labs, 616 F.3d 1267 (Fed. Cir. 2010)

  In re Kao, 639 F.3d 1057 (Fed. Cir. 2011)

- Patent-eligible subject matter issue (*Mayo*)
  - Preempts all applications of a "natural law"?
  - Are receiving + assaying + informing all "conventional" steps, so not enough?
  - Key is that the steps *in combination* are not conventional

Personalized Medicine

Claim 8

A method comprising:

determining that a blood sample from a cancer patient expresses Genes A-E according to expression pattern X;

based on that determination, determining that the patient's cancer is likely to respond to immunotherapy; and

administering immunotherapy to the patient.

Personalized Medicine

- Patent-eligible subject matter issue (*Mayo*)
  - Although first and third steps *individually* are too "conventional" to help, the combination of the two is not "conventional"
  - Might help to specify a *particular* immunotherapy (e.g., Keytruda®) so as not to preempt all applications of the natural law
    - This avoids "preemption" only if the "natural law" applies broadly to all immunotherapies

Personalized Medicine

Where the invention is essentially a law of nature rather than a new type of assay,

the task is devising a claim that…

Personalized Medicine

- Contains at least one non-mental step
- Does not rely on content of “informing” step for novelty & nonobviousness
- Does not preempt all applications of the “natural law”
  - Include a treatment step at the end
- Covers a single direct infringer (e.g., the lab ***or*** the Dr.), or, if joint infringers, they together constitute a legally sufficient “direct infringer”

Companion Diagnostics

- Related to personalized medicine
- “Companion” means associated with use of a particular drug to treat a particular condition
- A diagnostic test is a “companion diagnostic” if a drug is approved for use solely in patients who have a particular biomarker that is detected by the diagnostic test

Companion Diagnostics

- First co-development of a drug and CD was in 1998 – Herceptin® and HercepTest®
- As of 2018, FDA has approved/cleared 43 CDs; some drugs approved with multiple CDs; some CDs approved for multiple drugs
- FDA database for CDs: **http://www.fda.gov/companiondiagnostics**

Claiming Companion Diagnostic Inventions

- Composition of Matter Claims
  - Kits
  - Systems
- Method Claims
  - Diagnosing/Assaying
  - Selecting a Treatment
  - Diagnosing and Then Treating
  - Treating an Already-Diagnosed Patient

Kits

- Kit claims

A **kit** comprising
diagnostic agent X, and
instructions for use of agent X in determining whether a subject should be treated with drug Y.

A **kit** comprising
drug Y, and
instructions for use of drug Y to treat patients determined to have ABC mutation.

Kits

- Issue
  - Content of instructions is ignored when assessing anticipation or obviousness, unless content "interrelates" with the "substrate"

    In re Ngai, 367 F.3d 1336 (Fed Cir 2004)

- Fixes
  - If diagnostic agent X would be packaged with drug Y, include both in the claimed kit
  - Try adding purpose to preamble and argue instructions are necessary to achieve the purpose

    In re Gulack, 703 F.2d 1381 (Fed Cir 1983)
    Pitney Bowes v. Hewlett-Packard, 182 F.3d 1298 (Fed Cir 1999)
    Vizio v. ITC, 605 F.3d 1330 (Fed Cir 2010)
  - Rely instead on **method** claims

Systems

- System claim

A **system** for generating a report identifying a therapeutic agent for an individual with lung cancer, the system comprising

a device configured to assay a plurality of targets comprising A, B, C, and D;

a computer database comprising…

a computer-readable program code comprising instructions to identify a therapeutic agent…

a computer-readable program code comprising instructions to generate a report…

Systems

- Issue: § 101
  - Instructions = “abstract idea”
  - Assays are “routine data-gathering”
- Fix
  - Applicant submitted declaration saying the system assists in selecting treatment for lung cancer patients, so “provides an improvement in another technology or technical field” (medical field)

Method of Diagnosing/Assaying

- Diagnostic method claim

  A **diagnostic method** comprising **determining** that a tumor sample from a patient harbors an ABC mutation,
  wherein the presence of an ABC mutation in the tumor indicates that the patient's tumor will respond to Drug Y.

- Issues
  - **101:** the sole step ("determining") can be done mentally, and the "wherein" clause describes a law of nature.
  - **102:** "wherein" clause describes inherent fact, so claim is anticipated if it was known in the art that the mutation occurs in tumors, *even though link to Drug Y response was not known*.

Method of Diagnosing/Assaying

- Fix:
  - Add a **treatment** step to solve both 101 and 102.
  - *Not* helpful, at least re 102: adding a step of **communicating** the results or diagnosis to someone, as that falls under the "printed matter" doctrine, so is ignored

King Pharm. v. Eon Labs, 616 F.3d 1267 (Fed Cir 2010)
AstraZeneca v. Apotex, 633 F.3d 1042 (Fed Cir 2010)
Praxair v. Mallinckrodt, 890 F.3d 1024 (Fed Cir 2018)

Method of Diagnosing/Assaying

- Assaying claim

  A method comprising **assaying** a biological sample from a subject to determine if the subject has mutation ABC.

- Issues:
  - **101**: No correlations or mental steps recited, so no abstract idea or law of nature, so no patent eligibility issue.
  - **101**: Similar to a (patentable) example in May 2016 USPTO Guidelines (http://www.uspto.gov/patents/law/exam/interim_guidance_subject_matter_eligibility.jsp ("A Method of Detecting JUL-1 in a patient…")
  - **101**: Per *Mayo v. Prometheus Labs*, 132 S. Ct. 1289, 1297 (2012), steps of administering a drug and determining resultant level of 6-thioguanine in the patient "are not themselves natural laws."
  - **102/103**: Of course, this claim satisfies 102/103 only if mutation is not known in the art. If mutation was known, add another limitation (reagent; identity of subject; type of sample).

Method of Selecting a Treatment

- “Selecting a treatment” claim

A method of **selecting a treatment** for a subject having a tumor, the method comprising

a) determining expression levels of genes A, B, and C in a cell from the tumor;
b) assigning an index to the tumor based on the expression levels; and
c) selecting a treatment for the subject based on the index.

Method of Selecting a Treatment

- Issues
  - **101**: All steps can be carried out mentally (adding details about what index correlates with what treatment won't help)
  - **Divided infringement**: would same party do all 3 steps?

- Fixes for **101** issues:
  - Add a final step requiring **administering the selected treatment** (but then face divided infringement issue), or
  - Add a lot more detail about the index and the selecting step (see claims 26 and 2 of US 9,846,762), or
  - Specify use of a computer

Method of Diagnosing and Then Treating

- Diagnosing + treating claim

  (based on (patentable) example in May 2016 USPTO Guidelines)

  A method of diagnosing and treating julitis, the method comprising
  a) obtaining a plasma sample from a patient;
  b) detecting whether JUL-1 is present in the sample;
  c) diagnosing the patient with julitis when the presence of JUL-1 is detected; and
  d) administering an effective amount of anti-TNF antibodies to the diagnosed patient.

Method of Diagnosing and Then Treating

- Issues
  - **101**: per PTO, that claim is OK – though (c) is law of nature and other steps are routine, combo is not routine
  - **102**: step (b) says "whether" and step (c) says "when," so claim does not require JUL-1 to be detected, so implicitly covers situations where it is not detected and no treatment specified. So, if prior art ever assayed for JUL-1 and did not detect it in a given sample, the claim is anticipated.
  - **Divided Infringement**: Who "detects"? Who "administers"?
  - "Anti-TNF antibodies" (plural)

Method of Diagnosing and Then Treating

Better wording of the PTO's claim:

A method of treating julitis, the method comprising

a) determining that JUL-1 is present in a plasma sample from a patient; and
b) administering to the patient an amount of an anti-TNF antibody effective to treat julitis in the patient.

Method of Diagnosing and Then Treating

- Diagnosing + treating claim
  (based on claim 1 of US 8,586,610, which the Fed Cir upheld in *Vanda v. West-Ward,* 887 F.3d 1117 (Fed Cir 2018))

A method for treating a schizophrenic patient, the method comprising

a) determining whether the patient is a CYP2D6 poor metabolizer by obtaining or having obtained a biological sample from the patient, and performing or having performed a genotyping assay on the sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and

b) if the patient has a CYP2D6 poor metabolizer genotype, administering iloperidone to the patient in an amount of 12 mg/day or less, and

c) if the patient does not have a CYP2D6 poor metabolizer genotype, administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day,

wherein the risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the administration of 12 mg/day or less than it would be if iloperidone were administered in an amount greater than 12 mg/day, up to 24 mg/day.

