Recent Trends in Biologics and Biosimilars

Panelists:
Andrew Allen, Dr. Reddy's Laboratories
Rachel Moodie, Fresenius Kabi
Abby Struthers, Sandoz
Alexandra Valenti, Goodwin
Lauren Fornarotto, McKool Smith, Moderator

Purple Book

Purple Book now publishes patents originator believes cover biosimilar(s)

- “Purple Book Continuity Act of 2019” went into effect June 25, 2021
- Biologic reference product sponsors (“RPS”s) are required to publish list of all patents asserted to cover a biosimilar (“3(A) list” patents) in the Purple Book
- Listed patents focus on biosimilar, not reference product, in contrast to Orange Book patent list
- The newly required patent information provides insight for non-first-filer biosimilar developers on which patents RPSs may consider most important/valuable for litigation

How does the legislation change the Purple Book?

Purple Book	Orange Book
✓ Reference product and approval date	✓ Reference product and approval date
✓ Approved biosimilar products and approval date	✓ Generic approval status*
✓ Approved interchangeable products and approval dates	
✓ Regulatory exclusivity **(now required)**	✓ Regulatory exclusivity
✓ **Patents asserted to cover biosimilar (“3(A) list”)**	✓ Patents covering reference product

Biosimilars, Label Carve-Outs, and Induced Infringement

Labeling Regulations – Generics vs. Biosimilars

FDA requires small-molecule generic drugs to have same label as reference product (apart from carve-outs)

No same-label requirement for biosimilars

- In practice, FDA has strongly encouraged biosimilar applicants to use the RPS labeling as a template and to make changes only when necessary and adequately justified
  - *See* FDA Guidance for Industry: Labeling for Biosimilar Products (July 2018)
- Changes have been allowed when necessary to carve out an indication or other condition of use that is protected by exclusivity (e.g., orphan drug exclusivity) or patents
  - No “use codes” that define the parameters of a carve-out
- FDA has also allowed changes to reflect differences between biosimilar and RP, such as presentation (e.g., pen injector versus vial)

Induced Infringement Background

35 U.S.C. § 271(b): "Whoever actively induces infringement of a patent shall be liable as an infringer."

- To succeed on a claim of induced infringement, "the patentee must show, first that there has been direct infringement" and "second, that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement."
- "Evidence of active steps taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe."
  - *MEMC Electronic Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378-79 (Fed. Cir. 2005)

Induced Infringement and Biosimilars

As in Hatch-Waxman litigation, induced infringement claims in BPCIA litigation will most likely arise in the context of method of treatment claims

- To date, no court in a BPCIA litigation has addressed whether a biosimilar applicant will induce or has induced infringement of a method claim

Prior to the biosimilar launch, these claims will likely hinge on the content of the proposed product label, as has been seen in the Hatch-Waxman context

- A biosimilar applicant may be able to avoid infringement liability by carving out the claimed indication

Post-launch claims: will biosimilar manufacturers market their products?

Immunex v. Sandoz

Sandoz submitted an aBLA seeking approval for indications for psoriatic arthritis and plaque psoriasis, but later withdrew those indications

FDA ultimately approved a label that did not contain indications for psoriatic arthritis and plaque psoriasis

In litigation, Immunex asserted a patent covering the carved-out methods of use and moved for summary judgment of infringement, arguing:

- The original act of submitting an aBLA seeking approval of the psoriatic arthritis and plaque psoriasis indications (including with clinical trial data for plaque psoriasis) constitutes infringement under § 271(e)(2)(C)
- Irrelevant whether Sandoz subsequently withdrew those indications from review because infringement has already occurred

Immunex v. Sandoz

The court issued a sealed order on August 21, which may have been a decision on Immunex's motion

- Public version of the order is not available (despite an order granting a request to unseal)

Trial began on September 11, 2018 and concluded on September 25, 2018

- Neither of the patents asserted at trial were the psoriasis treatment patent that was the subject of Immunex's motion
- This likely means that either the court denied Immunex's motion or granted summary judgment of non-infringement, such that Immunex did not assert the psoriasis patent at trial

Developments in the Law of 35 U.S.C. § 112

Overview

Recent Federal Circuit decisions impacting § 112 strategies in biosimilars litigations:

- *Amgen Inc. v. Sanofi Aventisub LLC, et al.* 987 F.3d 1080 (Fed. Cir. 2021)
- *Bayer Healthcare LLC v. Baxalta Inc., et al.*, 989 F.3d 964 (Fed. Cir. 2021)
- *Juno Therapeutics, Inc., et al. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021)

Amgen, Inc., et al. v. Sanofi, et al.

