Biologics & Biosimilars: Where Do We Go From Here?

March 10, 2021

Hosted by the NYIPLA Patent Litigation & Women in IP Law Committees

Speaker Bios

Panelist – Raymond M. Doss, Ph.D.

- Raymond M. Doss is Senior Counsel in Amgen's IP Law group where most of his efforts have been focused in the field of biotechnology and oncology. As in-house counsel, Raymond has had the opportunity to work with clients in developing patent prosecution and FTO strategies for programs as they progress through preclinical, clinical, and marketing stages of development. Raymond has also supported deals and negotiations with 3rd parties. In addition, Raymond has taken an interest in encouraging scientists to think about intellectual property as they progress research programs, including developing forums where the intersection of research and patent law is discussed and the "patent process" is "demystified."

- Previously, Raymond was in private practice and counseled clients in the fields of pharmaceuticals, biotechnology, flavor development, medical devices, and engine technologies in connection with intellectual property issues. Raymond worked with clients to establish strategies for developing patent portfolios while considering the competitive patent landscape, competitors, 3rd party collaborations, and other business considerations. In addition to aiding clients in securing sound and enforceable patent rights, Raymond drafted freedom-to-operate, invalidity, and patentability opinions.

- Raymond received his J.D. from Fordham University, a Ph.D. from California Institute of Technology and a BS in Chemistry/Mathematics from NYU.

Panelist – Karin Hessler

- Karin Hessler is Vice President & Deputy General Counsel for the Association for Accessible Medicines (AAM). She provides legal advice to AAM staff and member company representatives on issues relating to generic and biosimilar medicines in the U.S. She works on advocacy strategy and engagement, provides advice on Hatch-Waxman and pharmaceutical patent issues and helps manage amicus briefs on behalf of AAM.
- Before joining AAM in March 2019, Karin was a partner at Wiley Rein LLP, where she represented clients on intellectual property matters, with a special focus on patent litigation in the biotechnology and medical device industries. She has played a lead role in all phases of numerous Hatch-Waxman litigations, including expert discovery, fact discovery, claim construction, trials, regulatory analysis and settlement negotiations. Karin has significant experience in FDA regulatory issues as well as IPR process.
- Karin received her J.D. from NYU School of Law, an M.A. in biochemistry from Duke and her B.S. in biochemistry from Lafayette College.

Panelist – Margareta Sorenson, Ph.D.

- Margareta Sorenson is Senior Director of Intellectual Property at Amicus Therapeutics, where she handles IP for key biologics programs, including enzyme replacement and gene therapies. Her work includes securing patent and trademark protection as well as freedom-to-operate. She also assists with licensing and collaboration agreements.

- Prior to joining Amicus, Margareta worked on both patent litigation and prosecution in private practice. She worked extensively on biosimilar litigation and *inter partes* review proceedings, but also on infringement and Hatch-Waxman litigation. Her prosecution experience spans many areas including antibodies, gene therapy, plants, cosmetics and materials. Her *pro bono* work includes several successful social security appeals for clients with disabilities, including a child with a rare genetic disorder. She currently volunteers for the CORONA project, a comprehensive literature review to identify drugs that can be repurposed for COVID-19.

- Before becoming a patent attorney, Margareta earned her Ph.D. from the Rockefeller University, where she solved the x-ray crystal structure of a protein-protein complex. She continued to study protein structure as a postdoctoral fellow at Harvard Medical School before escaping the lab to pursue a legal career.

Panelist – Rachel Turow

- Rachel Turow is Associate General Counsel, Regulatory Law & Policy at Teva Pharmaceuticals USA, Inc. and Head, U.S. Regulatory Policy. In this role, Rachel provides regulatory legal support to Teva's specialty and generic pharmaceutical businesses and supports Teva's drug-device combination products and digital health projects. Rachel also serves as head of regulatory policy for the U.S.

- Previously, Rachel was Director, Regulatory Policy, at Novo Nordisk Inc. Prior to joining Novo Nordisk, Rachel spent five years at FDA. She was a Regulatory Counsel in CDER's Office of Regulatory Policy and she served as Special Assistant to Jeff Shuren, Director of CDRH.

- Rachel holds a J.D. and MPH from the University of Michigan and a BA in Biology from Stanford University.

Moderator – Huiya Wu

- Huiya Wu, a partner in Goodwin's New York office, is an intellectual property litigator who has spent more than 20 years litigating and trying cases in both federal and state courts, and has appeared before the Patent and Trademark Office (PTO), the Patent Trial and Appeal Board (PTAB), as well as the International Trade Commission (ITC). . She is a registered patent attorney and has particular expertise in litigation under the Hatch-Waxman Act and the Biologics Price Competition and Innovation Act. She represents clients all over the world has been recognized in Intellectual Asset Management's Patent 1000 as one of the world's leading patent litigators, 2016-2020.

