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Antibody Patenting After Amgen v. Sanofi: U.S. and European Perspectives

Meeting Written Description and Obviousness Requirements

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Topics

- Claiming antibodies in the U.S.: the statute, court decisions, and the USPTO
  - How much support is needed on filing?
  - How broadly can you claim?
- European Perspective on claiming antibodies
  - How much support to enable in Europe?
  - Higher inventive step bar than in the U.S.
  - Surprising results and plausible technical effects
- Additional considerations for antibody patenting
  - Prosecution History Estoppel
  - Equivalents in Europe
- Practical considerations for antibody patenting in the era of biosimilars
  - Goals in antibody patenting
  - Optimal timing for patent filings
  - Claim strategies

Claiming Antibodies in the U.S.:

the Statute, Court Decisions, and the USPTO

35 U.S.C. 112

(a) The specification shall contain a written description of *the invention*, **and** of the manner and process of *making and using it*, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, …

- Must enable
- Must provide written description?

The "Antibody Exception": USPTO Written Description Guidelines (2001)

- Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well-defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.
- **Conclusion**: The disclosure meets the requirement under 35 USC 112 first paragraph as providing an adequate written description of the claimed invention.

Enzo Biochem v. Gen-Probe (Fed. Cir. 2002)

- Background:
  - Not an antibody case, but sets the stage for later antibody cases.
  - Inventors identified certain sequences that selectively hybridize to *N. gonorrhoeae.*
  - Claims directed to a genus of nucleic acid probes, with dependent claims calling out particular probes by sequence.
  - Enzo deposited those sequences with the ATCC.
- District Court: claims invalid for lack of written description
  - Claims defined the probes only by their biological activity/function.
  - Not sufficient to satisfy the written description requirement.

Enzo Biochem v. Gen-Probe (Fed. Cir. 2002)

- Federal Circuit "dicta" on support for antibody claims:
  - USPTO Guidelines "are not binding on this court, but may be given judicial notice"
  - "For example, the PTO would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature."
  - "We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement."

Enzo Biochem v. Gen-Probe (Fed. Cir. 2002)

- Federal Circuit: reversed and remanded
  - Under USPTO Guidelines, the written description requirement would be met for all of the claims of Enzo's patent if the functional characteristic of preferential binding to *N. gonorrhoeae* were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed.
  - Remanded to the district court to apply that standard and determine whether the broader generic claims satisfy the written description requirement.
  - However, the Federal Circuit held that the deposit of biological material for the three named probes constituted an adequate description for claims directed to those probes.

Noelle v. Lederman (Fed. Cir. 2004)

- Appeal from USPTO *ex parte* examination
- Invention: anti-CD40 ligand antibodies
- Claims at issue:
  - Mouse antibodies
  - Human antibodies
  - Monoclonal antibodies
- Specification:
  - Only disclosed mouse antibodies

Noelle v. Lederman (Fed. Cir. 2004)

- USPTO:
  - Genus and human claims unpatentable for lack of written description
- Federal Circuit: affirmed
  - Acknowledged that in *Enzo* the court "adopted the USPTO guidelines as persuasive authority for the proposition that a claim directed to any antibody which is capable of binding antigen X would have sufficient support in a written description that disclosed *fully characterized antigens*."
  - "as long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

Noelle v. Lederman (Fed. Cir. 2004)

- Federal Circuit: (continued)
  - But because the specification characterized only the mouse CD40 ligand, the human and genus claims lacked written description support.
  - "If Noelle had sufficiently described the human form of [CD40 ligand], he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen."

Ariad v. Lilly (Fed. Cir. 2010)

- Another non-antibody case, but sets the stage for Supreme Court appeal in *Amgen v. Sanofi*
- Ariad's patent included broad genus claims covering "the use of all substances that achieve the desired result of" inhibiting NF-κB activity.
- Although the specification recited the desired functional goal, Ariad's patent did not disclose any "working or even prophetic examples of methods that reduce NF-κB activity, and no completed syntheses of any of the molecules prophesized to be capable of reducing NF-κB activity."
- Ariad argued section 112 only required sufficient description of how to screen for inhibitors of NF-κB activity (i.e., how to "make and use" the claimed invention), which the patent provided

Ariad v. Lilly (Fed. Cir. 2010)

- Federal Circuit held *en banc* that § 112 contains both a written description requirement and an enablement requirement because a contrary interpretation would read words out of the statue and disregard precedent
- Although Ariad's specification used the same broad functional language as in the claims (*ipsis verbis* support), it disclosed only hypothetical methods – i.e., it described a problem—not a solution.
- With a genus claim, it is not enough to describe the boundaries; rather the patent must disclose "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"

Centocor v. Abbott (Fed. Cir. 2011)

- Claims at issue (U.S. Pat. No. 7,070,775):
  - An anti-TNF-α antibody comprising a human constant region, that
    - (i) competitively inhibits binding of [a particular antibody] to human TNF-α, and
    - (ii) binds with an affinity of at least $1x10^8$ liter/mole.
  - The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises a ***human constant region*** and a ***human variable region.***

Centocor v. Abbott (Fed. Cir. 2011)

- Patentee lacked possession of antibodies with human variable regions
  - Centocor disclosed mouse and chimeric antibodies only
  - "the written description requirement does not demand either examples or an actual reduction to practice. What it does demand is that one of skill in the art can 'visualize or recognize' the claimed antibodies based on the specification's disclosure."
  - "Centocor simply failed to support its contention that generating fully-human antibodies with the claimed properties would be ***straightforward*** for a person of ordinary skill in the art given the state of human antibody technology in 1994."
- In contrast, the court explained that "written description . . . can be satisfied by disclosing a well-characterized antigen, for newly characterized antigens, where creation of the claimed antibodies is routine"

AbbVie Deutschland v. Janssen (Fed. Cir. 2014)

- The Product:
  - Stelara® (ustekinumab), an IL-12 antibody indicated for the treatment of adults with moderate-to-severe plaque psoriasis.
- Representative Claim:
  - A neutralizing isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and disassociates from human IL-12 with a K_{off} rate constant of $1x10^{-2}$ s^{-1} or less, as determined by surface plasmon resonance.
- The specification taught ~300 fully human antibodies that bind and neutralize IL-12
  - All disclosed Abs have variable regions with at least 90% amino acid similarity to one starting Ab
  - More than 200 of the disclosed antibodies differed by only a single amino acid residue (99.5% similarity in variable regions).