987 F.3d 1080 (Fed. Cir. 2021)

U.S. Patent No. 8,829,165

1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.

29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO: 3 and blocks the binding of PCSK9 to LDLR by at least 80%.

U.S. Patent No. 8,859,741

1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.

7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

Amgen, Inc., et al. v. Sanofi, et al.

987 F.3d 1080 (Fed. Cir. 2021)

"The purpose of the enablement requirement is to ensure that the public is told how to carry out the invention, i.e., to make and use it. We have held that such disclosure must be commensurate with the scope of the claims." *Amgen*, 987 F.3d at 1084.

"Although the specification does not need to describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of that range." *Amgen*, 987 F.3d at 1085.

In re Wands

858 F.2d 731, 737 (Fed. Cir. 1988)

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Amgen, Inc., et al. v. Sanofi, et al.

987 F.3d 1080 (Fed. Cir. 2021)

"What emerges from our case law is that the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those claims, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen*, 987 F.3d 1086.

"While functional limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Amgen*, 987 F.3d 1087.

"The binding limitation is itself enough here to require undue experimentation." *Amgen*, 987 F.3d 1087.

Amgen, Inc., et al. v. Sanofi, et al.

850 Fed.Appx. *794 (Mem)*

"Invention of a genus means to conceive and reduce to practice a reasonable number and distribution of species constituting the genus." *Amgen*, 850 Fed.Appx. at 796.

"Claims defining a composition of matter raise special problems because one may not know whether a species is within the scope of a generic claim until one has made it and one can ascertain whether it possesses the claimed function, hence that it has been enabled." *Amgen*, 850 Fed.Appx. At 797.

Amgen, Inc., et al. v. Sanofi, et al.

850 Fed.Appx. *794 (Mem)*

"What is new today is not the law, but generic claims to biological materials that are not fully enabled. Enablement is required, even for generic claims to biological materials. But, as with genus claims to chemical compounds, if they encompass more subject matter than just a few species, they need to be enabled accordingly." *Amgen*, 850 Fed.Appx. at 795.

Bayer Healthcare LLC v. Baxalta Inc.

989 F.3d 964 (Fed. Cir. 2021)

U.S. Patent No. 9,364,520

We claim:

1. An isolated polypeptide conjugate comprising a functional factor VIII polypeptide and one or more biocompatible polymers, wherein the functional factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or an allelic variant thereof and has a B-domain, and further wherein the biocompatible polymer comprises polyalkylene oxide and is covalently attached to the functional factor VIII polypeptide at the B-domain.

In another aspect of the invention, a three-step method was developed to allow site-specific PEGylation of FVIII (FIG. 3). In step 1, the purified FVIII cysteine mutein at about 1 μM is mildly reduced with reductants such as about 0.7 mM Tris(2-carboxyethyl)phosphine (TCEP) or 0.07 mM dithiothreitol (DTT) for 30 minutes at 4° C. to release the "cap." In step 2, the reductant is removed along with the "cap" by a size-exclusion chromatography (SEC) method such as running the sample through a spin column (BioRad®) to allow FVIII disulfides to reform while leaving the introduced cysteine free and reduced. In step 3, at least 30 minutes after the removal of the reductant, the freed FVIII cysteine mutein is

Bayer Healthcare LLC v. Baxalta Inc.

989 F.3d 964 (Fed. Cir. 2021)

Bayer presented evidence to the jury "bridging the gap between the patent's disclosures" and what was known in the art at the time of the invention.

- Inventor testimony described known methods to make the claimed invention at the time of the invention.

- Expert testimony described methods of making the invention as part of a "very old technology."

The specification included "detailed instructions as to the reaction conditions required to practice the claimed invention using cysteine PEGylation, and includes a working example for non-random cysteine PEGylation at the B-domain." *Bayer*, 989 F.3d at 981.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

U.S. Patent No. 7,446,190

1. A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising

(a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,

(b) a costimulatory signaling region, and

(c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.