Method of Diagnosing and Then Treating

- Issue: 101
  - Fed Cir said the claim is OK. Claim is "directed to" a method of treatment, not any underlying correlation (though it *recites* a correlation)
  - Unlike the claim in *Mayo v. Prometheus*, it is limited to particular treatment dictated by the assay results

Method of Diagnosing and Treating (Where Positive Diagnosis Means "Don't Treat")

- Diagnosing + treating claim

  (styled after claim 1 of US 8,586,610, assigned to Mallinckrodt)

A method of treatment comprising

a) identifying a **plurality** of patients who have condition X and so are candidates for treatment with Drug Y;
b) determining that a **first patient of the plurality has mutation A** in or one both alleles of gene B;
c) determining that **a second patient of the plurality does not have mutation in A** in either allele of gene B;
d) treating the second patient with Drug Y; and
e) excluding the first patient from treatment with Drug Y.

Method of Diagnosing and Treating (Where Positive Diagnosis Means "Don't Treat")

- Issues
  - This "plurality of patients" claim is a way to deal with a difficult-to-claim situation: presence of biomarker means DO NOT TREAT, and for various reasons detection of absence of the biomarker cannot be claimed. Ensures there is a positive treatment step that follows from the determinations.
  - **101**: Though PTO allowed the claims of US 8,586,610, Judge Sleet (Dist.Ct. Del) invalidated them under 101 (now on appeal)

Method of Treating an Already-Diagnosed Patient

- Treating diagnosed patient claim

  (hypothetical, derived from *Vanda* claim)

  A method of treatment comprising

  identifying a patient as suffering from schizophrenia and having a CYP2D6 poor metabolizer genotype; and

  administering iloperidone to the patient in an amount of 12 mg/day or less.

Method of Treating an Already-Diagnosed Patient

- Issues:
  - Infringed regardless of how the genotype is determined
  - Infringed even if patient's CYP2D6 genotype was first determined years earlier by unknown party, and the doctor now merely reads the recorded results
  - **101**: Omits the *Mayo*-like "wherein" clause that describes a law of nature
  - **Divided infringement**: Eliminates obtaining sample step and assay step of the *Vanda* claim, so clearly a single direct infringer

Method of Treating an Already-Diagnosed Patient

- Treating diagnosed patient claim
  (based on an allowed claim of USSN 15/028,515)

  A method of treatment comprising
  (i) identifying a subject comprising leukemic cells having a mutation in receptor X, wherein the mutation results in hyperactivation of receptor X signal transduction; and
  (ii) administering a therapeutically effective amount of Drug A to the subject.

- Issue: **101**
  - Administration step (ii) is sufficient to add "something more" to the "law of nature" in (i)

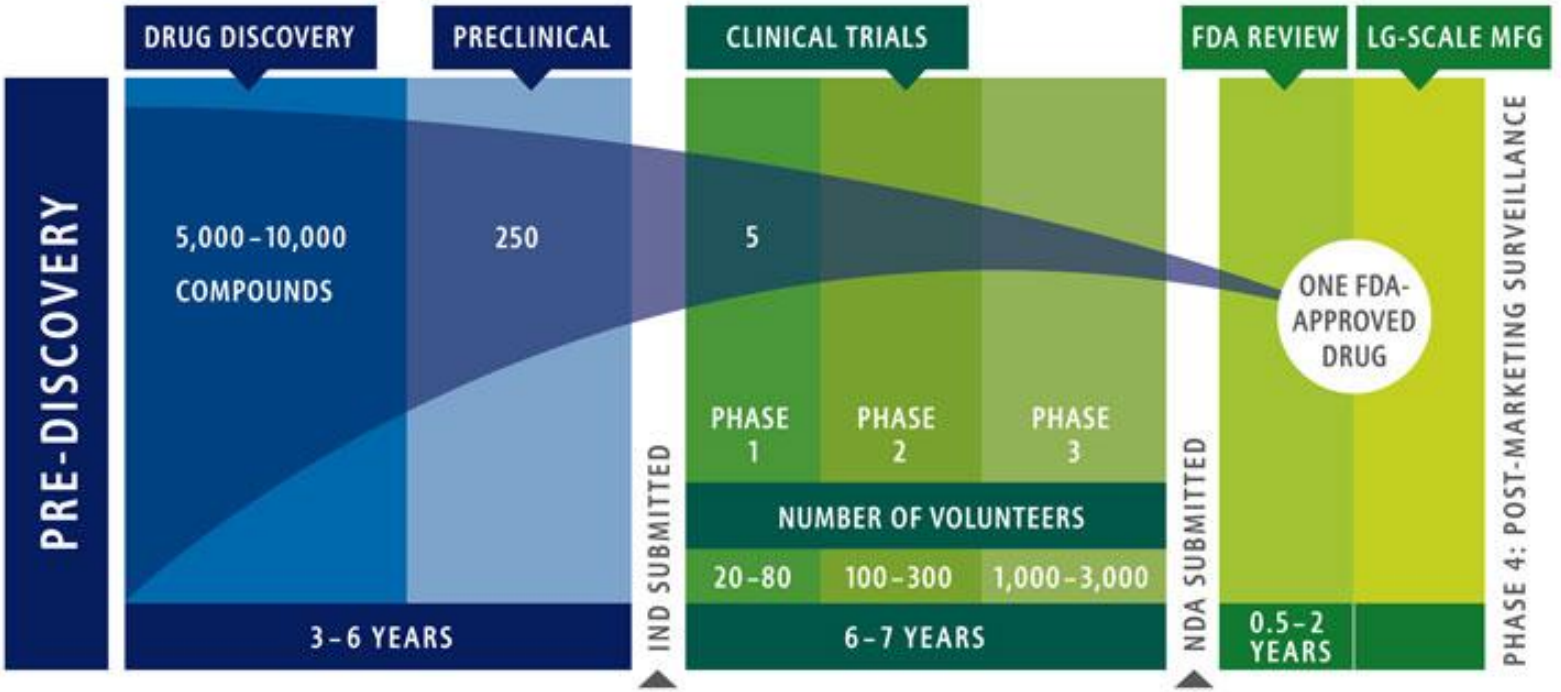
“The specification and claims of a patent, particularly if the invention be at all complicated, constitute one of the most difficult legal instruments to draw with accuracy…”

