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Formulation Patents for Biologics

Considerations, Challenges and Strategies for Innovators and Biosimilar Developers

5th Annual MIBio Conference
21st October 2015
Magdalene College, Cambridge UK

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Executive Summary

- Formulation patents play an important role in patent life cycle management strategy for biopharmaceuticals
- In ANDA context, formulation patents generally considered weaker than patents on compound
  - Prior art issues
  - More likely to design around
- But difficulties inherent in formulating biologics increase value of formulation patents for biopharmaceuticals
  - More likely to have unexpected results to counter obviousness/inventive step rejections
  - More difficult for competitors to design around

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Executive Summary

- Analysis of sample formulation patents for biologics
- Case studies: insulin glarginine and adalimumab
- Strategy for Patenting Formulations
  - Merely claiming combinations of known excipients can be a challenge
  - Knowledge of closest prior art is important
  - Carefully crafted functional limitations increase chances for allowance
  - Applications should be drafted to explain why claimed formulation was difficult to obtain or has unexpected properties
  - Assay data comparing claimed formulation to closest prior art is helpful

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Patent Life-Cycle Management

- Strategic use of patents to maintain product exclusivity and revenue stream over life of blockbuster drug or biologic
- Involves obtaining additional patents that extend protection beyond the original patents covering the active per se
- Common practice for small molecules

Patent Life-Cycle Management

- Pharma companies have countered generics by increasing the breadth and complexity of the patent "fence" around their crown jewels
  - "traditional" protection covered NCE, method of making, method of using (treating), and a pharmaceutical formulation
  - Today, patents are typically also filed on:
    - New indications
    - Polymorphs
    - Mechanisms of action
    - Combination products/therapies
    - Dosing regimens
    - Dissolution/bio profiles
    - **NEW FORMULATIONS**
    - Isomers

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Formulation Patents for Biologics

- Formulation development involves optimizing the excipients present in a pharmaceutical composition (e.g.,liquid or lyophilized powder) in order to minimize the physical (denaturation, aggregation) and/or chemical (oxidation, deamidation, isomerization, hydrolysis) degradation of the active agent

- For small molecules, formulation patents generally viewed as weaker than compound patents
  - But remain key elements of protection around blockbusters
  - Increase burden (in terms of risk, litigations costs, and time) on generic challengers

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Formulation Patents for Biologics

- Formulation development of biopharmaceuticals presents distinct challenges not encountered during formulation of small molecules

- Inherent protein properties such as tendency to self-aggregate, and solubility and viscosity in solution pose challenges in the development of high concentration formulations

- Difficulties inherent in formulating complex biological molecules create patenting opportunities
  - Easier to show that formulation was neither routine nor mere optimization
  - Can be harder/riskier to design around

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Formulation Patents for Biologics

- US biosimilar statute (BPCIA) contains additional incentives for obtaining patent protection on formulations not present in Hatch-Waxman Act
- Under Hatch-Waxman, brand company can get three years additional market exclusivity for new dosage forms that required further clinical investigation
- BPCIA contains *"anti-evergreening" provisions* that prevent reference product sponsor from getting additional exclusivity:
- 12-year exclusivity period not available for:
  - "a subsequent application ***filed by the same sponsor or manufacturer of the biological product that is the reference product*** (or a licensor, predecessor in interest, or other related entity) for—

    (I) a change (not including a modification to the structure of the biological product) that results in a new indication, ***route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength***;

