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The Top Ten Bio/Pharma Decision Topics of the Last Two Years

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MIND + MUSCLE

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#10: Process Limitations in Product Claims

1. *The Medicines Co. v Hospira* (Fed. Cir. 2016): Ignore process limitations for patentability

   Product by Process Claim 1 of '343, not invalid over putative "on-sale" of product:

   - Pharmaceutical batches of a drug product comprising bivalirudin…and a pharmaceutically acceptable carrier, for use as an anticoagulant in a subject in need thereof~~, said batches prepared by a compounding process comprising:~~

     ~~(i) dissolving bivalirudin in a solvent to form a first solution;~~

     ~~(ii) efficiently mixing a pH-adjusting solution with the first solution … and~~

     ~~(iii) removing the solvent and pH-adjusting solution solvent~~ …;

     wherein the ~~batches~~ have a pH adjusted by a base… [etc.]

2. *The Medicines Co. v Mylan* (Fed. Cir. 2017): Product claim construed as a prod-by-process

   Product Claim 1 of '727, not infringed by Mylan:

   - Pharmaceutical batches of a drug product comprising bivalirudin...wherein the batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum impurity level of Asp9-bivalirudin that does not exceed about 0.6% as measured by HPLC

     [~~…prepared by a compounding process comprising… efficient mixing…~~]

#9: On-Sale Bar: Pre and Post AIA

1. *The Medicines Co. v Hospira* (Fed. Cir. 2016): Pre AIA 102(b) = "on sale in this country…" requires a *commercial* sale.
   - Claim 1 of '343 (construed as product for patentability)
   - Pharmaceutical batches of a drug product comprising bivalirudin…and a pharmaceutically acceptable carrier, for use as an anticoagulant in a subject in need thereof [~~three process steps~~] wherein the batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum impurity level of Asp9-bivalirudin that does not exceed about 0.6% as measured by HPLC.
   - Contract for manufacturing services: Title to batches does not change hands ➔ not a "commercial sale"
   - Stockpiling after manufacturing without right to sell ➔ not a "commercial sale" either

2. *Helsinn v Teva* (Fed. Cir. 2017) - Post AIA 102(a)(1) = "or otherwise available to the public…" has not changed the law. It does not mean details of sale must be *publicly* known.
   - Claim: "A single-use unit-dose IV formulation…comprising…palonosetron…[etc.]"
   - Patentee had a Supply and Purchase agreement whose existence was made public
   - Details of the claimed invention were NOT made public in the contract
   - After the AIA, if the existence of the sale is public, the details of the invention need NOT be publicly disclosed in the terms of sale. *Held* ➔ On sale bar (It was also "ready for patenting" under *Pfaff*)

#8: Inherency – Two Sides: Possession and Anticipation

(1) Possession

1. ***Cubist Pharma v Hospira*** (Fed. Cir. 2015)
   - Claim is to daptomycin with erroneous L-stereoconfiguration of an Asn residue
   - A Cert of Correction was filed changing L-Asn to D-Asn throughout the specification and claims .
   - ***Held***: Not new matter to correct inherent errors
2. ***Yeda v Abbott GmbH*** (Fed. Cir. 2016)
   - **Claim 1.** ('915 patent)

     A purified and isolated TNFα-binding protein which has a molecular weight of about 42,000 daltons and has at the N terminus the amino acid sequence

     Xaa Thr Pro Tyr Ala Pro Glu Pro Gly Set Thr Cys Arg Leu Arg Glu

     where Xaa is hydrogen, a phenylalanine residue (Phe) or the amino acid sequences Ala Phe, Val Ala Phe,…[etc]
   - Foreign priority document does not describe the complete N-terminus of the claim but parties stipulated that, due to several other described properties, it is the same protein as later claimed
   - ***Held***: Inherent possession sufficient for benefit of priority.

#8: Inherency – Two Sides: Possession and Anticipation

(2) Anticipation

Eli Lilly v LA Biomedical (Fed. Cir. 2017 – appeal from PTAB decision in an IPR)

- **Claim 1** ('903 patent).