AbbVie Deutschland v. Janssen (Fed. Cir. 2014)

- Stelara® met the functional claim limitations:
  - fully human
  - anti-IL-12
  - neutralizes IL-12 activity
- But was structurally distinct from antibodies in the patent:

	Stelara	J695	Joe-9
Sequence Similarity	50%	90%	90%
CDR Length	Different	Identical	Identical
Epitope Binding Site	Side Binder	Bottom Binder	Bottom Binder
V_H Family	V_H5	V_H3	V_H3
Light Chain Type	Kappa	Lambda	Lambda

AbbVie Deutschland v. Janssen (Fed. Cir. 2014)

- What is sufficient description of a genus?
  - "AbbVie's patents need not describe the alleged infringing Stelara in exact terms."
- No prohibition of functional limitations:
  - if a **reasonable structure-function correlation** is established;
  - or if **representative examples** are provided.
- But "merely drawing a fence around a perceived genus is not a description of the genus. One needs to show … that one has conceived and described sufficient representative species encompassing the breadth of the genus."
- "AbbVie's patents only describe one type of structurally similar antibodies and [] those antibodies are not representative of the full variety or scope of the genus."

Daiichi Sankyo v. Alethia (IPR2015-00291)

- Representative claim:

  A method of ***impairing osteoclast differentiation*** in a mammal in need thereof, the method comprising administering an antibody or antigen binding fragment which ***specifically binds*** to human Siglec-15 (SEQ ID NO:2) or murine Siglec-15 (SEQ ID NO:108) to said mammal.
- Issue: Are claims entitled to priority date?
- Parent application disclosed:
  - Siglec-15 protein sequence as a potential target
  - assay for screening potential inhibitory compounds
  - conventional methods of producing antibodies
- Parent application did NOT disclose:
  - epitopes/unique antigenic regions of Siglec-15
  - working examples of a Siglec-15 antibody having the claimed ***functional properties***

Daiichi Sankyo v. Alethia (IPR2015-00291)

- PTAB found inadequate written description and enablement
  - Distinguished from antibody exception cases because claims at issue contain a ***functional limitation***
  - Citing *Centocor*, found that full characterization of the antigen (Siglec-15) did not suffice to provide adequate written description support for a Siglec-15 antibody that also produces a desirable biological result

Amgen v. Sanofi (Fed. Cir. 2017)

- Amgen owns two patents directed to anti-PCSK9 antibodies
  - PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to receptors for low-density lipoprotein
- Claims recite isolated monoclonal antibodies that bind to specific residues on PCSK9 and thereby block interaction with LDL receptors
- Examples in the specification provide testing data on the epitope contact residues of two antibodies that prevent LDLR signaling, as well as competitive binding experiments used to “bin” a series of additional antibodies based on epitope binding

Amgen v. Sanofi (Fed. Cir. 2017)

- Amgen sued Sanofi for marketing an anti-PCSK9 antibody (Praluent™) used in treating high cholesterol
- Sanofi argued the claims were invalid for lack of written description and enablement because they covered a large genus of antibodies without providing sufficient examples or a structure-function correlation for antibodies targeting the claimed epitope, including the structure of Praluent™
- Amgen argued the claims were analogous to the "antibody exception"
  - discovered a newly characterized epitope "sweet spot" that effectively disrupts PCSK9 signaling

Amgen v. Sanofi (Fed. Cir. 2017)

- CAFC held that the "newly characterized antigen" test "flouts basic legal principles of the written description requirement"
  - District court had instructed jury that "the correlation between structure and function may also be satisfied by the disclosure of a newly characterized antigen … if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine"
- CAFC stated that previous cases recognized an antibody exception only in dicta and provided "extremely limited" precedential value
  - Analyzed *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), and *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341 (Fed. Cir. 2011).
  - Concluded the cases conflicted with *Ariad*'s requirement for representative examples or a structure-function correlation
  - reiterated separate WD and enablement standards

Amgen v. Sanofi (Fed. Cir. 2017)

- Remanded because jury did not hear Sanofi's post-priority-date evidence on **written description**
  - Praluent's structural differences from the antibodies in the patent
  - CAFC: while "written description is judged based on the state of the ***art as of the priority date***," citing *Ariad*, "[e]vidence showing that a claimed genus does not disclose a ***representative number of species*** may include evidence of species … [that] ***postdate the priority date***"
  - CAFC stated this was implicit in *AbbVie Deutschland v. Janssen* when considering the difference between the JOE-9 Abs and Stelara®
- Likewise, for **enablement**, Sanofi can introduce evidence of the differences between Praluent and other post-priority date antibodies
  - CAFC: allowed if offered to show the "lengthy and potentially undue experimentation" required to identify Praluent and other antibodies across the full scope of the claims rather than to show a "change in the state of the art"

Conclusions from Amgen v. Sanofi

- Court rejects the antibody exception to the written description requirement
- Holds that identifying an epitope is not, by itself, enough to satisfy the written description requirement
  - How much additional data would be enough?
  - Note that the claims here also had a function (blocking LDL-R signalling), not just that they bound the epitope
- Confirms that pre- and ***post-filing*** evidence can be considered in assessing written description and enablement

USPTO Guidance Based on Amgen v. Sanofi

- Memorandum to the Examining Corps, issued in response to *Amgen*, explained that the March 25, 2008, Written Description Training Materials "should **not** be relied upon as reflecting the current state of the law regarding 35 U.S.C. §§ 101 and 112." (Feb. 22, 2018, Memorandum to Examining Corps, 2 (emphasis in original)
- "In view of the *Amgen* decision, adequate written description of a newly characterized antigen alone should not be considered adequate written description of a claimed antibody to that newly characterized antigen, even when preparation of such an antibody is routine and conventional."
- Rather, Examiners should apply the conventional tests for written description spelled out in *Ariad*.