***Topliff v. Topliff*, 145 U.S. 156, 171 (1892)**

Generic Drug
And
Biosimilar
Patent Litigation Procedures

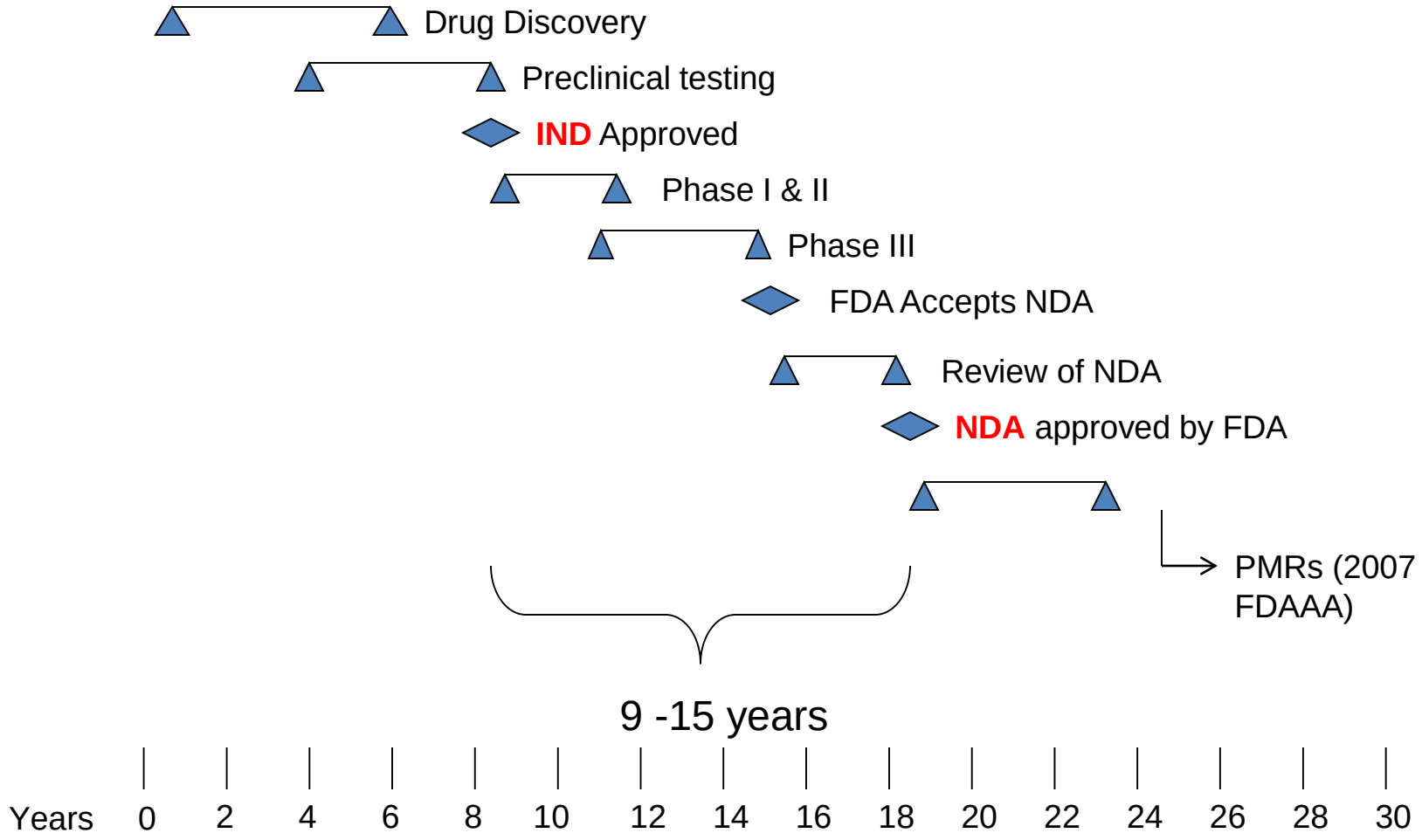
(With thanks to my colleague Terry Mahn)

Drug Discovery and Development: A LONG, RISKY ROAD



Source: Pharmaceutical Research and Manufacturers of America

Drug Discovery & Development



Pre-1984

- Before Hatch-Waxman law passed in 1984, multiple patent-related “distortions” adversely affected the drug industry
  - Pioneer’s patent term running during lengthy drug development/clinical trials/FDA process, leaving little time to market the approved drug before the patent expires
    - This reduces incentives to develop new drugs

Pre-1984

- Competitor seeking to market identical drug
  - Not allowed to rely on clinical studies already done by Pioneer, so had to repeat them, and
  - Prohibited from beginning studies on the drug until the Pioneer's patents all expire, delaying time the competing drug will be ready to enter the market until long after patent expiration

Pre-1984

- Public also loses
  - Fewer new drugs developed and brought to market
  - Delayed access to generic drugs
  - High cost of generic drugs due to high cost of doing the required studies

Hatch-Waxman Act 1984

Hatch-Waxman

- H-W addressed the Pioneer's loss of useful patent term by offering Patent Term Extension (PTE) of up to 5 years
  - PTE calculated from formula based on time spent on clinical trials and during regulatory review period
  - Applies to all types of drugs—small molecule and biologics

Hatch-Waxman

- H-W addressed the other distortions:
  - Created the 35 USC 271(e)(1) “Safe Harbor” from patent infringement for use of patented invention **for purposes of generating data for submission to FDA**
  - Established a complex set of laws permitting Generic Applicant to rely on Pioneer’s clinical data (rather than having to repeat the trials), but guaranteeing a period of data exclusivity to the Pioneer separate from any patent exclusivity
  - Set up an elaborate framework for the two sides to litigate any relevant patents prior market entry by the Generic Applicant

Hatch-Waxman

- Three routes to drug approval for small molecule drugs (and a few biologics)
  - "New Drug Application" (NDA) – full clinicals
  - "paper NDA" – limited clinicals
  - "Abbreviated New Drug Application" (ANDA) – true generic
    - Bio-equivalency testing
    - Rely on Pioneer's clinical data

Hatch-Waxman

- H-W data exclusivity periods
  - Unrelated to patents
  - Prevents Generic Applicant from relying on Pioneer's clinical data until after expiration of applicable period
  - **Five-year** period (for New Chemical Entity)
    - ANDA for the same active moiety cannot be submitted to FDA until the end of the 5-year period, unless Generic Applicant challenges the Pioneer's patents—then ANDA can be submitted after 4 years
  - **Three-year** period (for subsequently approved indications)
    - ANDA for same "conditions of approval" cannot be approved by FDA until the end of the 3-year period

Non-Hatch-Waxman Exclusivities

- Other (non-H-W) exclusivity programs
  - Orphan Drug Exclusivity
    - For “medically distinct population” of <200,000
  - Pediatric Exclusivity
    - For drug that was studied in a pediatric population
  - Qualified Infectious Disease Product Exclusivity
    - For drug to treat a drug-resistant pathogen

Hatch-Waxman

- "Safe Harbor" from infringement
  - Purpose: permit generic drugs to be tested prior to patent expiration
  - Statute (35 USC § 271(e)(1)):

    "It shall not be an act of infringement to make, use, offer to sell within the US or import into the US 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."

  - Courts have interpreted it very broadly to cover many activities, even unrelated to generic drugs

Hatch-Waxman

- Orange Book patents
  - OB applies only to small molecule drugs and a few biologics
  - Pioneer must list in OB all patents covering approved drug and approved methods of use
  - For each OB-listed patent, the ANDA filed by Generic Applicant must certify to FDA that the patent:
    - Has expired, or
    - Will have expired before the generic drug will be marketed, or
    - Is invalid, or
    - Will not be infringed by use or sale of the generic drug

Hatch-Waxman

- Filing ANDA certifying that the patents are invalid or not infringed is deemed an act of infringement (§ 271(e)(2))
  - Generic Applicant must send Pioneer and patentee a detailed factual and legal basis for the patent challenge (Para. IV certification)
  - Pioneer or patentee then has 45 days to file suit against the Generic Applicant
    - Filing suit triggers automatic 30-month stay of FDA approval of generic
    - If 30 month stay elapses before the suit is resolved, Generic Applicant will obtain FDA approval and can choose to start marketing (but at risk of later adverse judgment and damages)
    - If patentee loses the suit, Generic Applicant can start to market as soon as the exclusivity period (5 or 3 years) has expired and FDA has given approval

Biologics Price Competition and Innovation Act of 2009 (BPCIA)

BPCIA

- Created a procedure for biosimilars applications
- Set out a complex procedure for interaction of Biosimilar Applicant and Pioneer to identify patents for licensing/litigation
- Created a new artificial act of infringement (similar to ANDA filing for small molecule generics)

BPCIA

- Defined two categories: “biosimilar” and “interchangeable biosimilar”
  - “Biosimilar” means “highly similar” to the Pioneer product notwithstanding minor differences in clinically inactive components and where there are no clinically meaningful differences between the biological product and the Pioneer in terms of safety, purity and potency.
  - “Interchangeable” means a biological product found to be Biosimilar and can be expected to produce the same clinical result as the Pioneer in any given patient, and, if the product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and the Pioneer is no greater than the risk of using the Pioneer without such alteration or switch.
  - A Biosimilar found to be interchangeable may be substituted for the Pioneer without the intervention of “the health care provider who prescribed the reference product.”

BPCIA

- Both categories require animal toxicity studies and human clinical studies (unlike small molecule generic drugs)

- “Interchangeable” is especially rigorous

BPCIA

- Pioneer exclusivities
  - 12 years of marketing exclusivity for new biological structure
  - 4 years of data exclusivity
  - Pediatric exclusivity would add 6 months to each

BPCIA: "Patent Dance"

- Biosimilar applicant "required" to provide Pioneer with confidential access to Biosimilar application, including manufacturing process, within 20 days of FDA "acceptance for review"
  - ***Optional***, per 2017 Supreme Court decision in *Amgen v. Sandoz* (Neupogen)

- Within 60 days of confidential access, Pioneer required to provide Biosimilar applicant with list of patents that could reasonably be asserted and a designation of patents available for license ("initial Pioneer list")

BPCIA: "Patent Dance"

- Within 60 days of receiving Pioneer patent list, Biosimilar applicant:
  - May provide a list of patents that Biosimilar applicant believes could reasonably be asserted by Pioneer ("initial Biosimilar list").
  - Shall provide the Pioneer with a claim by claim analysis for each patent listed by the Pioneer or the Biosimilar applicant, of the factual and legal basis as to why patent is invalid, unenforceable or will not be infringed, or a statement that Biosimilar applicant does not intend to begin marketing its product before such patent expires.
  - Shall provide Pioneer with a "response" regarding each patent designated by Pioneer as being available for licensing.