  A method comprising: a) administering a cyclic guanosine 3', 5'-monophosphate (cGMP) type 5 phosphodiesterase (PDE5) inhibitor according to a continuous long-term regimen to an individual with at least one of a penile tunical fibrosis and corporal tissue fibrosis; and b) arresting or regressing the at least one of the [fibroses], wherein the PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg **[*per*] *day for not less than 45 days.***
- Whitaker discloses "8-12 weeks"… "chronic administration means at least 3 days or more"… exemplifies 3 weeks… but does not expressly disclose daily dosage.
- Lilly: A POSITA would understand that erectile dysfunction can last longer than 45 days.

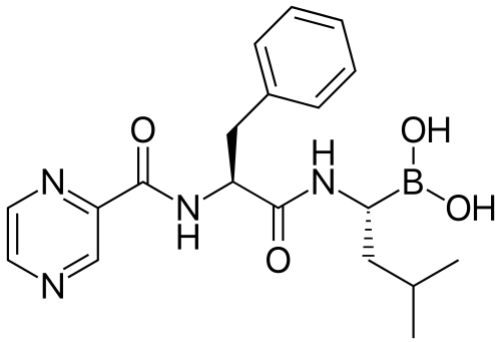
Held: prior art at best *suggests* long term daily administration but does not explicitly or inherently disclose daily for 45 days or more.

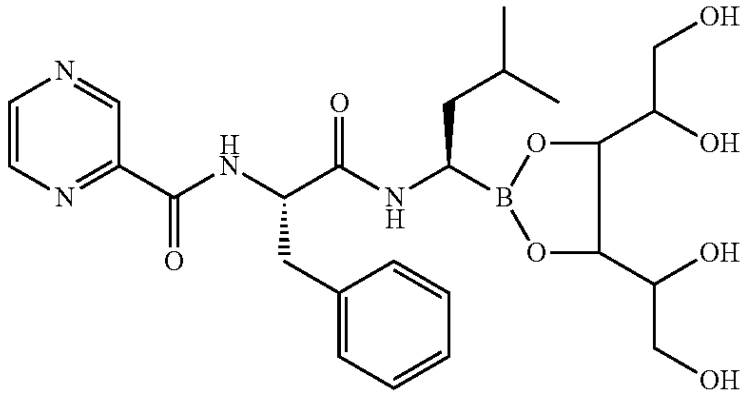
- 8-12 weeks (56-84 days) is "not less" than 45 days, but "[***daily***] ***for 45 days"*** is missing.
- At best an obviousness challenge.

#7: …and a Third Side: Inherent Obviousness

Millennium v Sandoz, et al (Fed. Cir. 2017: the Velcade® case)

- **Claim 20** The lyophilized compound D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate.





Bortezomid DRUG	Velcade® PRO DRUG
Degrades, insoluble, unstable in liquid, not approved by FDA	Stable, useful clinically, approved by FDA

#7 - Inherent Obviousness (2)

- **Prior art**: Lyophilizing unstable compounds in the presence of bulking agents (*e.g.* mannitol) was known
- **Lower Court** ➔ Claim obvious as the "natural result" of combining bortezomid with mannitol, and lyophilizing.
  - Any commercial success is due to bortezomid
- **CAFC (Newman, J.)**: Reversed on several grounds
  - No specific reason to combine bortezomid with mannitol
  - Unexpected that a new compound formed with long-hoped for properties
  - **Sandoz**: result may have been be unexpected but it was inevitable and thus inherent
  - **CAFC**: Mannitol ester is responsible for Velcade's success
  - "The unexpected properties of an unexpectedly produced new compound, and the ensuing pharmaceutical efficacy and benefit, negate the district court's ruling of obviousness."
- **Secondary considerations are alive and well in inherent obviousness analyses!!**

#6: *UCB v Yeda* (Fed. Cir. 2016): After-Arising Antibody Embodiments…The Saga Continues