Amgen Cert. Petition

- "§ 112(a) requires 'a written description of the invention, and of the manner and process of making and using it.' It thus requires a single written description covering two topics. The Act provides a single standard for evaluating that written description: It must be 'in such full, clear, concise, and exact terms as to enable' those skilled in the art to practice the invention. The Federal Circuit, however, has split the written-description requirement into 'enablement' and 'written-description' requirements, holding that the former is governed by the statutory standard but the latter is not. The Court's rationale for that result is grammatically impossible. And it has the bizarre effect of leaving § 112(a) with no standard for evaluating written description of the invention." Cert. Petit. at 17.

Amgen Cert. Petition

1. Section 112(a)'s grammatical structure makes that inescapable. It imposes the requirement of "a written description," followed by three sequential prepositional phrases ([1]-[3] below):

> The specification
>
> [A] *shall* contain *a written description*
>
> [1] *of* the invention, and
>
> [2] *of* the manner and process of making and using it,
>
> [3] *in* such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains * * * to make and use the same * * * .

Amgen Cert. Petition

- "Having unmoored itself from § 112(a)'s standard, the court created a standard of its own. '[W]ritten description of the invention,' the court declared, requires inventors to demonstrate 'possession of ' the invention 'as of the filing date.' … But that 'proof the inventor had possession' standard is nowhere in §112(a)—or this Court's written-description precedent. The Federal Circuit has added further sub-tests (e.g., the 'representative-species' test, 'structure-function' test, and 'common-structural-features' test). Those sub-tests have no more basis in § 112 than the 'possession' standard. With no anchor in statutory text, they have proved unstable and uncertain." Cert. Petit. at 17

Amgen Cert. Petition

- "This case sets that instability [of a judicially-created test] in stark relief. The jury instructions on the 'possession' sub-tests were lifted from 15 years of Federal Circuit precedent. … On appeal, the Circuit changed its mind; eliminated one of its own tests as inconsistent with its current view of its 'possession' standard … ." Cert. Petit. at 4.

- "The decision below upset a second line of precedent, again based on the 'possession' sub-tests. Validity generally is determined based on the state of the art on the patent's 'priority date.' … In the decision below, the Federal Circuit reversed course on that issue, too. … Infringing embodiments developed after the priority date, the court ruled, might show the disclosed examples are not sufficiently 'representative.' … That ruling does not merely represent a second upheaval in the law. It makes patent protection transient." Cert. Petit. at 30-31.

Amgen Cert. Petition

- Timeline
  - Sanofi's respondent brief opposing the grant of cert. is due November 19, 2018
  - Next Supreme Court conferences are December 7, 2018 and January 4, 2019.
  - Average time to decision on cert. petitions: 6 weeks

Sanofi-Aventis v. Immunex (C.D. Cal. 2017)

- Re-run of the Amgen suit on PCSK9 antibodies?
  - Declaratory judgment plaintiffs are Sanofi and Regeneron, patent assigned to Immunex, which Amgen acquired.
- DJ complaint filed on March 20, 2017, based on US 8,679,487
  - Seeking declaration that anti-IL4 eczema drug Dupilumab does not infringe an Amgen patent on anti-IL4 antibodies claimed by epitope
  - Alleges that Amgen would be misusing a patent intended to cover one specific anti-IL4 antibody (AMG-317) that “failed” in phase 2 clinical trials for asthma

Sanofi-Aventis v. Immunex (C.D. Cal. 2017)

- Amgen's '487 patent claims antibodies that compete for binding with AMG-317:

1. An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) [sic] receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.

Sanofi-Aventis v. Immunex (C.D. Cal. 2017)

- Specification discloses several antibodies sequences and mentions (but does not identify) antibodies that compete for binding
- Sanofi argues that "the activity of the 'antibody' recited in the claims of the '487 Patent is described in purely functional terms … based on a desired result, *i.e.*, 'compet[ition]' for binding to the IL-4 receptor."
  - Sanofi therefore construes the functional claims as inherently limited to the disclosed antibody sequences
  - 35 USC 112, sixth paragraph

Sanofi-Aventis v. Immunex (PTAB 2017)

- In 2017, Sanofi filed three IPR petitions against the ’487 Patent
- The first petition challenged the ’487 patent’s entitlement to priority (IPR2017-01129)
  - Intervening art disclosed a human antibody that binds IL-4R
  - The PTAB denied institution in October 2017, pointing to inconsistent claim construction positions adopted in district court and in the IPR petition with respect to whether the term “antibody” imports “means plus function” language under 35 USC 112, sixth paragraph, into the claim

Sanofi-Aventis v. Immunex (PTAB 2017)

- Sanofi filed two subsequent IPR petitions in 2017 and both were instituted:
  - The first argued anticipation by art describing a fully human anti-human IL-4 receptor antibody shown to compete (IPR2017-01879)
  - The second argued obviousness over art teaching an anti-IL4R antibody that inherently competes for binding and humanization techniques applicable to that antibody (IPR2017-01884)
- The Board declined to exercise its discretion under Section 314 to deny institution of the subsequent petitions
  - The Board accepted Petitioner's argument that it only realized additional prior art would apply against the claims of the '487 patent once Amgen "endorsed" particular assays to use in evaluating whether a given antibody "competes for binding" in a November 2016 filing in a related EPO proceeding
- Combined oral arguments for both instituted cases are schedule for November 14, 2018.