BPCIA: "Patent Dance"

- Within 60 days of receiving initial Biosimilar list and claim-by-claim analysis, Pioneer must provide claim-by-claim rebuttal for each claim addressed in initial Biosimilar list

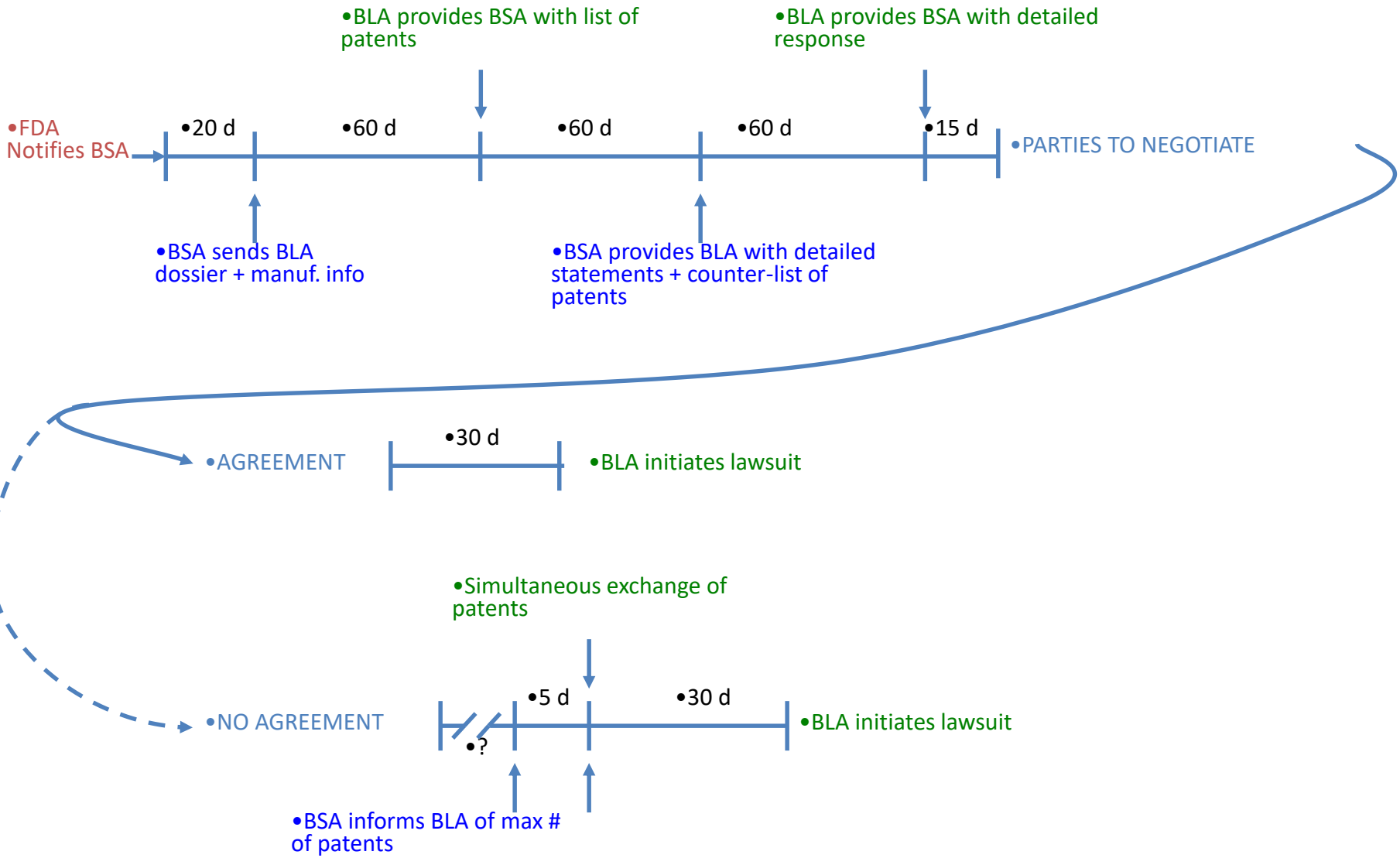
- For up to 15 days after Pioneer provides the rebuttal, the parties are required to negotiate to try to arrive at a list of patents that will be subject to an infringement action ("negotiated list")

- If parties agree on a negotiated list within 15 days, Pioneer must bring an infringement action within 30 days for each patent on negotiated list

BPCIA: "Patent Dance"

- If no agreement on a negotiated list after 15 days, "patent exchange" procedures are triggered:
  - Biosimilar Applicant notifies Pioneer of the number of patents it will exchange (e.g., 1, 6, zero)
  - Within 5 days after that notification, the parties simultaneously exchange lists of patents ("exchanged lists") that each believes should be subject to an infringement action
  - The number of patents listed by Pioneer cannot be greater than the number notified by Biosimilar Applicant, unless Biosimilar Applicant's number is **zero**, in which case Pioneer may list **one** patent
  - Pioneer must then bring an infringement action within 30 days for each patent on both exchanged lists

Patent Exchange Time Line



BPCIA: 2nd Wave Litigation

- Biosimilar applicant must provide Pioneer with 180 day notice of intent to market commercially.

- Pioneer may seek Preliminary Injunction (PI) on any patents on the “initial Pioneer list” or “initial Biosimilar list” that are not also included on the “negotiated list” or the “exchanged lists”

- Both parties required to reasonably expedite discovery in any infringement action seeking PI.

Newly Issued/Licensed Patents

- Defined as patent issued/licensed after date of “initial Pioneer list”
- Within 30 days of issuance or licensing, Pioneer must supplement its initial list
- Within 30 days of receiving supplement, Biosimilar applicant must provide statement on claim-by-claim basis as to non-infringement, invalidity or unenforceability of newly issued/licensed patent
- Newly issued/licensed patents do not become part of the negotiated/exchanged patent procedures but are subject to Preliminary Injunction procedures

Approved Biosimilars

- Sandoz's Zarxio (BS to Neupogen (filgrastim)) approved 3/15; launched 9/15
- Celltrion's Inflecta (BS to Remicade (infliximab)) approved 4/16; launched 11/16
- Sandoz's Erelzi (BS to Enbrel (etanercept)) approved 8/16; in litigation
- Amgen's Amjevita (BS to Humira (adalimumab)) approved 9/16; settled (no launch before 2023)
- Samsung/Bioepsis Renflexis (BS to Remicade (infliximab)) approved 4/17; launched 7/17

- BI's Cytelzo (BS to Humira (adalimumab)) approved 8/17; in litigation
- Amgen/Allergan Mvasi (BS to Avastin (bevacizamab)) approved 9/17
- Mylan's Ogivri (BS to Herceptin (trastuzumab)) approved 12/17; under license
- Biosimilar Applications filed:
  - Hospira (Epogen)
  - Coherus (Neulasta)
  - Sandoz (Rituxan)
  - Apotex, Coherus, Sandoz (Neulasta)
  - Sandoz (Humira)
  - Sandoz (Remicade)
  - Celltrion (Rituxan)
  - Adello (Neupogen)
  - Apotex (Neupogen)
  - Celltrion (Herceptin)
  - Amgen (Herceptin)
  - Mylan (Neulasta)
  - Apotex (Neulasta)
  - Apotex (Neupogen)

FAQs

- **What happens if Pioneer leaves a patent off its initial patent list?**
  - Unless Biosimilar applicant includes the patent on its initial list, Pioneer cannot sue on it prior to launch.