	Antigen	Claim limitations	WD in spec	Held	Rationale
Noelle (2004)	Novel (CD40CR)	None	Mouse CD40CR; no human CD40CR	Valid/ invalid	Mouse CD40CR only describes Mab against mouse Ag, but not against human Ag
Alonso (2008)	Novel	None	One Mab deposited	Invalid	One Mab not representative of genus
Centocor v Abbott (2011)	Not novel (TNF-α)	1) K_{ass} 2) Human regions	Mouse regions	Invalid	Mouse regions not representative of human ones
Biogen IDEC v GSK (2013)	Not novel (CD-20)	Method of treating CLL	Rituxan®	Valid, but…	…Limited to large loop of CD-20 and not infringed by Arzerra®
AbbVie Deutschland v Janssen (2014)	Not novel (IL-12)	1) k_{off} 2)Human Mabs	300 human Mabs of VH_3/λ	Invalid	VH_3/λ human Mabs not representative of VH_5/κ human Mabs (like accused Stelara®)
UCB v Yeda (2016)	Novel	None	Murine Mabs	Valid, but…	…Construed not to read on chimerics due to estoppel

#5: Clarifying Eligibility under *Alice*

1. ***Rapid Lit. Management v CellZDirect*** (Fed. Cir. 2016)
   - A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes being capable of ***being frozen and thawed at least two times***, and in which greater than 70% of the hepatocytes of said preparation are viable after the final thaw, said method comprising:
     (A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes…
     (B) recovering the separated viable hepatocytes, and
     (C) cryopreserving the recovered viable hepatocytes…wherein greater than 70% of the hepatocytes.. are viable after the final thaw.
   - **Held**: Eligible.
   - **Lourie, J**. If [this claim were not eligible] we would find patent-ineligible methods of, say, producing a new compound (as directed to the individual components' ability to combine to form the new compound), treating cancer with chemotherapy (as directed to cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin).
2. ***Cleveland Clinic v True Health*** (Fed. Cir. 2017) – reaffirms the ***Classen*** rule (Fed. Cir. 2011):

'552 - One-party claim: Assessing risk of atherosclerosis by levels of MPO	'260 - Two-party claim: 1) Assessing MPO levels and 2) administering therapy
Ineligible under *Alice*	Never attacked for ineligibility, but…failed for split infringement (next slide ➔ ➔ ➔)

#4: Precision Medicine Claims

(1) Split Infringement

1. ***Cleveland Clinic v True Health*** (Fed. Cir. 2017) **Clinical Lab-Doctor split: No evidence of direct inducement**
   - **Claim 1 ('260)**. A method for administering a lipid lowering agent to a human patient based on elevated levels of myeloperoxidase (MPO) mass and/or activity comprising:
     (a) ***performing an…ELISA*** comprising contacting a serum or plasma sample with an anti MPO antibody and a peroxidase activity assay to determine MPO activity in the serum or plasma sample;
     (b) ***selecting a patient*** who has elevated levels of MPO mass and/or activity compared to levels of MPO mass and/or activity in apparently healthy control subjects; and
     (c***) administering*** a lipid lowering agent to the selected human patient.
2. ***Eli Lilly v Teva*** (Fed. Cir. 2017) **Patient – Doctor split: They were in an *Akamai*-type conditional relationship ➔ joint infringement.**
   - **Claim 12.** An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
     a) ***administration*** of between about 350 µg and about 1000 µg of ***folic acid*** **prior** to the first administration of pemetrexed disodium;
     b) ***administration*** of about 500 µg to about 1500 µg of ***vitamin B12*****, prior** to the first administration of pemetrexed disodium; and
     c) ***administration*** *of pemetrexed disodium*.