How Broadly to Claim and How Much Support?

EPO Requirements

MATHYS & SQUIRE
INTELLECTUAL PROPERTY

Claiming Antibodies at the EPO

- How much data is needed in the application as filed?
- When can post-filing data be used?

- No written description requirement
- Enablement/sufficiency of disclosure
  - Can the invention as claimed be carried out across the scope of the claims?
- Inventive Step
  - Does your argument for inventiveness apply to substantially all the claimed embodiments?

Enablement/Sufficiency at the EPO

- Methods for producing, modifying, humanizing antibodies are all considered routine
  - If the antibody target is provided, then most new antibodies against that target will be considered enabled
- If the antibody is defined using further functional features or effects, then further information may be needed
  - Does the application explain how to obtain/screen for those features/effects?
  - Is it at least plausible that antibodies across the scope of the claims, having those features or effects, could be produced?
  - If a therapeutic use of the antibody is claimed, then is it plausible from the application as filed that the therapy would be achieved across the scope of the claim?
- Post-filing data can only be used to confirm what was already at least plausible from the application as filed

Inventive Step at the EPO

- Problem and solution approach
  - What is the difference between your invention and the closest prior art and what problem does that difference solve?
- Invention based on new antigen/target
  - If your antigen is new, you may get a broad claim at the EPO to any antibody that specifically binds that antigen
  - Inventive step derives from the new antigen
- Invention based on new antibodies to a known target
  - More difficult…

Obviousness of Antibodies

- EPO makes a number of assumptions about antibodies
  - Antibody structure/function relationships well known
  - Methods for producing, modifying, humanizing etc. all considered routine
  - Routine antibody production methods allow production of large numbers of antibodies against a given target

- *"**Methods to obtain** monoclonal antibodies, including human, chimeric or humanized monoclonal antibodies, directed against every well-known and defined antigen, **and to screen** said antibodies in order to select those presenting specific characteristics are considered **routine in the art**"*

Structural Non-Obviousness?

EP 2297206 (Eli Lilly)

- Preliminary opinion of Board of Appeal
  - *"the skilled person starting from the closest prior art … faced the technical problem of providing additional monoclonal anti-CXCR-4 antibodies useful for treating diseases in which pathogenesis is mediated by CXCR4 and SDF-I … and having knowledge of how to prepare such antibodies … would have been motivated to apply those known techniques to arrive at antibodies that solve the technical problem in an obvious manner.* ***All such antibodies would therefore have been obvious*** *to the skilled person, the claimed antibody being one of many potential anti-CXCR-4 antibodies,* ***each of which representing an obvious solution to the technical problem***."
- Structural non-obviousness is usually not enough for an antibody against a known target

Unexpected Properties

- New or improved activity
- Improved affinity
- Cross-reactivity
- Low immunogenicity

- Pharmacokinetic properties
- Expression level
- Stability in solution
- Reduced toxicity *in vivo*

Unexpected Properties

EPO Case Law - T 2045/09

"An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3"

- Claim lacked an inventive step – obvious to target any part of the complex
  - *"there is **no evidence** before the board that the anti-ErbB3 antibodies of the present invention have **superior activities** in reducing the heregulin-induced ErbB2 activation compared to the anti-ErbB2 antibodies disclosed in the closest prior art document"*

Unexpected Properties

EPO Case Law - T 2045/09

"An antibody which binds to ErbB3 protein and (i) reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell which expresses ErbB2 and ErbB3, and (ii) reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3, and (iii) increases the binding affinity of heregulin for ErbB3 protein"

- Claim allowed
  - unexpected that the anti-ErbB3 antibodies would **increase** the binding affinity of heregulin for ErbB3, rather than inhibiting/interfering with its binding

Are Some Advantages Better Than Others?

- "*The skilled person with a knowledge of* [other antibodies against the same target] *and intent on producing further antibodies would produce a mixture of antibodies with different properties and select them according to their functionality or affinity, depending upon the intended application*"

- A "better" antibody against a known target might not be patentable at the EPO

EP 1957106 Opposition (Labrys)

"An anti-CGRP antagonist that is a human antibody or a humanized antibody with a binding affinity (KD) to human alpha-CGRP of 50 nm or less as measured by surface plasmon resonance at 37°C"

- Making and selecting high affinity antibodies was obvious over known antibodies against that target - lack of inventive step

- Amendment to **specify epitope sequence** did not fix the problem
  - *"…the specific selection of amino acids 25-37 of alpha-CGRP is considered arbitrary in the absence of data proving that said selection leads to a particular, unforeseeable technical effect"*
- Amendment to **specify VH and VL sequences** did not fix the problem
  - *"The particular antibody … in the absence of any particular technical effect which could not be derived from prior art, lacks inventive activity."*
- Amended to **medical use** claim – for use in the prevention or treatment of headache
  - Claim upheld as an inventive new use

Scope of the Claims

- An unexpected advantage which gives an inventive step must be one which can be **fairly assumed to be produced by substantially all the claimed embodiments**
  - If you are relying on an advantage for your inventive step, your claim can only cover the antibodies that would share that advantage

- *"…inventive step could only be acknowledged for an antibody which would have a technical effect that sets it apart from the … antibodies of the prior art.* ***Such an antibody would however have to be defined by the structural features which are responsible for achieving this particular effect****, i.e. the sequences of all its six CDR regions in the structural context of its corresponding framework regions which are well known in the art to provide the correct conformation of the CDRs and have a significant effect on the antibody's affinity."*

Unexpected Properties

EPO Case Law - T 2045/09

*"An antibody **which binds to the epitope bound by** the 8B8 antibody obtainable from the hybridoma cell line ATCC no. HB-12070"*