Asserted dependent claims 3 and 9 specify the "binding element" is a single-chain antibody variable fragment (scFv), and those claims broadly cover ***any*** scFv for binding ***any*** target cell (such as a cancer cell)

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

Jury found asserted dependent claims valid and infringed and awarded $585 million damages + a 27.6% running royalty.

District court bumped up award to $778 million based on intervening sales and added a 50% enhancement for willful infringement.

CAFC (Moore, Prost & O'Malley) reversed for lack of written description

Juno is another in a line of recent Federal Circuit decisions taking a hard line on generic, functional claiming in biotech cases by strictly enforcing the requirements of Section 112.

Result wiped out a $1.2 billion judgment for the plaintiff.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

"The hallmark of written description is disclosure. *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

A specification adequately describes an invention when it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

What is required to meet the written description requirement "varies with the nature and scope of the invention at issue, and with the scientific and technical knowledge already in existence." *Ariad*, 598 F.3d at 1351.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

"For a genus claim using functional language, like the binding function [of the scFvs] claimed here, the written description 'must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *Juno*, 104th at 1335.

Factors to evaluate generic claims for adequacy of disclosure:

- The existing knowledge in the particular field,
- The extent and content of the prior art,
- The maturity of the science or technology, and
- The predictability of the aspect at issue.

Ariad, 598 F.3d at 1351.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

"Generally, a genus can be sufficiently disclosed by 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."

"A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials.'"

Juno, 10 F.4th at 1335 (internal citations omitted)

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

KITE'S ARGUMENTS

- Patent discloses neither representative species nor common structural features of claimed scFv genus to identify which members of genus would function as claimed.
- Claims cover millions of billions of scFv candidates, only a fraction of which satisfy the functional binding limitation for any given target.
- scFv field is unpredictable since an scFv's binding ability depends on a variety of factors.

JUNO'S ARGUMENTS

- Members of the scFv genus were well-known (as was how to make them), and multiple members for specific targets were well-known.
- The patent describes two working embodiments that are representative of the entire genus, and the genus was in use well before the patent's priority date.
- Members of the genus are interchangeable and have common structural features.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

No reasonable jury could have found the written description demonstrated the inventors' possession of the broad scope of the claimed invention

- "The 190 patent's written description contains scant details about which scFvs can bind which target antigens"
- "The 190 patent contains no details about these scFvs species beyond the alphanumeric designations J591 and SJ25C1 for a skilled artisan to determine how or whether they are representative of the entire claimed genus."
- "To satisfy the written description requirement, the patent needed to demonstrate to a skilled artisan that the inventors possessed and disclosed in their filing the particular species of scFvs that would bind to a representative number of targets."

Juno, 10 F.4th at 1336-37

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

10 F.4th 1330 (Fed. Cir. 2021)

Insufficient representative species

No structural features common to the genus members sufficient to distinguish scFvs capable of binding a specific target from those incapable of binding that same target

Please pick up my new car from the dealership. Mine is the one with four wheels.

Juno Therapeutics, Inc. v. Kite Pharma, Inc.

JUNO THERAPEUTICS, INC., SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH,

Plaintiffs-Appellees,

v.

KITE PHARMA, INC.,

Defendant-Appellant.

Appeal from the United States District Court for the Central District of California
in Case No. 17-cv-07639, Judge Philip S. Gutierrez

PLAINTIFFS-APPELLEES' PETITION FOR PANEL REHEARING OR REHEARING EN BANC

Panel's inadequate written description finding based on failure to describe old, well-known scFv claim element, not the novel two-part CAR backbone.

§ 112 does not require a written description separate from enablement, and the statute has no inventor-possession requirement, which is an atextual CAFC creation.

- *Ariad* rejected this same argument en banc. Juno presumably lining up a cert petition.