- Huiya is an editor of Goodwin's biosimilars blog, www.bigmoleculewatch.com, as well as its Chinese counterpart, www.bigmoleculewatch.cn.

- Huiya received a J.D. from The George Washington University Law School, B.S. degrees in Chemistry and Chemical Engineering from the University of Massachusetts.

Purple Book: Updates and Implications, Future Direction?

Raymond Doss, Ph.D.
Senior Counsel Intellectual Property & Litigation, Amgen

Importance of Biologics Is In Focus

- The COVID-19 pandemic has highlighted the important role of biologics in human health
- Vaccines will play a major role in any return to normalcy
- mAbs will play a role in ongoing COVID-19 care
- Reasonable to expect that FDA continues to evolve the Purple Book

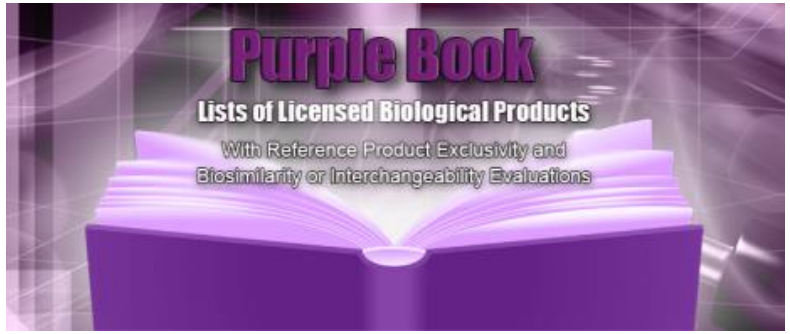
What Biological Products Are We Talking About?

CDER	CBER
• mAbs for in vivo use • Most proteins intended for therapeutic use – e.g., cytokines, enzymes, and other novel proteins • Immunomodulators • Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo	• Vaccines and vaccine-associated products • Cellular products – e.g., composed of human, bacterial or animal cells, or from physical parts of those cells • Gene therapy products. • Allergenic extracts for diagnosis and treatment of allergic diseases and allergen patch tests • Antitoxins, antivenins, and venoms • Blood, blood components, plasma derived products • Human cells, tissues and cellular and tissue-based products

What You Need To Know – Biosimilars In the U.S.

- Biosimilars approval process authorized by Biologics Price Competition and Innovation Act (BPCIA) of 2009
- BPCIA goals: provide more treatment options, increase access to lifesaving medications, and lower health care costs
- Complexity of biologics compared to small molecules ➡ challenges in characterizing and manufacturing
- FDA review of biosimilars assesses the manufacturing process and the manufacturer's strategy to control within-product variations

Purple Book History



- Biologics Price Competition and Innovation Act (BPCIA) did not require FDA to publish a list of licensed biological products
  - Nor applicable patent and non-patent exclusivities

- In 2014, FDA created a reference guide – The Purple Book
  - Originally a compilation of two lists: (1) Center for Biologics Evaluation and Research (CBER) List of Licensed Biological Products; and (2) Center for Drug Evaluation and Research (CDER) List of Licensed Biological Products

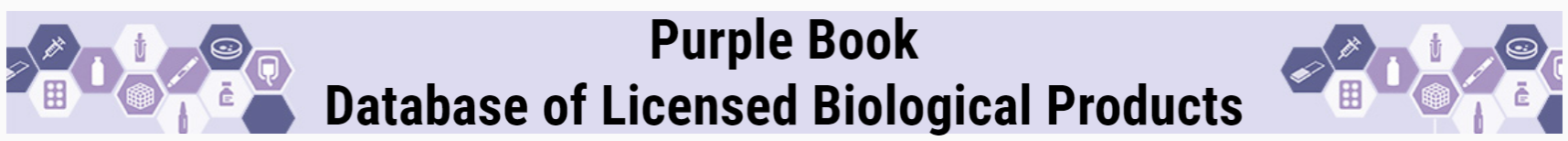
- In 2020, FDA:
  - Transitioned the Purple Book to a single, searchable online database of licensed biologics
  - All biological products approved in NDAs that were deemed to be BLAs (transition biological products) were included in the Purple Book

BPCIA Patent Disclosures

- Patent Dance – under BPCIA, biologics license holders and companies seeking to market a biosimilar engage in a statutorily-prescribed exchange of information about the patents to be litigated
- Before: this exchange of information was confidential
- Biosimilar applicants completed their own freedom-to-operate searches
- Later-filers could only see what patents were ultimately asserted