Formulation Patents for Biologics

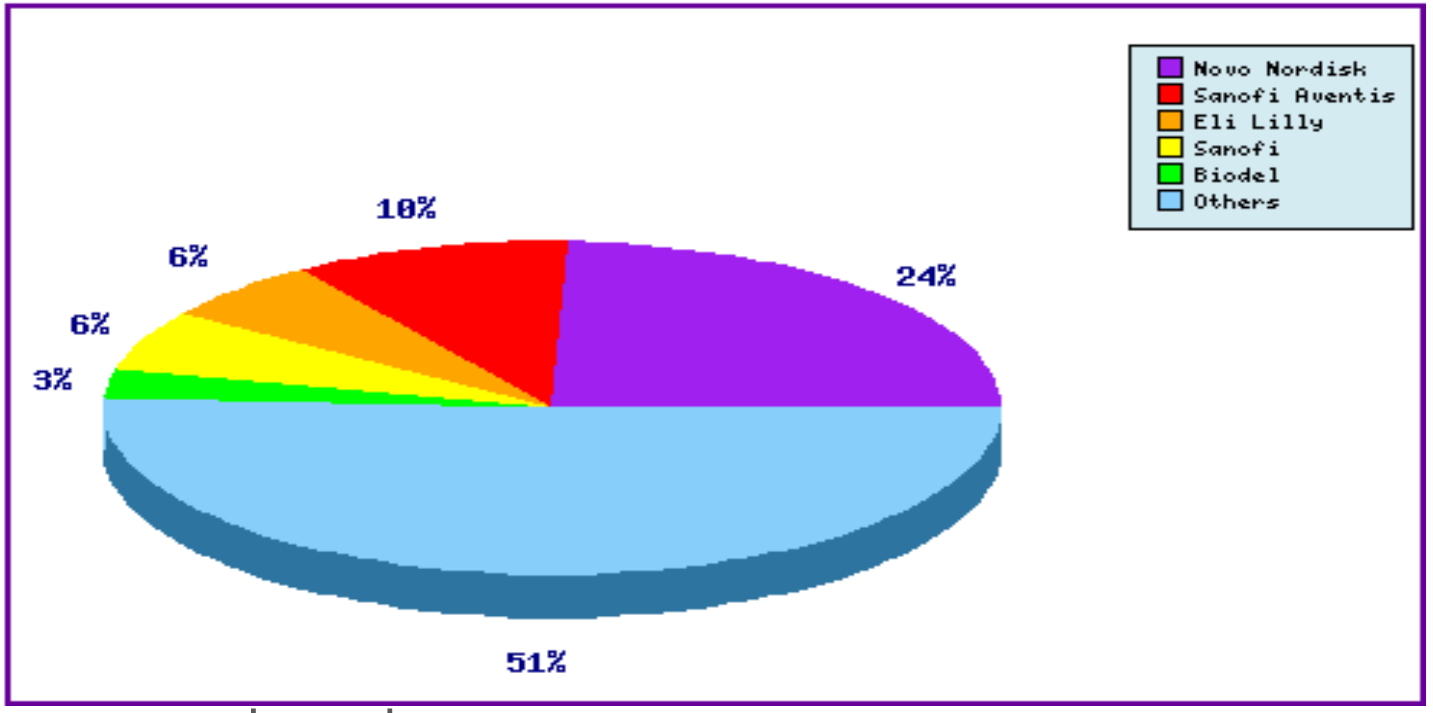
- FDA Guidances on biosimilars contains incentives to patent biologic formulations
  - "*Differences in formulation* between the proposed product and the reference product are among the factors that *may affect the extent and nature of subsequent animal or clinical testing*." *Scientific Considerations Guidance*
  - "*Differences in formulation* and primary packaging between the proposed product and the reference product are among the factors that *may affect whether or how subsequent clinical studies may take a selective and targeted approach*" *Quality Considerations Guidance*
  - "Additional factors that FDA may consider regarding the *extent of bridging data* include, but are not limited to . . . [w]hether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same . . . ." *Questions and Answers Guidance*