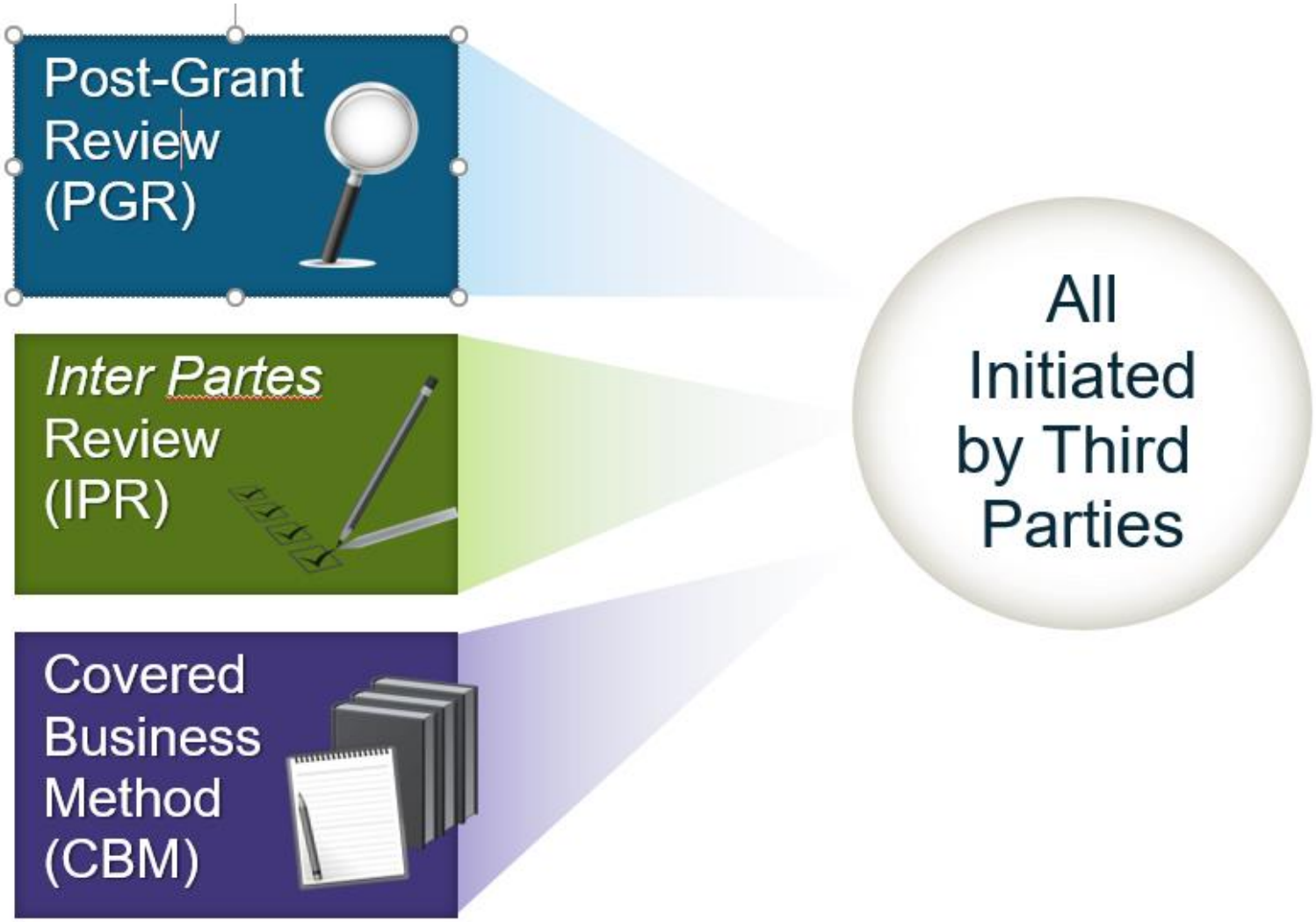
- **Can a Pioneer be forced to license its patents?**
  - Yes, if a Pioneer fails to bring an infringement action within 30 days of (1) a negotiated patent resolution, or (2) following exchange of patent lists where there is no resolution
  - Yes, if a Pioneer brings an infringement action within 30 days but the suit is dismissed without prejudice or the suit is not prosecuted in good faith.

- **What happens if a newly issued/licensed patent is not notified to Biosimilar applicant within 30 days?**
  - Patent cannot be litigated prior to Biosimilar launch.

Overview
Of
Post-Grant Proceedings

(With thanks to my colleague, Dorothy Whelan)

Types of Post-Grant Proceedings



Essential Features

- Take place at the U.S. Patent Office (“PTAB”) before 3 administrative law judges
- Claim construction: Broadest reasonable interpretation (may change to litigation standard soon)
- Burden of proof: Preponderance of the evidence
- Limited discovery
- Limited ability to amend claims

Essential Features

- Fast relative to U.S. district court litigation
- Estoppel (consequences for unsuccessful petitioner)
- Can be settled
- Cannot file anonymously
- If petitioner has been sued for infringement of the patent, any petition must be filed within one year after service of the complaint

Essential Features

IPR and PGR are most applicable to life sciences

IPR: Available for all patents. Grounds limited to anticipation and/or obviousness based on patents and printed publications.

PGR: Available only for patents having a priority date on or after March 16, 2013. Any ground. Must file within 9 months after issuance.

Timing and Key Events

- Within 6 months after the petition is filed, the PTAB will issue an "institution" decision either granting the petition in full or denying it in full.
- Institution decisions generally are not appealable.
- If the PTAB grants the petition, it will conduct the full proceeding and issue a final written decision on the merits within one year of the institution decision.
- Once the final written decision issues, a losing party may appeal that decision to the Court of Appeals for the Federal Circuit.

Timing and Key Events

- Between the institution date and the final written decision date, the parties may do the following:
  - File briefs (Patent Owner Response, Petitioner Reply, Patent Owner Sur-reply), which may include expert declarations
  - Depose experts who have submitted declarations
  - File motions (additional discovery, claim amendments, motions to exclude evidence)
  - Participate in an oral hearing before the PTAB judges

Types of Evidence

- Expert declarations
  - Experts will be deposed
  - No live testimony
- Patents and publications
  - Strict rules for proving whether a publication is prior art

Discovery

Very Limited!

Two types of discovery:

- Routine Discovery
  - Production of exhibits cited in a paper or testimony
  - Cross-examination of opposing declarants by deposition
  - “Non-cumulative information that is inconsistent with a position advanced during the proceeding”
- Additional Discovery
  - PTAB must authorize - moving party must demonstrate that additional discovery sought is “in the interest of justice”
  - PTAB nearly always denies requests for additional discovery

Claim amendments

- Limited ability to add new or amended claims
  - Limited in number – one-to-one substitution
  - Must prove need for substitute claims
  - RARELY granted
- Requires patent owner to distinguish prior art of record, focusing on added limitations
- Ultimate burden to show unpatentability of the new/amended claims is on the petitioner