#4: Precision Medicine Claims

(2) Obviousness

- ***Prometheus v Roxane*** (Fed. Cir. 2015)
  - **Claim 5**. A method for treating a diarrhea-predominant female IBS patient, while excluding those with predominant constipation, said method comprising:
    - ***assessing*** whether said diarrhea-predominant female IBS patient has experienced symptoms for at least six months; and
    - ***administering*** an effective amount of alosetron or a pharmaceutically acceptable derivative thereof to said patient who has experienced symptoms for at least six months, wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.
    - **Dyk, J:** The genus-species distinction may have particular relevance in the field of personalized medicine, where, for example, a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset of patients [citation omitted]. Singling out a particular subset of patients for treatment (for example, patients with a particular gene) may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally. An obviousness rejection likely would not be appropriate where the new patient subset displayed unexpected results.

#3: Export of Components

- ***Promega v LTI Corp.*** (S. Ct. 2017) **–*Taq* polymerase, exported to the UK to be assembled into a U.S.-claimed PCR kit, is not "a substantial portion of the components" of the kit.**
  - **Claim 42.** A kit for analyzing polymorphism in at least one locus in a DNA sample, comprising: a) at least one vessel containing… primers … ; ***b) a vessel containing a polymerizing enzyme [Taq] suitable for performing … [PCR] ;*** c) a vessel containing [A, G, C, and T] …; d) a vessel containing a buffer…; and e) a vessel containing a template DNA…
  - **271(f)(1):** Whoever without authority supplies or causes to be supplied in or from the United States all or ***a substantial portion of the components of a patented invention***, where such ***components*** are uncombined in whole or in part, in such manner as to actively induce the combination of such ***components*** outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.
  - **CAFC (2014):** *Taq* polymerase is a "substantial portion" of the components of the LTI kits.
  - **S. Ct. (2017)** Nope: "[A] single component can [never] constitute a 'substantial portion.'… Section 271(f)(1) consistently refers to 'components' in the plural. The section is targeted toward the supply of all or a substantial portion 'of the components,' where 'such components' are uncombined, in a manner that actively induces the combination of 'such components' outside the United States. Text specifying… 'components,' plural, indicates that multiple components constitute the substantial portion."