Impact of Patent Thickets

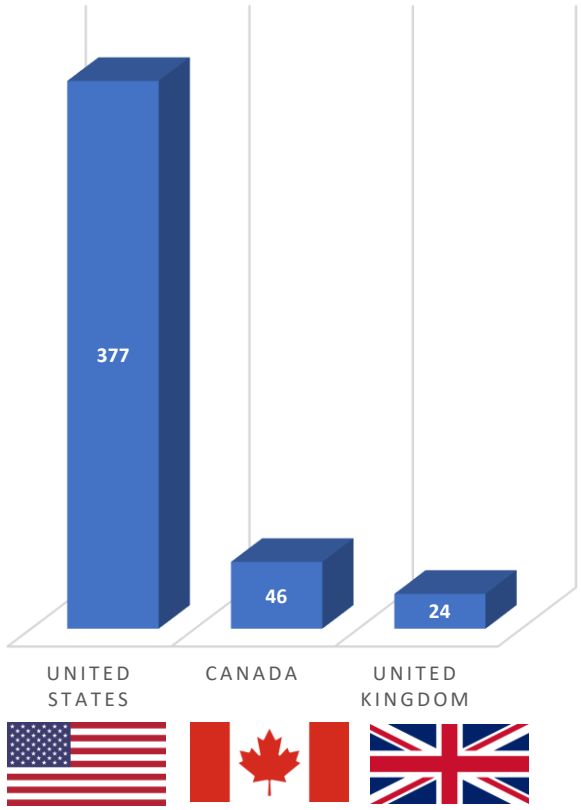
A study exploring the impact of biopharma patent thickets

Dr Rachel Moodie & Professor Bernard Chao

Fresenius Kabi

Denver University, Sturm College of Law

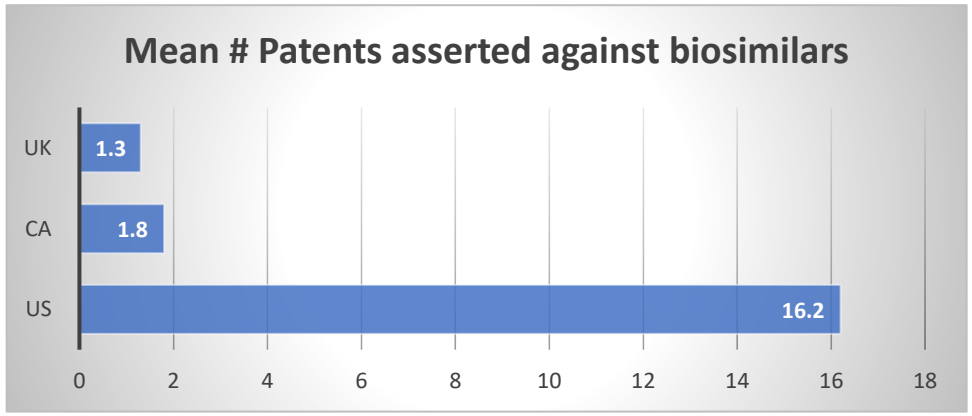
Patent thickets – an American Problem



Study covers all biosimilars that have been submitted for regulatory review in US, CA and UK

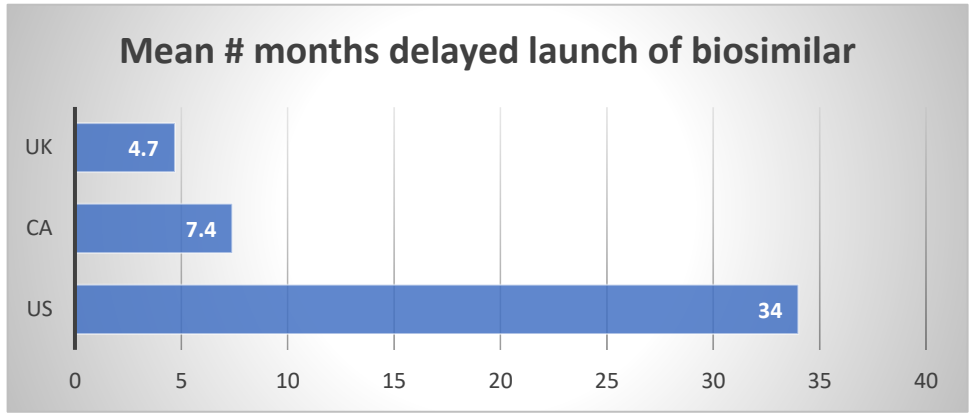
- This figure shows **the total number of patents litigated** against all 30 biosimilars in each of the US, Canada and UK.
- In the US, over 15 times more patents were asserted against these 30 biosimilars, as compared to the same biosimilars in the UK.
- In the US, over 7 times more patents were asserted against biosimilars, as compared to the same biosimilars in the Canada.
- The US stands out as an outlier in terms of the high numbers of patents litigated against biosimilars.

