CHALLENGES AND OPPORTUNITIES IN LIFE SCIENCES TODAY

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INTELLECTUAL PROPERTY DEVELOPMENTS

- Biosimilars – where are we?
- Antibody Protection and Enforcement
- New Developments in Second Medical Use Issues

BIOSIMILARS UPDATES

The Big Thing? The Next Big Thing?

- Europe: > 45 approved biosimilars as of the end of 2018; > 20 since 2017
- US: > 12 approved biosimilars as of the end of 2018; of those 8 approved in 2017 or 2018
- US: according to FDA commissioner Gottlieb, 2% of patients are being prescribed biologics, but > 40% of prescription drug costs are for biologics
  - Gottlieb –incentives in the US prescription drug supply chain – manufacturers, prescription benefit managers, group purchasing agents – to favor expensive biologics

BIOSIMILARS UPDATES

US Developments

- Legal / Regulatory Updates – US
  - Patent Right to Know Drug Prices Act (October 2018) – requires settlements to be disclosed to the Fair Trade Commission and the Department of Justice for Antitrust Review
  - Pending – Court challenge to the constitutionality of the Affordable Care Act (a/k/a “Obamacare”) which threatens BPCIA as part of that Act
    - Texas Court – unconstitutional
    - Fifth Circuit Court of Appeals – oral hearings last week

BIOSIMILARS UPDATES

Why is Europe Ahead of the US?

- EMA Biosimilars law went into effect in 2006; US BPCIA part of Affordable Care Act (“Obamacare”) in 2010; final regulatory guidance not until 2015
- US law – complex procedural framework which has resulted in protracted litigation over the “patent dance”
- US law – requirement of “interchangeability,” which has been interpreted to require clinical studies to show that the biosimilar and the reference drug can be safely and effectively interchanged with the same patient (so-called “transitioning studies”)

BIOSIMILARS UPDATES

Legal Cases to Watch

- Coherus v Amgen (DDel) – Coherus suing Amgen of violating process patents for manufacture of adilimumab (Humira):
  - Coherus challenging Amgen's Amgevita, which is approved in Europe
  - Coherus asserting "stable aqueous pharmaceutical composition of adalimumab," e.g.,
    - "a stable aqueous pharmaceutical composition comprising adalimumab, a buffer, polysorbate 80, and a sugar, wherein the composition is free of mannitol, citrate and phosphate buffer, and sodium chloride, and wherein the composition has a pH of about 5 to about 6"

BIOSIMILARS UPDATES

Legal Cases to Watch

- Neupogen/Nulasta cases – Amgen's filgrastim and pegfilgrastim (treatment for low blood neutrophils after chemo or in association with HIV and other conditions
- Amgen challenging Sandoz's Zarxio (filgrastim) and Coherus' Udenyca (pegfilgrastim) –cases are now on appeal to the Federal Circuit

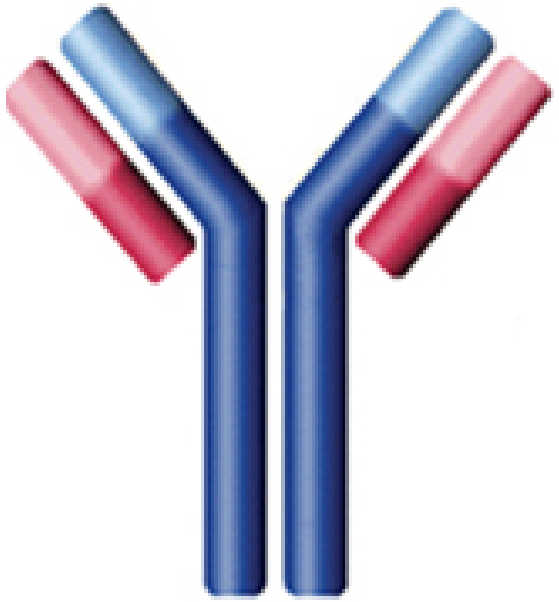
BIOSIMILARS UPDATES

Legal Cases to Watch

- AbbVie Humira settlement – being challenged in class actions alleging that settlements are anti-competitive
  - Settlement structure – different entry dates for different generics; earlier entry in Europe; delayed in US
  - highlights “patent thicket” problems in the US and elsewhere – AbbVie > 200 patents covering Humira

ANTIBODIES – WHAT CAN BE CLAIMED/PROTECTED?

- What can be claimed?
  - A specific antibody by its amino acid sequence?
  - The genus of antibodies that performs the function of binding to a specified antigen?



ANTIBODIES – WHAT CAN BE CLAIMED/PROTECTED?