Formulation Patents for Biologics

- "Dosage form" – Under BPCIA, biosimilar applicant must demonstrate that the *dosage form* of the proposed biosimilar or interchangeable product is the same as that of the reference product 351(k)(2)(A)(i)(IV)
  - For proposed biosimilar products to be injected, FDA considers an *injection* (e.g. a solution) to be a different dosage form from "*for inection*" (e.g., a lyophilized powder) *Additional Questions and Answers Proposed Guidance*
  - *If reference product is an "injection", an applicant could not obtain licensure of a proposed biosimilar "for injection"*, even if proposed biosimilar when constituted or reconstituted met all other requirements for biosimilar application
  - FDA also considers emulsions and suspensions of products intended to be injected to be distinct dosage forms
- Thus, while exact same formulation not required for biosimilar products, varying formulation increases cost (e.g. clinical testing) and risk of being found not biosimilar

Case Study - Lantus®

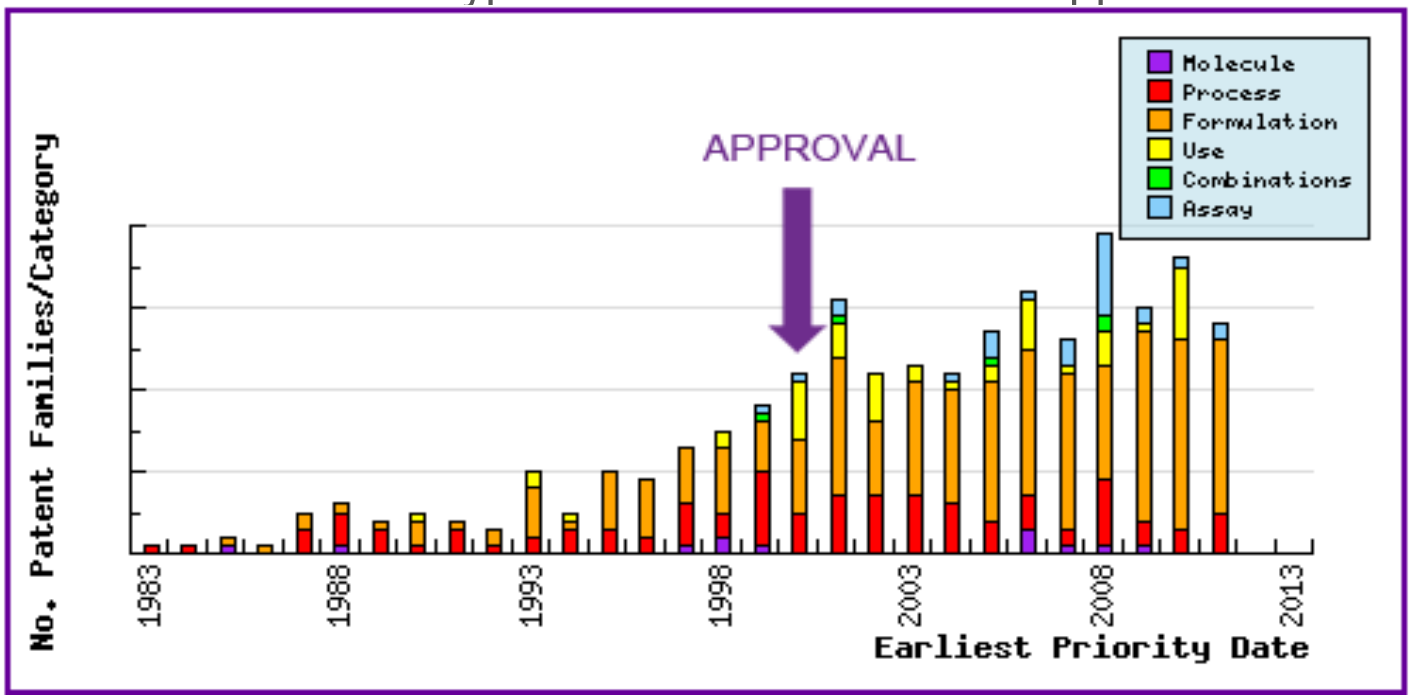
- Case Study – Lantus® (insulin glargine) (Sanofi-Aventis)
- Most significant patent filers for insulin glargine (note primarily brand)