- Claim enabled
  - *"The declaration indeed emphasises that several months would be necessary to produce these antibodies, but acknowledges (i) that nothing else than standard technology would be required for their production … and (ii) that the skilled person would be able to achieve this task … In the board's view while this evidence may demonstrate that the preparation of antibodies binding to the epitope of the 8B8 antibody is time-consuming, it does not show that the amount of time needed for their generation is so high that they could only be produced with undue burden"*
- Claim inventive
  - Surprising properties of 8B8 expected to be present in other antibodies binding the same epitope

Supporting the Scope of the Claims

- Which characteristics of your antibody are responsible for the advantage that you rely on?
- Which variations would the skilled person expect to retain the advantage?
  - Variations in particular parts of the molecule
  - Particular types of variation (e.g. conservative substitution)
- Include specific description of these characteristics and variations in your application as filed
- Post-filing evidence can only be taken into account if it is **already plausible from the disclosure in the application as filed** that the problem is solved
  - When drafting, think carefully about the evidence or statements that should be included to support this

Support and Post-Filing Data

EPO Case Law - T 488/16

- "Compounds described in the following Examples have been tested in one or more of these assays, and have shown activity"
  - claimed 1 of 580 compounds, supported by post-filing data
- "*a mere verbal statement that "compounds have been found active" in the absence of any verifiable technical evidence is not sufficient to render it credible that the technical problem is indeed solved*" – particularly "*where the invention is directed to a very broadly defined class of compounds encompassing millions of structurally rather different candidates with unknown properties*"
- "*If, as in the present case, the nature of the invention is such that it relies on a technical effect, which is* ***neither self-evident nor predictable or based on a conclusive theoretical concept, at least some technical evidence is required*** *to show that a technical problem has indeed been solved*"
  - Post-filing data not taken into account, claims lacked an inventive step

Support and Post-Filing Data

EPO Case Law - T 1243/12

- Combination of rituximab and methotrexate for treating RA
- Patentee argued for unexpected synergy and relied on post-filing data
- Board of Appeal:
  - effect cannot be taken into account if it could not be deduced by the skilled reader of the application as filed
    - nothing in the application as filed suggested synergy
    - post-filing data not taken into account
  - closest prior art described other combination RA therapies using methotrexate
  - rituximab was a new RA agent so was obvious to try

EPO Conclusions

- Becoming more difficult to establish an inventive step for a new antibody against a known target
  - Structural non-obviousness unlikely to be enough
  - Need some kind of unexpected advantage or effect
- Scope of the claims should match the technical contribution that had been made plausible at the filing date
- How much data in the application?
  - Enough to make it plausible that the effect can be achieved
  - Enough to give a technical reason why it might work across the claims
- Post-filing data not considered if it looks like you hadn't made the invention at the filing date

Additional Considerations in Antibody Patenting: Prosecution History Estoppel

Prosecution History Estoppel

Biogen v. GSK (Fed. Cir. 2013)

- Takeaway: Obtaining antigen or epitope claims can be difficult, increasing the risk that broad claims may be narrowed by prosecution history
- Biogen owns US Patent No. 7,682,612, which claims the administration of a generic anti-CD20 antibody to treat Chronic Lymphocytic Leukemia
- During prosecution of the ’612 patent, the Examiner rejected the claims for lack of enablement, arguing the specification only disclosed treating with rituximab rather than any other suitable antibody ***having the same epitope and specificity***
  - Biogen overcame the rejection by arguing that “one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN®.”
  - Biogen did not contest the Examiner’s implicit interpretation of the claim to require an antibody ***having the same epitope and specificity*** as rituximab

Prosecution History Estoppel

Biogen v. GSK (Fed. Cir. 2013)

- After obtaining the ’612 patent, Biogen sued GSK for marketing Arzerra®, another anti-CD20 antibody, to treat CLL
  - Arzerra® has higher affinity than rituximab and binds a different epitope
- GSK argued that Biogen limited the claims of the patent during prosecution to “rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab” by not contesting the Examiner’s claim construction when responding to the enablement rejection

Prosecution History Estoppel

Biogen v. GSK (Fed. Cir. 2013)

- The CAFC agreed that Biogen had limited their claims by PH estoppel
  - In response to the enablement rejection, "rather than challenging the examiner's understanding of the crucial terms, the applicants argued that the specification was enabling for anti-CD20 antibodies with similar affinity and specificity as Rituxan®."
  - "If an applicant chooses, she can challenge an examiner's characterization in order to avoid any chance for disclaimer, but the applicants in this case did not directly challenge the examiner's characterization."
  - "While disavowing statements must be 'so clear as to show reasonable clarity and deliberateness,' this requirement does not require the applicant to parrot back language used by the examiner when clearly and deliberately responding to a particular ground[] for rejection."

Prosecution History Estoppel in Europe

- Different EP courts take different views
  - Some take no notice of prosecution file
  - Some will take into account clear statements made by applicant
  - UK Supreme Court in Actavis v Lilly (2017): refer to the file wrapper only where:
    - the point at issue is truly unclear from the patent itself and the contents of the file unambiguously resolve the point, or
    - it would be contrary to the public interest for the contents of the file to be ignored

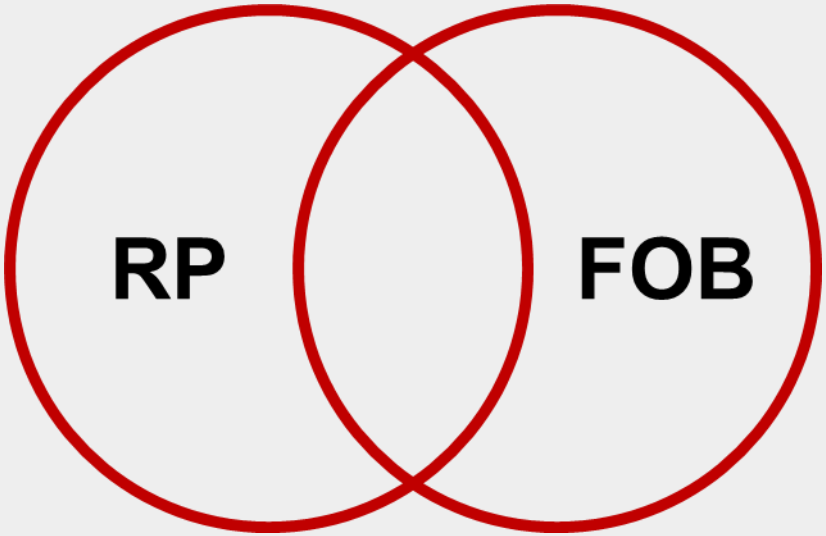
Additional Considerations in Antibody Patenting: Practical Considerations in the Biosimilars Era