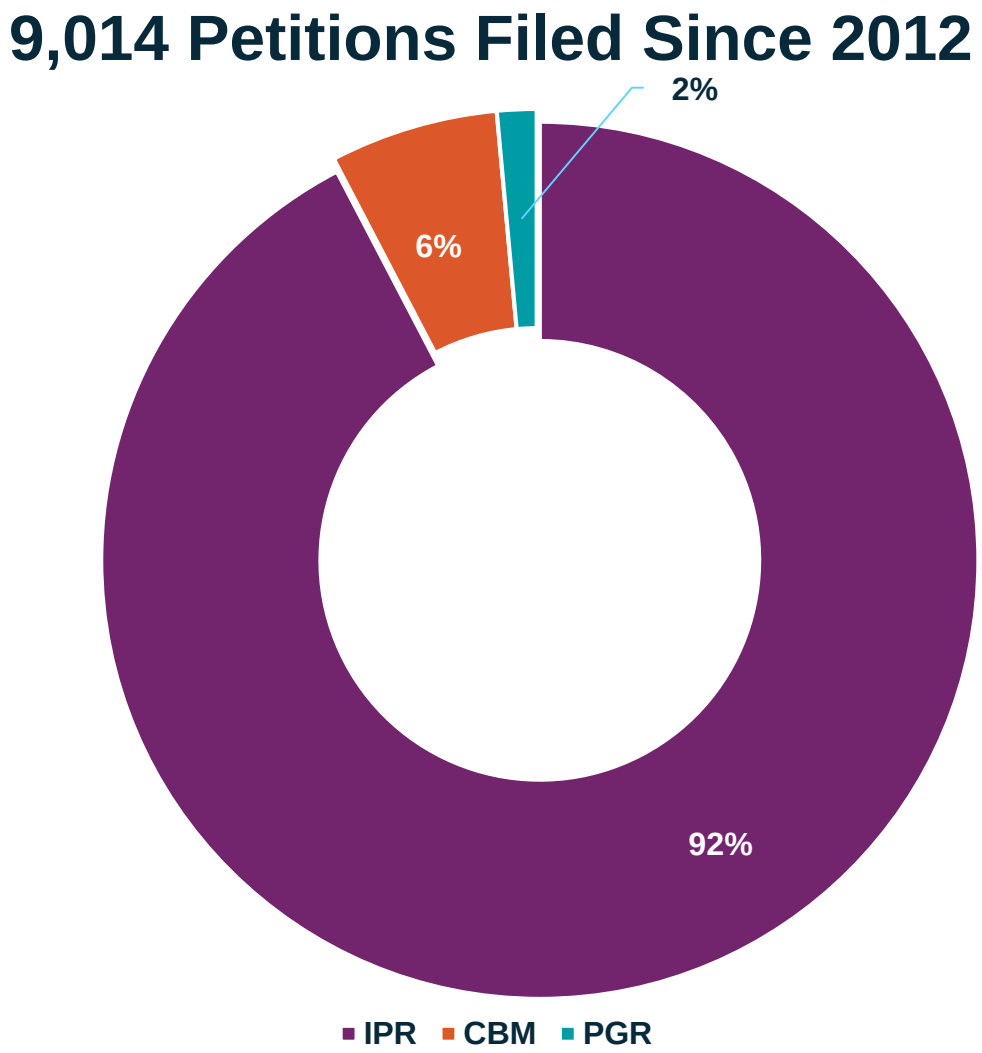
Estoppel

- If petitioner loses (patent is maintained) in IPR/PGR, *estoppel* attaches:

  petitioner cannot challenge the patent on any ground **raised or that reasonably could have been raised** in the proceeding

  - Attaches at the time the final written decision issues
  - Applies to U.S. district court, ITC, and PTO proceedings
  - Applies to petitioner and its “privies” (associated parties)

IPR / PGR / CBM Petitions



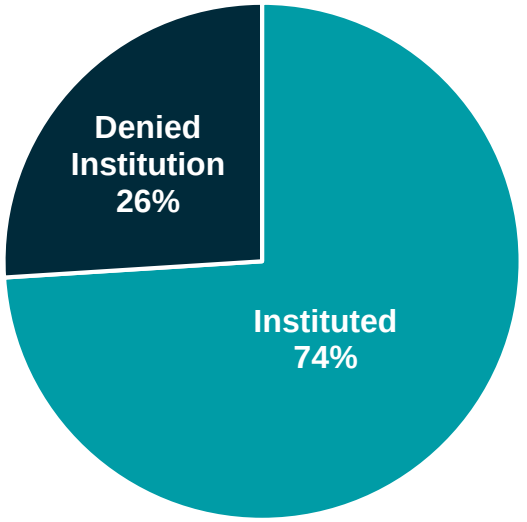
Source: Lex Machina, as of 9/04/2018

FISH.

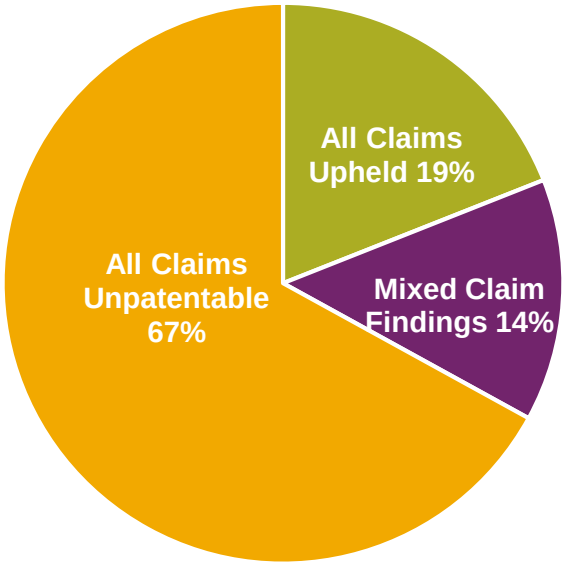
IPR Institution and Final Written Decision