- From www.genericsweb.com

Case Study - Lantus®

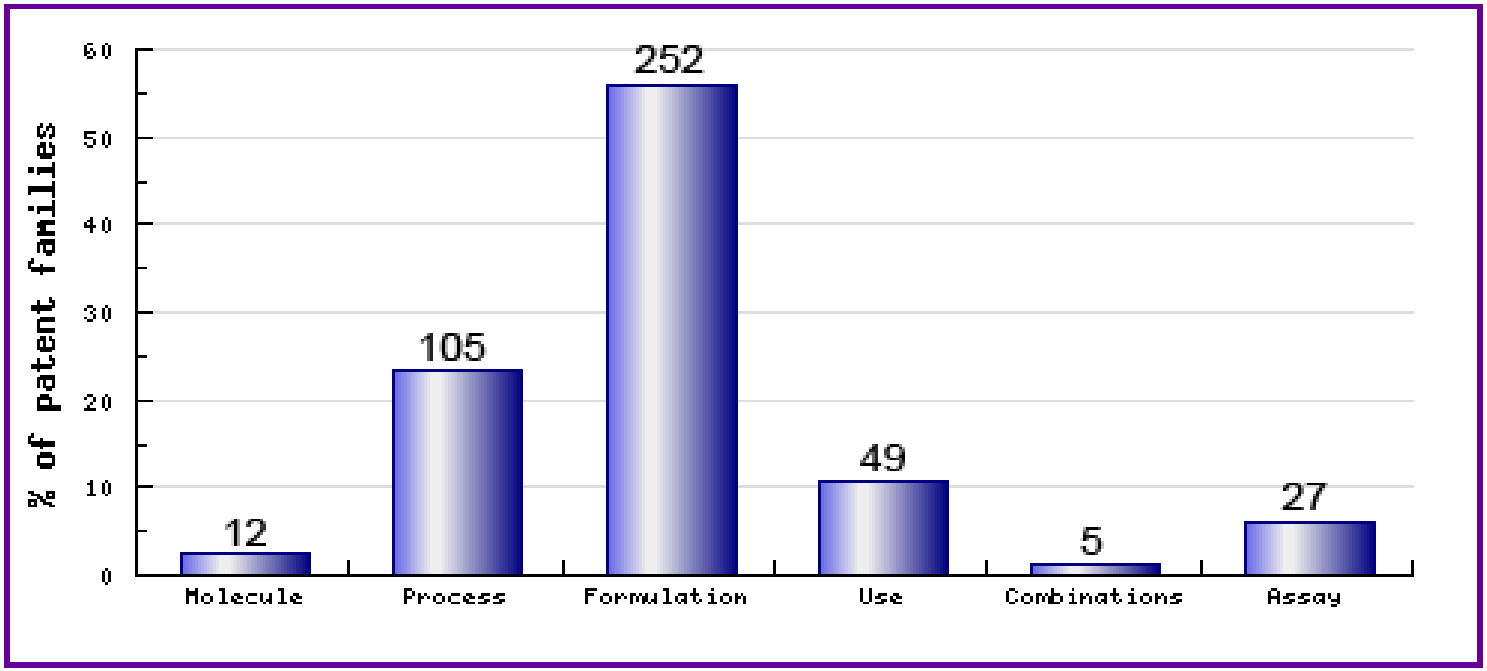
- Patent Filing Trends for insulin glargine
  - Shows timing of earliest priority filing date for each patent family identified for this molecule as well as types of claims found in the applications



  - From www.genericsweb.com

Case Study - Lantus®

- Patent Category Distribution
  - Shows the types, number and relative distribution of patents that have been filed for insulin glargine



  - From www.genericsweb.com

Examples of Patents on Biologic Formulations

- US Pat. No. 6,551,992 (Eli Lilly)

  1. A solution formulation comprising: a physiologically tolerated buffer selected from the group consisting of TRIS and arginine; a monomeric insulin analog; zinc; and a phenolic preservative; wherein the formulation is a solution formulation.