Antibody Landscape

- Two types of potentially infringing antibodies:
  - "Me too" antibodies that target the same antigen as the reference-listed product
  - Biosimilar antibodies that "copy" the reference-listed product
- For "me too" antibodies:
  - The "me too" sponsor is motivated to challenge broad claims that broadly cover multiple antibodies to the same target
  - The patent owner wants claims broad enough to protect such antibodies while not running afoul of patentability requirements
- For biosimilar antibodies:
  - Follow-on biologic applicant wants a molecule that FDA will consider "biosimilar" but will not infringe a claim
  - Patent owner wants claims broad enough to cover all possible "design arounds" that will be considered biosimilar

Hypothetical

- RP = reference product
- FOB = follow-on biologic (me-too or biosimilar)



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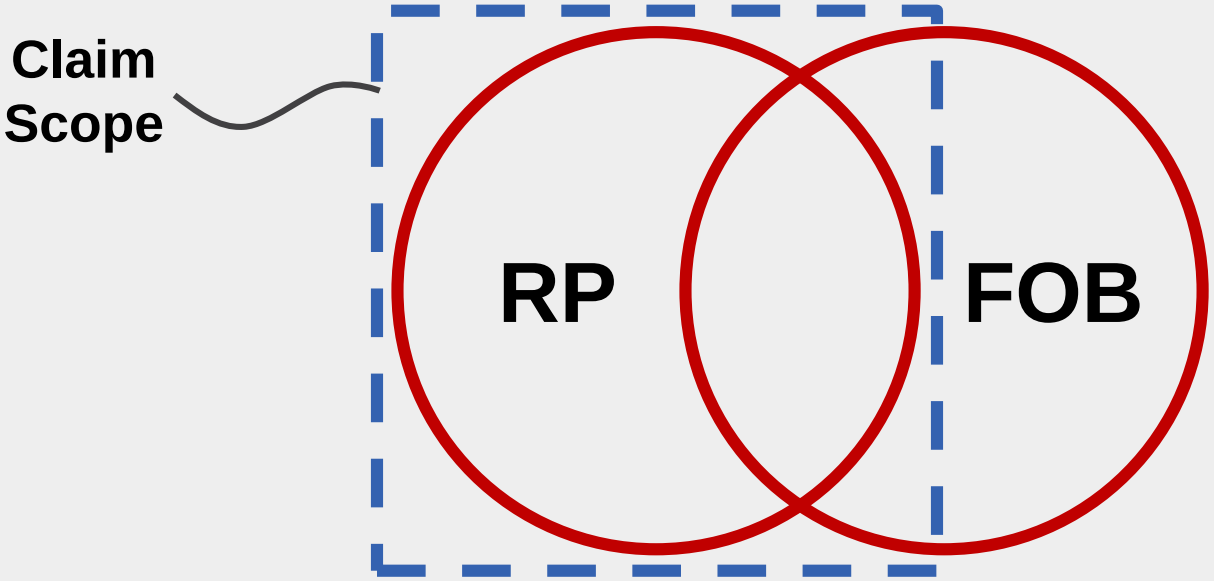
Hypothetical

- "Picture claim" to RP



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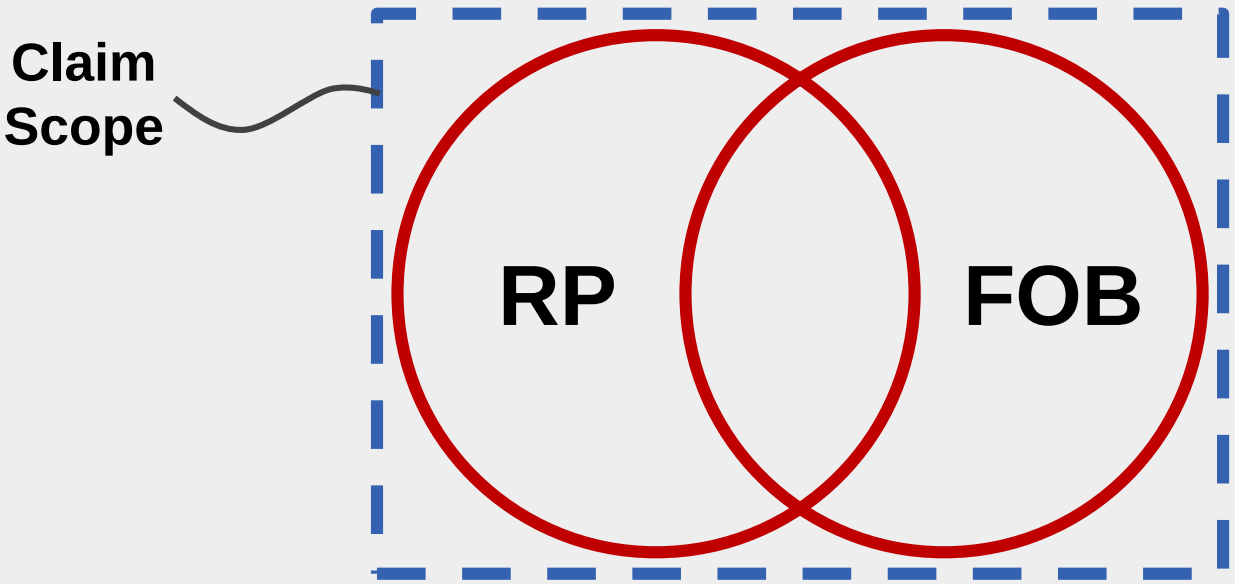
Hypothetical