8,320 IPR petitions have been filed

5,812 IPR petitions reached an **Institution Decision**

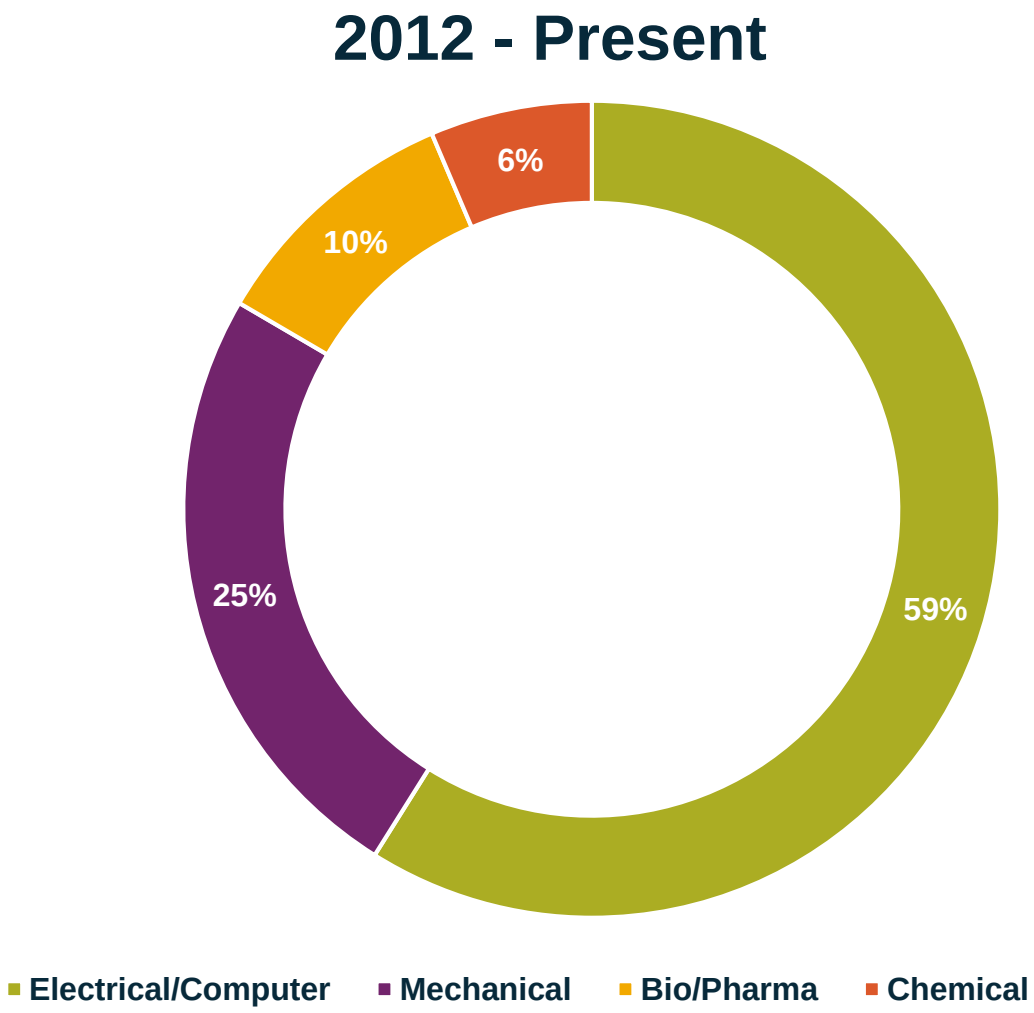


2,030 IPR petitions reached a **Final Written Decision**



Source: Lex Machina, as of 9/04/2018

Technology Breakdown



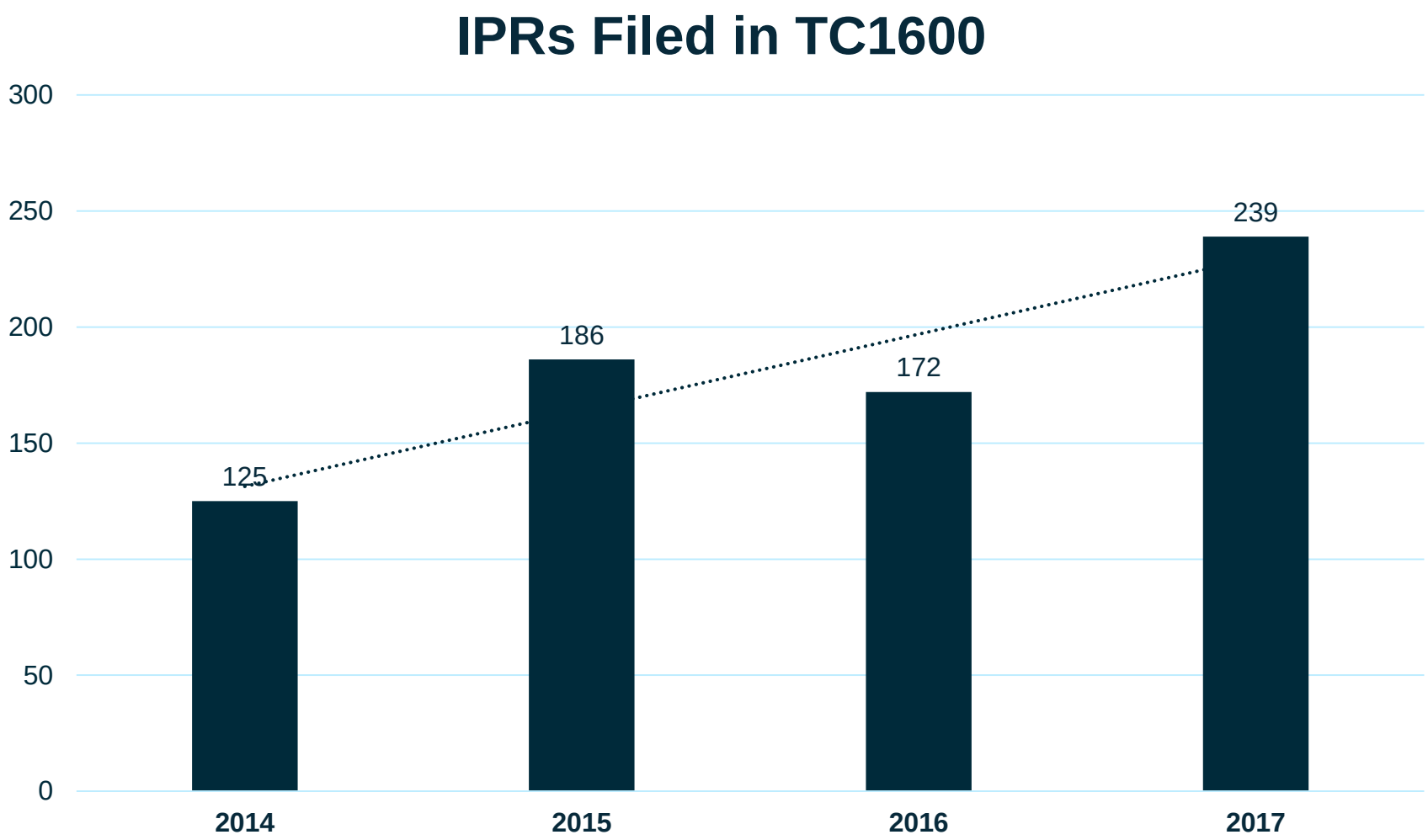
Source: Lex Machina, as of 9/04/2018. Design Patents make up <1% of remaining petitions

Final Written Decision in 2017

522 IPR petitions reached Final Written Decision in 2017

Source: Lex Machina, as of 1/9/2018

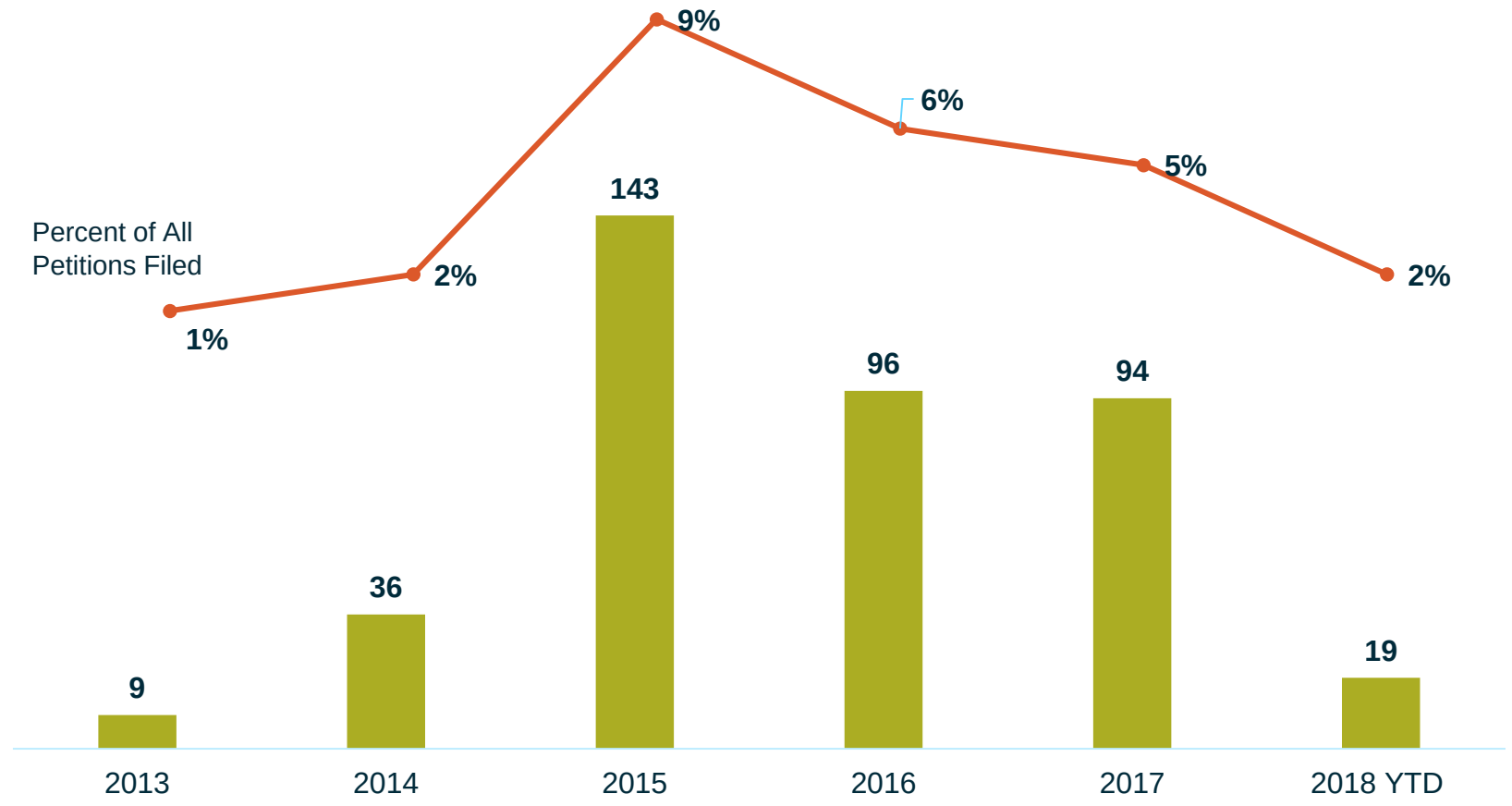
BioPharma IPR Filings



Source: Lex Machina, as of 1/9/2018

Number of Orange Book Patents Challenged by IPR

Petitions Challenging Orange Book-listed Patents



3 petitions challenging Orange Book-listed patents were filed in CY 2012

Source: Docket Alarm, as of 7/6/2018

Top IPR Petitioners of Orange Book Patents

1. Amneal Pharmaceuticals
2. Apotex
3. Teva Pharmaceuticals
4. Par Pharmaceutical
5. Wockhardt Bio AG
6. Lupin Pharmaceuticals
7. Dr. Reddy's Laboratories
8. Fresenius Kabi
9. Mylan Laboratories
10. Praxair Distribution
11. Akorn
12. Argentum Pharmaceuticals
13. Innopharma Licensing
14. Roxane Laboratories
15. I-Mak
16. Sun Pharma Global Fze
17. Breckenridge Pharmaceutical
18. Glenmark Pharmaceuticals
19. Accord Healthcare