  - Stabilizes against aggregation

Examples of Patents on Biologic Formulations

- US 6,991,790 (Genentech)
  - 1. A method of treating a B cell lymphoma in a mammal, comprising administering a stable aqueous formulation comprising a therapeutically effective amount of *an antibody that binds CD20*, the antibody *not subjected to prior lyophilization*, an *acetate buffer* from about pH 4.8 to about 5.5, a surfactant and a polyol, wherein the formulation lacks a tonicifying amount of sodium chloride.
  - Rituxan® is an anti-CD20 antibody

Examples of Patents on Biologic Formulations

- US Pat. 7,276,477 (Amgen)
  - 1. A *crystal of etanercept* in the form of a needle or a rod.
  - 7. A method of making a crystal of etanercept, wherein the method comprises combining a solution of etanercept polypeptide with a *crystallization buffer* comprising a salt.

Examples of Patents on Biologic Formulations

- US 7,648,702 (Immunex)
  - 12. A stable pharmaceutical composition comprising from about 10 mg/ml to about 100 mg/ml *etanercept*, and further comprising *L-arginine, sodium phosphate, sodium chloride and sucrose*.

  - "suitable for long storage of polypeptides containing an Fc domain"

Examples of Patents on Biologic Formulations

- US Pat. 7,682,609 (Genentech)
  - 20. A formulation comprising a *lyophilized mixture of huMAb4D5-8* in an amount from 5-40 mg/ml, a *sugar* in an amount from 10-400 mM, a *surfactant* in an amount from 0.001-0.5%, and *histidine buffer*, wherein the pH of the formulation is 6.0.
    - "high protein concentration reconstitutable formulation for subcutaneous administration"
    - huMAb4D5-8 is Herceptin®

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Examples of Patents on Biologic Formulations

- US Pat. 7,132,100 (MedImmune)
  - 1. An aqueous *palivizumab* formulation comprising, in an aqueous carrier: (a) at least 40 mg/ml of palivizumab, or an antigen-binding fragment thereof; and (b) histidine, wherein said formulation is *substantially free of surfactants and inorganic salts*.
    - "formulations exhibit stability, low to undetectable levels of aggregation and very little or no loss of biological activities"

Examples of Patents on Biologic Formulations

- US Pat. 7,790,679 (Amgen)
  - 1. A stable aqueous sterile formulation comprising (a) *Darbopoetin* . . . or *erythropoietin* . . . or an erythropoietin analog . . . (b) a destabilizing concentration of benzyl alcohol . . . or benzalkonium chloride . . . and (c) glycerol . . . or trimethylamine N-oxide . . . or proline . . . *wherein the concentration of glycerol, trimethylamine N-oxide or proline mitigates the destabilizing effect of said benzyl alcohol or benzalkonium chloride.*

Examples of Patents on Biologic Formulations

- US 2011/0076273 (Genentech)
  - 1. A highly concentrated, stable pharmaceutical formulation of a pharmaceutically active *anti-CD20 antibody* comprising:
    a. about 50-350 mg/ml anti-CD20 antibody
    b. about 1 to 100 mM of a *buffering agent* providing a pH of 5.5 ±2.0;
    c. about 1 to 500 mM of a *stabilizer* or a mixture of two or more stabilizers;
    d. about 0.01 to 0.1% of a nonionic *surfactant*; and
    e. *optionally an effective amount of at least one hyaluronidase enzyme*

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Patentability Challenges

- Term of a U.S. patent = 20 years from the earliest effective filing date
  - Exception where pre-GATT filing

- To extend the length of patent coverage on a biological product, the formulation patent normally must have a later filing date than the original patents on the product

- Thus, the *original patent is usually prior art* to the later filed formulation appl.