Results – Large patent estates correlate with delayed biosimilar market entry in the US



Footnote: data derived from the **first launched** biosimilar for each branded drug

On average, **9x more patents** are asserted against the "first launched" biosimilars in the US compared to Canada and **12x more patents** compared to the UK.



Footnote: delayed launch calculated as the time difference between regulatory approval of the biosimilar and launch of the biosimilar in each respective country

On average, there is **4x longer delayed launch** of these biosimilars in the US compared to Canada and **7x longer delayed launch** compared to the UK.

We hypothesize that increased patent numbers in the US is one cause of delayed biosimilar launches, which leads to increased drug prices in the US.

Why are biologics patent estates so large in the US?

Patenting the same invention more than once is known as double-patenting and is generally prohibited by patent offices around the world.

The USPTO, however, **will allow a patentee to overcome "obviousness-type double patenting"** by filing a terminal disclaimer, which aligns the expiry date of the two patents

In other words, **a patent owner may obtain multiple patents with non-patentably distinct claims**. This results in a cluster of patents, tied together by terminal disclaimers.

We hypothesize that biologics **patent estates are comprised mostly of such clusters**, which enables them to grow so large. We tested this hypothesis by examining the patent portfolio of one such branded biological drug.

Case study: Drug X patent portfolio
Clusters of US patents

= one patent

= a cluster of patents linked through terminal disclaimers (non patentably-distinct claims)

= a patent family (Inpadoc standard definition)

10	4	21	15	8	2	3	4
Product	**Primary indications**	**Formulation primary**	**Secondary indications**	**Purity level**	**Tertiary indications**	**Juvenile indications**	**Formulation secondary**
1 invention	**4 inventions**	**1 invention**	**4 inventions**	**1 invention**	**1 invention**	**1 invention**	**1 invention**
10 patent cluster	4 patent cluster + 3 distinct patents	21 patent cluster	15 patent cluster + 3 distinct patents	8 patent cluster	2 patent cluster	3 patent cluster	4 patent cluster

Summary: 73 patents; 14 distinct inventions; 59 patents are non-patentably distinct

Such “obvious-type double patenting” is permissible under the US patent rules

Case study comparison to Europe, Same Drug X patent portfolio in Europe

= one patent

= a cluster of patents linked through terminal disclaimers (non patentably-distinct claims)

= a patent family (Inpadoc standard definition)

2	2	2	1	Patent not granted	1	Patent not granted	Patent not granted
Product	**Primary indications**	**Formulation primary**	**Secondary indications**	**Purity level**	**Tertiary indications**	**Juvenile indications**	**Formulation secondary**
2 inventions	**2 inventions**	**2 inventions**	**1 invention**	**-**	**1 invention**	**-**	**-**
2 distinct patents	2 distinct patents	2 distinct patents	1 distinct patent	-	1 distinct patent	-	-

Summary: 8 patents; 8 inventions; 0 patents are non-distinct; 0% of the portfolio is duplicative

Double patenting is not permitted by the European Patent Office

How might large patent estates in the US lead to delayed biosimilar launches?

1) High cost to biosimilars

- The existence of so many duplicative patents is troublesome. While a patent may cost approximately $25,000 to obtain and maintain, it can cost $1 million to challenge that patent via an IPR/PGR.
- **Biosimilar companies cannot economically use IPR/PGR to challenge scores of patents**. Furthermore, it is unlikely that a federal court can effectively litigate scores of patents.
- **Therefore, patent estates may enable shielding low-quality patents from scrutiny.**

2) High risk to biosimilars

- "**Batting averages**": the biosimilar company must invalidate all patents in order to obtain freedom to operate whereas the patent owner need only prove that a single claim from a patent is valid and infringed in order to block a biosimilar.

How to arrive at a more balanced patent system

Litigation	Patent Office
Litigation cap: the reference product sponsor may assert against a biosimilar competitor only one patent from each cluster of patents that are tied together by terminal disclaimers.	Eliminate the use of terminal disclaimers. Patents would not be granted if it does not comply with obvious-type double patenting rules.
Patents tied together by terminal disclaimers (clusters) would stand or fall together in post-issuance challenges. Or if one patent in a cluster is found to be invalid then all other patents in that cluster become non-enforceable.	OR add new, non-patentably distinct claims to back to the original patent. This policy would reduce the number of repetitive patents, leading to more efficient patent litigation, but would count towards strengthening the original “head of family” patent.