- Generic claim that covers both RP and FOB



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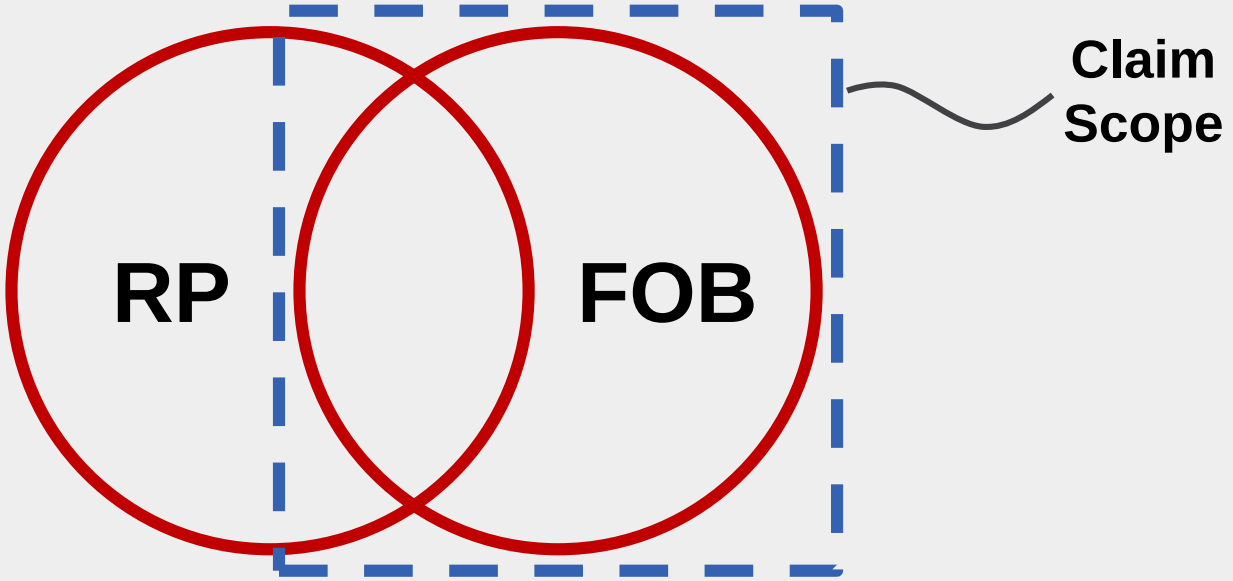
Hypothetical

- Blocking claim directed to FOB



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Types of Antibody Claims

- Antibody target
- Epitope binding sequence
- Antibody sequence
- Competitive binding
- Functional activities
- Method of treatment
- Combinations
- Formulations / Dosage / Dosing regimens
- Patient Selection
- Manufacturing methods

FDA Biosimilars Guidance

- FDA will consider these factors in evaluating biosimilarity:
  - Reference Product and Reference Standard (antibody sequence)
    - "In general, FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product. However, minor modifications such as N- or C-terminal truncations that will not affect safety and effectiveness may be justified and should be explained by the sponsor."
  - Receptor Binding and Immunochemical Properties (epitope)
    - "Three types of assays are of particular importance for biosimilar product development: ligand binding assays, concentration and activity assays, and PD assays. … Assays that rely upon antibody reagents and ***epitopes involved in pharmacological/biochemical interactions*** with targets are most likely to produce concentration data that are meaningful for target binding activity."

FDA Biosimilars Guidance

- FDA will consider these factors in evaluating biosimilarity:
  - Assessment of Physiochemical Properties (antibody structure)
    - "[I]t will be important to understand the heterogeneity of the proposed biosimilar product and the reference product (*e.g.*, the nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from post-translational modifications."
  - Expression System (manufacturing methods)
    - "Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered because the type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities (including potential adventitious agents) that may be present in the protein product."

FDA Biosimilars Guidance

- Epitope information required for a biosimilar?
  - "Three types of assays are of particular importance for biosimilar product development: … Assays that rely upon antibody reagents and ***epitopes involved in pharmacological/biochemical interactions*** with targets are ***most likely*** to produce concentration data that are meaningful for target binding activity."
  - *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*, FDA Guidance for Industry, December 28, 2016
- If RP manufacturer cannot/will not pursue epitope claims, consider keeping that information a trade secret

FDA Biosimilars Guidance

- FDA will also consider these factors in evaluating biosimilarity:
  - Manufacturing Process
  - Functional Activities
  - Impurities
  - Finished Drug Product
  - Stability

EMA Biosimilars Guidance

- Specific EMA guidelines on biosimilars containing monoclonal antibodies
  - comparative *in vitro* studies to assess differences in binding or function are required
  - determine whether *in vivo* non-clinical work is needed
  - comparative clinical studies between biosimilar and reference product are required
    - pharmacokinetics, pharmacodynamics/clinical efficacy, clinical safety
- "…for an active substance that is a protein, the amino acid sequence is expected to be the same…"
- "…changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach…"

Equivalents in Europe

- Many European courts increasingly willing to extend scope of protection to "immaterial" variants
  - If the difference between your claim and another antibody isn't something that you would expect to be essential to "the invention", then it may be considered an infringing equivalent
- UK Supreme Court in Actavis v Lilly (2017)
  - Claim was limited during prosecution to just the disodium salt of pemetrexed
  - Directly infringed by pemetrexed dipotassium because the choice of salt wasn't critical to the inventive concept and the dipotassium salt would be expected to work in the same way as the disodium salt
- May be useful to Patentee for blocking biosimilars
- New risks for FTO – be aware that a specific feature in a claim might not be limiting