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Patentability Challenges

- To obtain a patent on a new formulation of a biologic, applicant must show claimed formulation is *novel, nonobvious, etc.* over earlier patent to drug or biologic per se
  - Generally not difficult to show novelty
    - But must be careful regarding inherent anticipation
  - Focus is generally on obviousness

- *KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398* (2007)
  - Supreme Court "clarified" obviousness
  - Now easier for USPTO to establish *prima facie* case of obviousness and shift burden to applicant to prove otherwise

Patentability Challenges

- In response to *KSR* case, USPTO established training guidelines for examiners

- Identified acceptable "rationales" to support *prima facie* case of obviousness:

  A. Combining prior art elements according to known methods to yield predictable results

Patentability Challenges

- USPTO "Rationales" for Obviousness
  - B. Simple substitution of one known, equivalent element for another to obtain predictable results
    - E.g. one known excipient for another?
  - C. Use of known technique to improve similar products in the same way
    - Application of technique to similar product must be within ordinary skill in art
  - D. Applying a known technique to a known product ready for improvement to yield predictable results
    - E.g. lyophilization?
  - E. "Obvious to try" – choosing from a finite number of predictable solutions

Patentability Challenges

- *Ex parte Kaisheva* (BPAI 2010)
  - appeal from final rejection of claims to formulation of ZENAPAX for obviousness
  - Claims directed to a stable liquid pharmaceutical formulation comprising succinate buffer having a particular pH, polysorbate, sodium chloride, and a Daclizumab antibody
  - All claimed elements were in prior art
  - Applicants cited reference teaching stable formulations difficult to achieve in antibody art so no reasonable expectation of success

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Patentability Challenges

- HELD: rejection affirmed
  - Found claims directed to *known elements performing their known functions*
  - "Discovery of an *optimum value* of a result effective variable in a known process is ordinarily within the skill in the art."
  - *No evidence of unexpected results* with claimed pH parameters
  - Fact that formulation of Abs is *difficult does not necessarily mean nonobvious*
  - No reference to "remarkably" or "unexpected" within the specification

Patentability Challenges

- *Ex parte Matheus and Mahler* (BPAI 2011) (nonprecedential)
  - Appeal of rejection of claims to highly concentrated, liquid formulation of monoclonal antibody for obviousness and indefiniteness
  - Claims directed to process for preparing a highly concentrated, liquid formulation comprising Mab c225 or Mab h425 by ultrafiltration
  - Prior art disclosed clinical trial of cetuximab and reference teaching formulation of Abs by ultrafiltration

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Patentability Challenges

- HELD: rejection maintained
  - Rejected applicants characterization of invention as ready-to-use solutions having low viscosity and low application volumes, *since limitations not in claims*
  - Noted that *applicants had not established any particular problems with preparing a formulation of C225 with the requisite concentration*, or that they were required to proceed contrary to accepted wisdom
  - One of ordinary skill in art would have recognized *substitution of one known antibody for another as yielding predictable results*

Patentability Challenges

- *Ex parte Rhodes* (BPAI 2002) (nonprecedential)
  - Appeal from rejection of claims to vaccine formulation as being obvious
  - Claims directed to a vaccine formulation comprising an antigenic component and, as an adjuvant component, neuraminidase and galactose oxidase (NAGO)
  - Prior art taught that neuraminidase and galactose oxidase are immunostimulatory

Patentability Challenges

- HELD: rejections reversed
  - As of the date of invention, *only in vitro data* published concerning NAGO. In vivo effect was unknown
  - Applicants discovered that while NAGO produces a non-specific adjuvant response in vitro, it *produces the opposite response in vivo*, i.e., an antigen specific immune response
  - This *unexpected in vivo effect rendered claims nonobvious*

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Patentability Challenges

- Rebutting Obviousness Rejections
  - Submit technical evidence showing that subject matter claimed in later (improvement) patent could not have been predicted to work
  - Show that claimed subject matter (e.g. new formulation) has unexpected advantages (e.g., increased efficacy, stability, etc.)
  - Clinical studies provide good opportunities for patenting improvements, since in vivo effect are difficult to predict