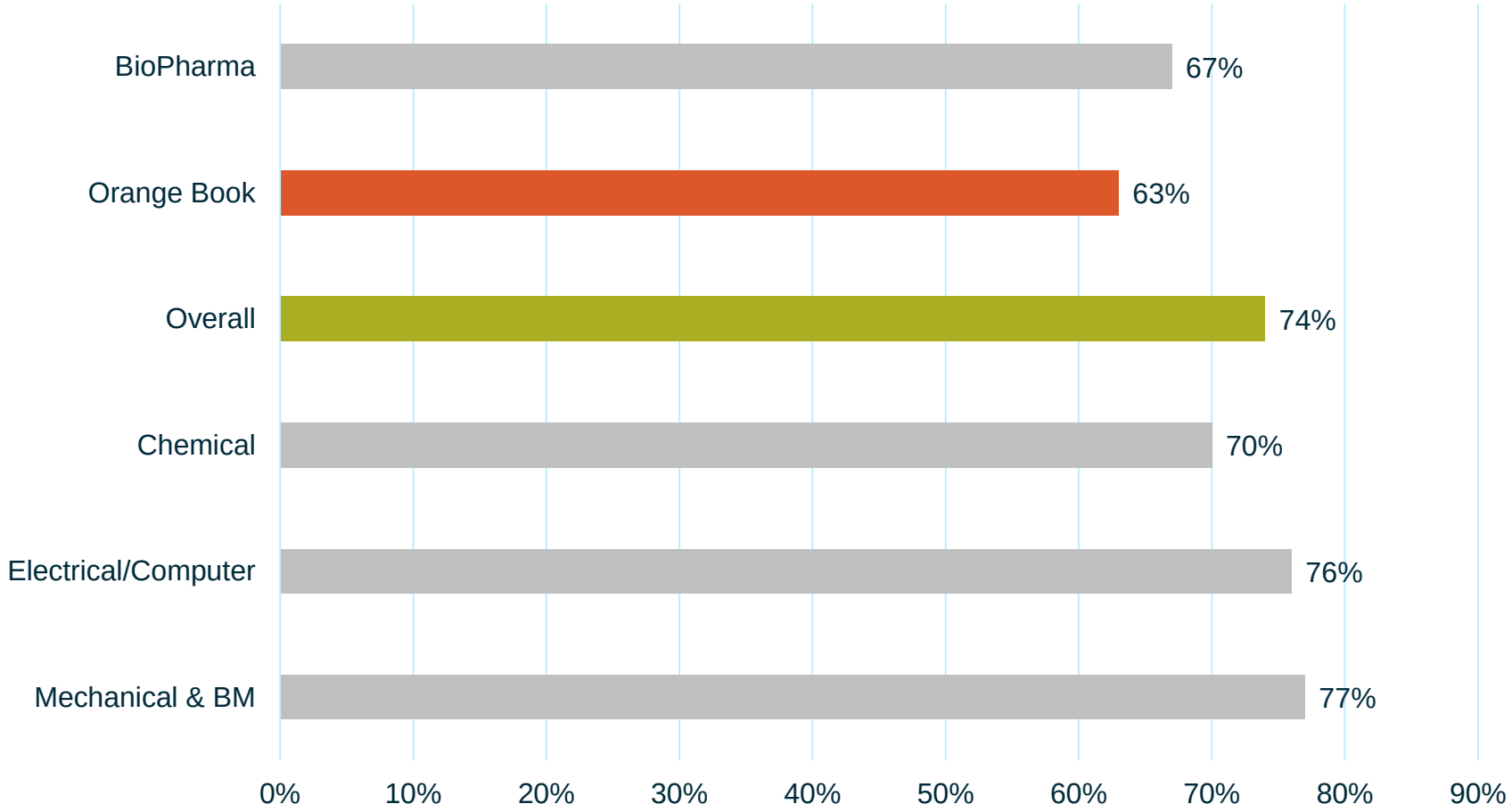
Source: Docket Alarm, as of 7/10/2018

Top Owners of Orange Book Patents in IPR

1. Allergan
2. Jazz Pharmaceuticals
3. Novartis AG
4. AstraZeneca
5. Senju Pharmaceutical
6. Eli Lilly and Company
7. Horizon Therapeutics
8. INO Therapeutics
9. Gilead Pharmasset
10. Pozen
11. Alcon Research
12. ICOS
13. UCB Pharma GMBH
14. Anacor Pharmaceuticals
15. Helsinn Healthcare
16. Hospira
17. Monosol RX
18. Roche Palo Alto
19. Abraxis Bioscience
20. Acorda Therapeutics

Source: Docket Alarm, as of 7/10/2018

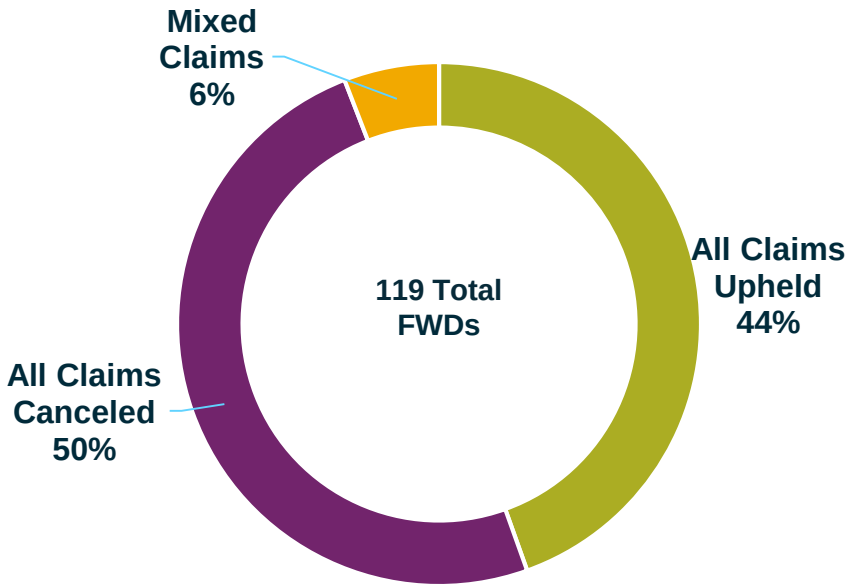
Institution Rates by Technology



Source: Docket Alarm (Orange Book) and Lex Machina, as of 7/6/2018

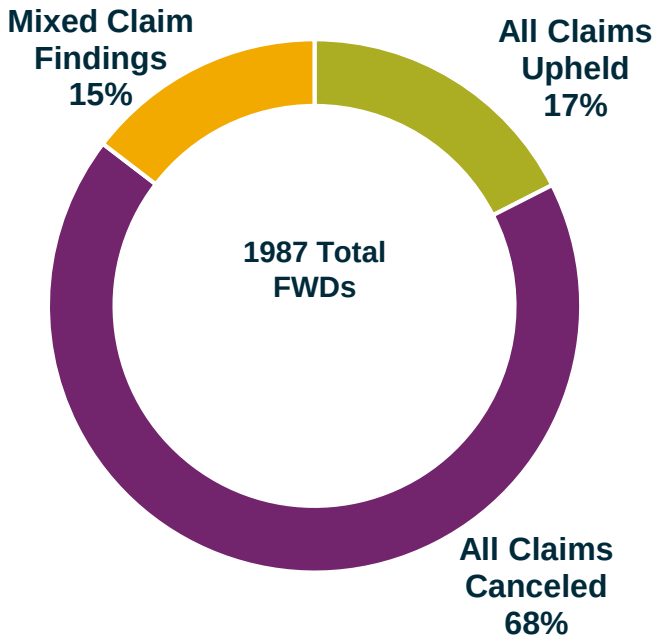
Status of Instituted Claims in Final WD

Orange Book-listed Patents



All Other Technologies

Excluding Orange Book-listed Patents



Source: Docket Alarm, as of 7/6/2018

Proposed Legislation

- Would prevent Generic and Biosimilars Applicants from using IPR or PGR to attack a Pioneer's patents

- Would prevent "short sales" of stock in a pharma/biotech company by anyone who files IPR or PGR against a patent owned by that company

“Incomprehensible jargon is the hallmark of a profession.”

---Kingman Brewster, Jr.

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