Antibody Patenting:

Best Practice Recommendations

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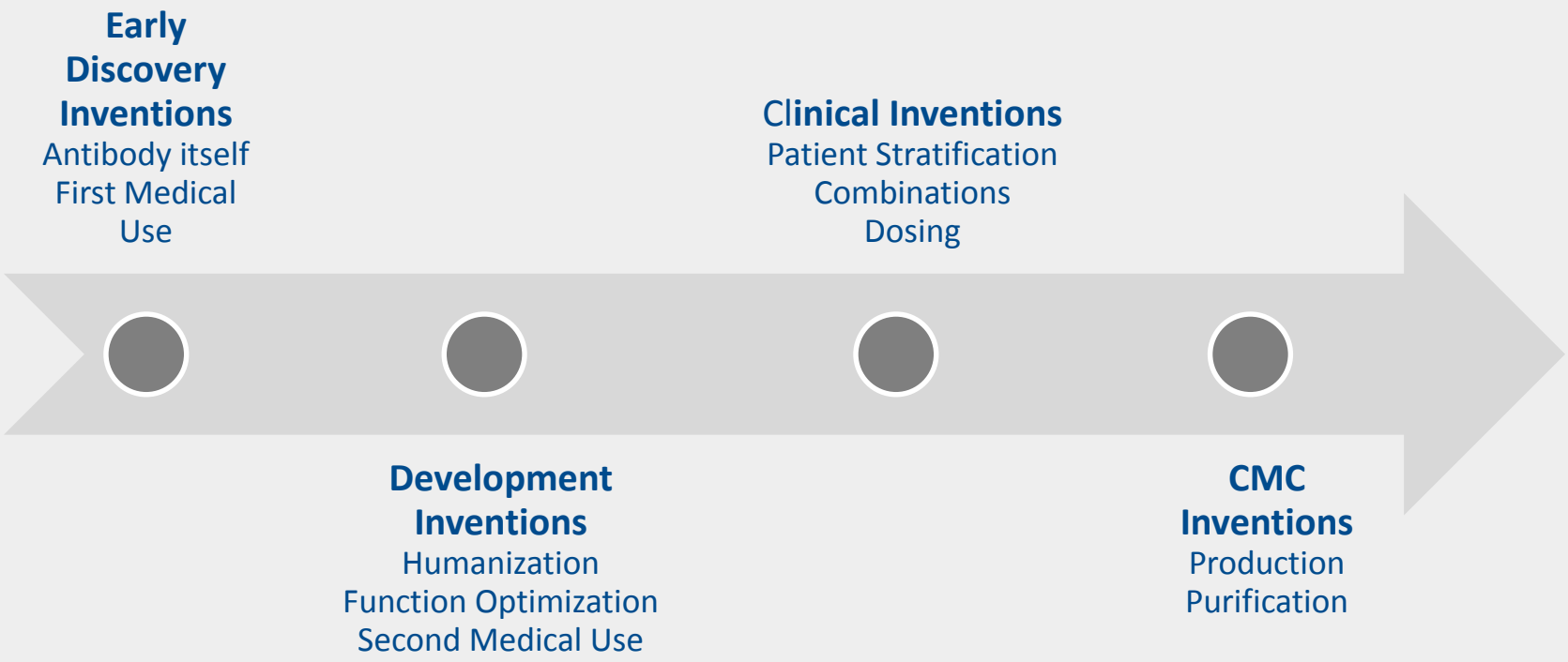
When to File?

- Therapeutic antibody life cycle:



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Best Practice Recommendations

- Look before you leap:
  - Start with claims that will cover the reference product
  - Consider design-around options
  - Consider limitations relating to factors that FDA will consider in evaluating a potential follow-on biologic
  - Consider limitations relating to mechanism of action, route of administration, etc. for second generation filings
  - Balance potential expanded patent rights against benefits of preserving trade secrets for some inventions that typically arise later in the development process

Best Practice Recommendations

- Different claims may work in different jurisdictions
  - Define your antibodies in the specification in as many different ways as possible to maximise claim options
  - Structure
    - CDRs (in multiple formats), variable domains, full sequences
    - isotypes, alternative antibody structures
    - compositions, combinations
  - Epitope
    - Full/partial epitope, specific amino acids in the epitope
    - Competitive binding
  - Function/uses
    - functional features, general and specific uses, therapies, patient groups, dosages, combinations
- Include data and specific description to support as many of these types of claims as possible

Best Practice Recommendations

- Remember “Structure is King” and supporting data is vital:
  - Unsupported functional claims may not stand
  - Provide data in the specification to correlate function with structure, to the extent possible
  - Be sure to include details of the assays used to measure function and define outcome-altering parameters of those assays
- Correlate Structure with Function
  - Create and test variants across full scope of the claimed genus.
  - Conduct epitope/competition studies
  - Mix-and-match or mutate CDRs (and include variability language tracking the mutation studies in the specification)
  - Test various relevant isotypes
  - Identify “neutral” mutations and substitutions

Best Practice Recommendations

- Consider the Patent Life Cycle
  - What will likely be included in the label and can it be covered with second generation filings?
  - In general, the later inventions face more prior art and are therefore narrower in scope
- More Claims are Better
  - Follow-on biologic applicants are required to prepare a “detailed statement” describing, **on a claim-by-claim basis**, the factual and legal basis for why the claims are invalid, unenforceable, and/or not infringed
  - The more claims in your patent thicket, the higher the bar for biosimilar challengers

Freedom to Operate

- Epitope and competitive binding claims are still relevant (consider appropriate key word and sequence searches)
  - May need to do epitope or competitive binding analysis on your own candidate antibody
- Check for claims to combination therapies, patient subpopulations, or dosing regimens that could potentially issue with expansive language
  - may be able to rely on disclosure in specification / prosecution history to exclude a focus on your product
- Equivalents in Europe

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Questions?

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