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Lessons from ANDA Cases

- *Sandoz Inc. v. EKR Therapeutics, LLC – IPR2015-00005*
  - Inter Partes Review decision for US Pat. No 8,455,524
  - `524 patent relates to "ready-to-use premixed pharmaceutical compositions of nicardipine or a pharmaceutically acceptable salt and methods for use in treating cardiovascular and cerebrovascular conditions"
  - Concurrent ANDA litigation: *Chiesi USA, Inc. v. Sandoz Inc.*
  - CARDENE® I.V.
    - Originally injectable intravenous form marketed in glass ampules in a concentration that must be diluted in a compatible intravenous fluid before administration
    - Diluted solution only stable for 24 hours at room temperature.

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Lessons from ANDA Cases

- *Sandoz Inc. v. EKR Therapeutics, LLC – IPR2015-00005*
  - 1. A method for treating acute elevations of blood pressure in a human subject . . . comprising parenterally administering a ***pre-mixed aqueous solution comprising about 0.1 to 0.4 mg/mL nicardipine*** or a pharmaceutically acceptable salt thereof; a tonicity agent, and a buffer; wherein the aqueous solution ***requires no dilution before administration and has a pH from about 3.6 to 4.7***. . . the aqueous solution when stored in a container for ***at least three months*** at room temperature exhibiting (i) ***less than 10% decrease in concentration of nicardipine*** or pharmaceutically acceptable salt thereof and (ii) ***total impurity formation of less than about 3%.***

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Lessons from ANDA Cases

- *Sandoz Inc. v. EKR Therapeutics, LLC – IPR2015-00005*
  - Sandoz petitioned for IPR on grounds claims obvious over prior art
    - Ref 1 taught conventional use of CARDENE IV
    - Ref 2 taught prefilled syringe having little absorption of drug and mentioned nicardipine hydrochloride as potential drug
    - Ref 3 taught stable pharm. comp containing nicardipine hydrochloride, isotonicity agent, buffering agent and aqueous vehicle for parenteral admin.

Lessons from ANDA Cases

- *Sandoz Inc. v. EKR Therapeutics, LLC – IPR2015-00005*
  - Sandoz argued that combination of prior art teachings would necessarily result in claimed pH, concentration and impurity-formation limitations
  - PTAB held: IPR denied (Sandoz had not shown a reasonable likelihood at least one claim invalid as obvious)
    - no evidence dilution of concentrated CARDENE would necessarily result in claimed pH (evidence showed wide range possible)
    - rejected Sandoz argument that total impurity formation over time is an inherent property of drug and container in which it is stored
    - Petitioner needed to present sufficient evidence, either from prior art or through its own testing, to show that formulations prepared as suggested by the prior art would necessarily satisfy the functional limitations of the claims

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Case Study – Adalimumab

- US 6,090,382 discloses V_H and V_L for adalimumab
  - Filed Feb. 9, 1996
  - 20 year patent term: Feb. 9, 2016 expiration date (not including PTE)
- Approved for treatment of rheumatic diseases and is typically administered by subcutaneous injection at 40 mg every one or two weeks
- Supplied in glass vials, prefilled glass syringes and in autoinjection device (HUMIRA pen)
- US 8,216,583 discloses the commercial liquid formulations currently used for adalimumab
  - Filed August 15, 2003
  - Est. expiration date = August 16, 2022

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Case Study - Adalimumab

- `583 claims:
  - 1. A stable liquid aqueous pharmaceutical formulation comprising a human anti-Tumor Necrosis Factor alpha (TNFα) antibody, or antigen binding fragment thereof, at a concentration of between about 20 and about 150 mg/ml, a polyol, a surfactant, and a buffer system comprising citrate and phosphate, wherein said formulation has a pH of about 4 to about 8, and wherein [provides CDRs of V_L]

- US 8,420,081 (AbbVie) claims alternative formulation of adalimumab
  - 1. An aqueous formulation comprising an antibody, or antigen-binding fragment thereof, *at a concentration of at least about 20 mg/ml* and water, wherein the formulation has a *conductivity of less than about 2.5 mS/cm* and the antibody or antigen-binding fragment thereof, has a molecular weight (Mw) great than about *47kDa*.