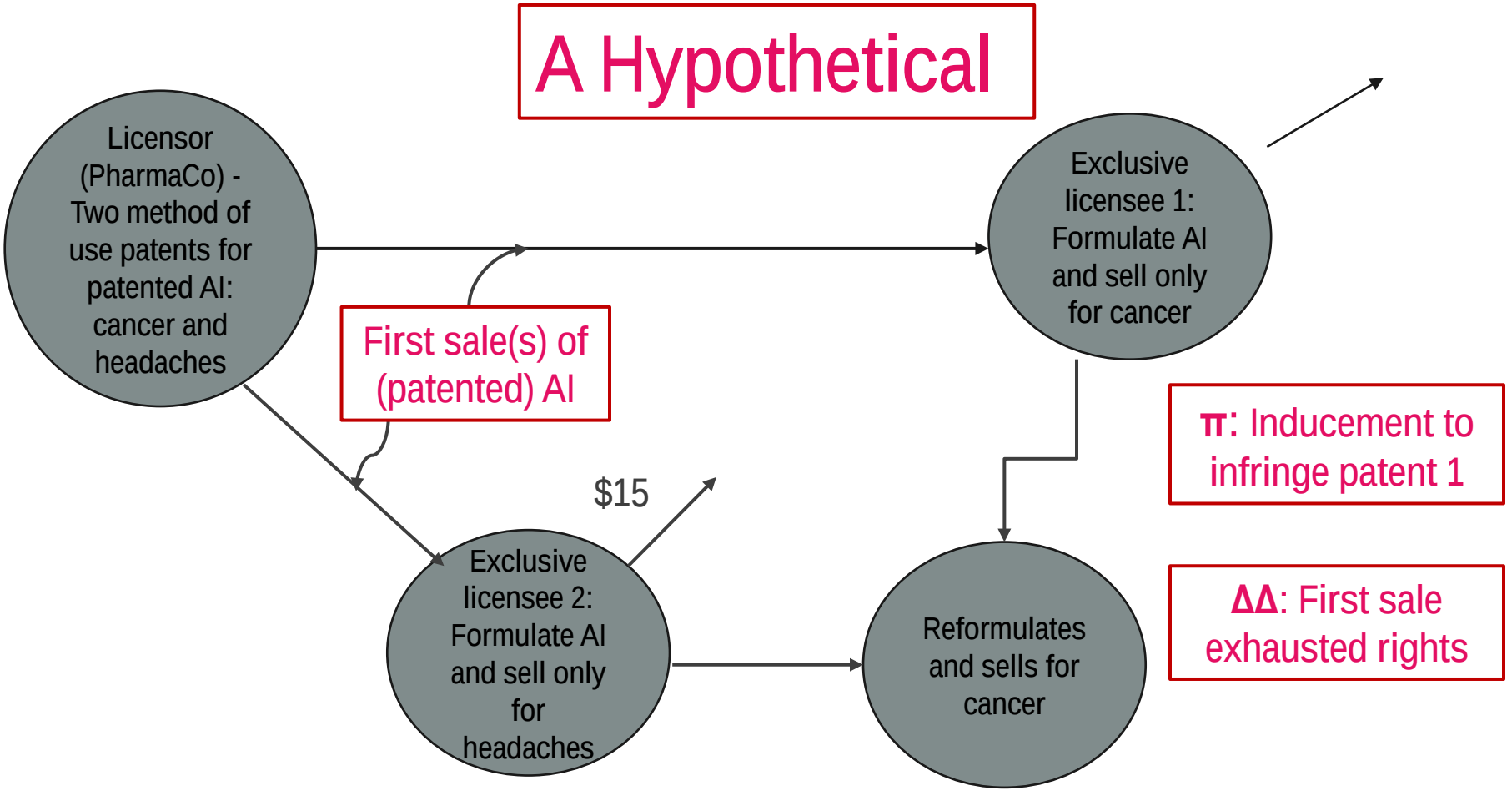
#2: Inequitable Procurement

- ***Regeneron v Merus*** (Fed. Cir. 2017) - **Sanctions for litigation misbehavior led to adverse inference of intent to defraud USPTO and, since withheld prior art was not cumulative and was material ➔ patent unenforceable.**
- **Patent:** The use of large DNA vectors to target and modify endogenous specific mouse genes and chromosomal loci, to develop antibodies useful for humans.
- **District Court** – spelled out patentee's litigation tactics and found "a pattern" of misconduct:
  - Failure to disclose infringement contentions broken down by element,
  - Choosing tactics over substance during claim construction,
  - Privilege broken by attorney's trial declarations, and then …
  - Shielding privileged documents from disclosure that were directly implicated by the trial declarations
- D. Ct. held patent unenforceable.
- **CAFC affirmed.** "[P]roposition that litigation misconduct cannot support finding of unenforceability of patent for inequitable conduct is inapposite, in that plaintiff is accused not only of post-prosecution misconduct, but also of engaging in inequitable conduct during prosecution."

#1: Patent Exhaustion

- ***Impression Prods. v Lexmark International* (S. Ct. 2017)**
  - First authorized sale of patented product inside or outside the U.S. exhausts U.S. patent rights.
  - Method claims also exhausted if product "substantially embodies" the method.
  - Post-sale restrictions on reuse of patented product or process are not enforceable by patent infringement.
    - Restrictions can still be enforced by contract/license.
  - Will licensing rather than sales become the norm?
    - Form over substance?

But…Post-sale Restrictions on *Patented* Methods of Use?



Query: Does 1st sale for patented use for headaches also "substantially embodies" the patented use for cancer?

Plus Three More

1. ***Oil States Energy Services LLC v. Greene's Energy Group LLC*** (*Cert* granted June 12, 2017) **=** Constitutionality of AIA proceedings

2. ***TC Heartland LLC v Kraft Foods* (S. Ct. 2017) =** Venue

3. ***Amgen v Sandoz* (S. Ct. 2017) =** Biosimilars patent dance

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Thank you…

and enjoy the rest of the day!

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