United States

- Section 112 – “Written Description” Requirement
- Genus Claims – Written Description may be met through “disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad v. Lilly*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*)
- “novel, well-characterized antigen” (*Centacor,* 636 F.3d 1341 (Fed. Cir. 2011)) no longer fully sufficient – *Amgen v Sanofi*, 872 F.3d 1367 (2017)

INTELLECTUAL PROPERTY PROTECTION FOR ANTIBODIES

Recent Developments - Europe

- No “written description” requirement
- Key concepts – novelty and sufficiency (enablement)
- Current developments – state of protection
  - An Ab with the amino acid sequence….
  - An Ab that binds to specific antigen X….
  - An Ab that binds to antigen X and competes with antibody Y

INTELLECTUAL PROPERTY PROTECTION FOR ANTIBODIES

Recent Developments - US

- PCSK9 Antibodies – Repatha (Amgen) and Praluent (Sanofi/Regeneron)
- Amgen filed patent infringement suit in October 2014, seeking permanent injunction
- Sanofi/Regeneron acknowledged infringement
- March 2016 – jury trial - patents valid
- November 2016 – District Court orders permanent injunction
- January 2017 – Court of Appeals stays injunction and takes up appeal
- October 2017 – Court of Appeals affirms on obviousness; remands on written descriptiontrial –
- February 2019 – jury patents valid
- Pending – Request for permanent injunction

INTELLECTUAL PROPERTY PROTECTION FOR ANTIBODIES

Recent Developments - Europe

- Amgen v Sanofi and Regeneron – PCSK9 actions:
  - PCSK9 Antibodies – Repatha (Amgen) and Praluent (Sanofi/Regeneron)
  - June 2018 – Sanofi/Regeneron filed complaint for preliminary injunction / compulsory license (Case No. 4c O 39/16)
  - September 2018 – Dusseldorf Regional Court denied Sanofi/Regeneron request for provisional license
  - June 4, 2019 – on appeal, Federal Court of Justice (Case No. X ZB 2/19) rejected Sanofi/Regeneron Appeal, noting: (1) Sanofi/Regeneron did not demonstrate sufficient efforts to obtain a license; (2) not substantiated that Praluent offers any tangible benefits over Repatha, therefore no public interest in compulsory license
  - July 11, 2019 – Dusseldorf Regional Court issued order that (1) Sanofi/Regeneron infringe; (2) Sanofi/Regeneron failed to establish doubt for invalidity; and (3) injunction to be entered.

DEVELOPMENTS IN SECOND MEDICAL USE CLAIMS

- **Importance of Second Medical Use Protection**
- **Patentability**
  - Patentable Subject Matter
  - Obviousness/Novelty Challenges
  - Sufficiency/Plausability (Europe)
- **Infringement**
  - Skinny Labels
  - Induced Infringement

SECOND MEDICAL USE

Key Cases - Lyrica

- Lyrica – pregabalin – Pfizer and Warner Lambert
- Cases in UK, Germany, Netherlands, France and other European countries
- Issues vary by country, but some general background:
  - Patent disclosure focuses on inflammatory pain, but claims in certain countries cover all pain (including neuropathic pain)

SECOND MEDICAL USE

Key Cases – Lyrica - UK

- UK:
  - Generic label – only for treatment of seizures and anxiety disorders
  - Claims covering all pain (inflammatory and neuropathic) found invalid for insufficiency
  - Dicta/obiter – had the claims been valid, they would NOT have been infringed – mixed reasoning: label dictates? Label plus reasonable expectation of infringing uses?

SECOND MEDICAL USE

Key Cases – Lyrica - Germany

- Generics – skinny label – should have protected them under established German principles, which focus on the label rather than the intent or knowledge of the generic
- BUT – generics entered into “tender” (a/k/a rebate agreement) with insurer which was not limited to indication on skinny label
  - Pharmacists does not know indication for prescription
  - Act of substitution by pharmacist – infringement
  - Therefore, induced infringement

SECOND MEDICAL USE

Key Cases – Lyrica - France

- Swiss-type claims and no manufacture in France, therefore no direct infringement
- Skinny label
- No indirect infringement because information about potential uses widely available to health professionals; therefore not “induced” by Sandoz

SOME RECENT CASES

U.S. (New uses)

- *GlaxoSmithKline LLC v. Teva Pharm. USA, Inc.*, 313 F. Supp. 3d 582, 591-98 (D. Del. 2018) (Stark, J.) -carvedilol (granting JMOL of no infringement during skinny label (or full label) period, finding insufficient evidence of inducement *by Teva* and sufficient evidence of other factors influencing doctor's decisions – even in the face of A/B rating)(on appeal)
- *Grunenthal GMBH v. Alkem Labs. Ltd.,* 919 F.3d 1333, 1339-40 (Fed. Cir. 2019) (affirming district court's finding of no induced infringement where generic indication could include infringing and non-infringing treatment – for polyneuropathic pain (patented) or mononeuropathic pain (not patented))

DISCUSSION / QUESTIONS?