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Case Study - Adalimumab

- As filed claims (which lacked concentration limitation) rejected as obvious over prior art patent appl. teaching a method for concentrating proteins (but not antibodies specifically) to produce a formulation having a conductivity of less than 2.5 mS/cm and another application teaching formulation of antibodies and water, including HUMIRA, at concentrations up to 250 mg/ml.
- Applicants amended claims to recite concentration of at least 20mg/ml and argued that main reference did not teach antibodies at all, much less at a concentration of at least 20 mg/mL
- Examiner maintained rejection
- Applicants further pointed to *challenges known in the art with respect to aqueous formulations of antibodies having high antibody concentrations* as no reasonable expectation of success
  - Prior art uses *ionic or ionizable excipients*
- Claims allowed

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Case Study - Adalimumab

- US 8,821,865 (AbbVie) claims alternative formulation of adalimumab
  - 1. A liquid aqueous formulation comprising: (1) 100 mg/ml of adalimumab; (2) 1.0 mg/ml of polysorbate-80; and (3) 42 mg/ml of mannitol;

    wherein the formulation has *a pH of 4.7 to 5.7* and *does not contain a buffer or a salt*, and wherein injection of the formulation into a human subject results in a *Pain Visual Analog Scale (VAS) score of less than 1.0*.
- Very broad claims as originally filed - not limited to adalimumab, specific surfactant or specific polyol.
- Claims rejected as obvious over earlier patent teaching adalimumab formulations generally and published application teaching antibody formulations comprising polysorbate and mannitol and a pain scale score of less than 1
  - Examiner said one of skill in the art would have been motivated to combine the references in order to stabilize the antibody formulation

Case Study - Adalimumab

- Applicants then amended claims to current form and argued against rejection on grounds that *prior art taught away from reducing pain by increasing the solution for injection, and degree of reduction in pain by present formulation was not reasonably expected*
- Claims allowed: “prior art does not teach or suggest specific concentrations or motivation to specifically select the concentration especially *in the absence of buffer or salt*.”

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Case Study - Adalimumab

- WO 2014/099636 (Merck Sharp & Dohme)
  - 1. A stable liquid aqueous pharmaceutical formulation comprising an anti-TNF antibody, a pH-buffered solution, sodium chloride, a stabilizer and a surfactant, wherein the anti-TNF antibody **is a biosimilar** form of adalimumab.
  - 2. The formulation of claim 1, wherein the anti-TNF antibody is a biosimilar form of adalimumab present at a concentration of between about 20 and about 120 mg/mL and more specifically between 40 and 100, even more specifically 45 to 55 mg/mL.
  - 3. The formulation of claim 2, wherein the buffer is selected from phosphate, phosphate and succinate, histidine and succinate.
- "The present invention provides stable liquid formulations for a fully human anti-TNF antibody referred to herein as biosimilar adalimumab, **which do not comprise a buffer system that includes a citrate buffer**."
- "Liquid formulations containing pH buffered solution at a pH of between about 5.4 to 5.6 comprising phosphate or a phosphate-succinate buffer species, sodium chloride, a stabilizer and a surfactant provide novel alternative liquid formulations for long-term storage of adalimumab-containing solutions."

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Conclusions

- Complexity and unpredictability of biologicals makes formulation patents particularly relevant
- Formulation patents are valuable tool for innovators to protect extend patent life-cycle on blockbuster biologics and hinder biosimilar competition
- FDA will look carefully at formulation of biosimilar products
- Techniques used to match reference product can create patenting opportunity for biosimilar developers

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Formulation Patents for Biologics

Thank You

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