Purple Book Continuity Law

- Passed on December 27, 2020
- FDA required to provide more information to the public about patented biological products
- This information includes:
  - a list of each biological product, by nonproprietary name, for which a biologics license is in effect;
  - the date of licensure and the application number;
  - the licensure status and, as available, the marketing status; and
  - exclusivity periods



Purple Book Continuity Law

- Now – BLA reference product holders who engage in the patent dance must provide FDA:
  - Within 30 days after sending patent list to the biosimilar applicant
  - The patent number and expiration date of each patent identified by the BLA holder
  - In either the originally exchanged list or a supplemental list

- Patent information submitted by the BLA holder is then published in the Purple Book
  - Disclosed patents will be made public via Purple Book beginning in June 2021

Orange Book vs. Purple Book

	Orange Book (2021)	Purple Book (2021)
Types of Drugs	Small molecule (NDAs)	Big molecules (BLAs)
Types of Patents	All associated with the reference product, including compound, formulation, methods of use	Any disclosed by RPS during patent dance
Types of “Generics”	Lists all generics, including 505(b)(2) products	Lists all biosimilars and interchangeables
Types of Exclusivity	Any that apply (orphan, pediatric, NCE), including 180-day ANDA exclusivity	Reference product exclusivity, pediatric exclusivity
Delisting Requirement	Within 14 days from final decision, but not before 180-day exclusivity expires	

New Requirements: Practical Effects

- No prescribed penalty for reference sponsors for failure to provide this information to the FDA

- Possible efficiencies for some biosimilar applicants:
  - First biosimilar applicant for a given product: likely no tangible impact
  - Second and later biosimilar applicants: will be informed of patents the reference product BLA holder identified in previous BPCIA litigations
    - Doesn’t preclude the BLA holder for asserting different or new patents in subsequent litigation

New Requirements: Practical Effects

- Purple Book patent lists may make licensed patents and manufacturing process/platform patents easier to identify

- May prompt some parties to challenge patents earlier at the PTAB
  - Subsequent biosimilar applicants may have patent information earlier allowing for identification of patents to be challenged at the PTAB

Interchangeable Biosimilars

Will Interchangeable Biosimilars Emerge?

- To-date, no interchangeable biosimilars have been approved
- FDA released (Nov. 2020) its most recent draft guidance on biosimilarity and interchangeability
  - Discussed FDA labeling of interchangeable products
  - Specified that interchangeable biosimilars have a notation alerting providers to an interchangeable product's features

Will Interchangeable Biosimilars Emerge?

- Benefits await the first interchangeable biosimilar (42 USC §262(k)(6)):
  - If a biosimilar receives a determination of interchangeability for any condition of use, FDA will not make a determination that a subsequent biological product is interchangeable for any condition of use until the **earlier of**:
    - (A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;
    - (B) 18 months after—
      - (i) a final court decision on all patents in suit in an action instituted under subsection (l)(6), or (ii) dismissal with or without prejudice of an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
    - (C)(i) 42 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (l)(6) and such litigation is still ongoing within such 42-month period; or
    - (C)(ii) 18 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (l)(6).

Authorized Biosimilars and the Biosimilar User Fee Act

Rachel Turow
Associate General Counsel, Regulatory Law & Policy
Teva Pharmaceutical Industries Ltd

Authorized Biosimilars

- Term first used by Lilly in its February 11, 2019 public comments to FDA's draft Q&A Guidance
- Discussed as: "A section 351(k) application submitted by the holder of a section 351(a) application that cites the sponsor's section 351(a) product as the reference product and proposes a modified or identical version of that reference product."
- Essentially asking FDA to allow the sponsor to maintain two applications (a full BLA and an aBLA) for the same product

Differs from “Authorized Generics”

- Authorized generics are genericized versions of the brand name marketed under a single application – the original NDA
- FDA is notified of the authorized generic through the annual report for the brand name drug, not a separate application

FDA Guidance

- FDA's "Deeming" Q&A Final Guidance issued March 2020
- FDA clarified that holders of standalone 351(a) BLAs may not use the 351(k) pathway to obtain approval of a biosimilar or interchangeable version of their own RP
- Instead, a 351(k) application must reference "another" RP, i.e., a different RP
- Authorized biologics, however, may still be marketed under the sponsor's 351(a) application
  - Just like "authorized generics"
  - Such authorized biologics should be substitutable for the brand since they are the same product marketed under the same BLA
  - However, no formal interchangeability determination by FDA or listing as such in Purple Book

Biosimilar User Fee Amendments (BsUFA)

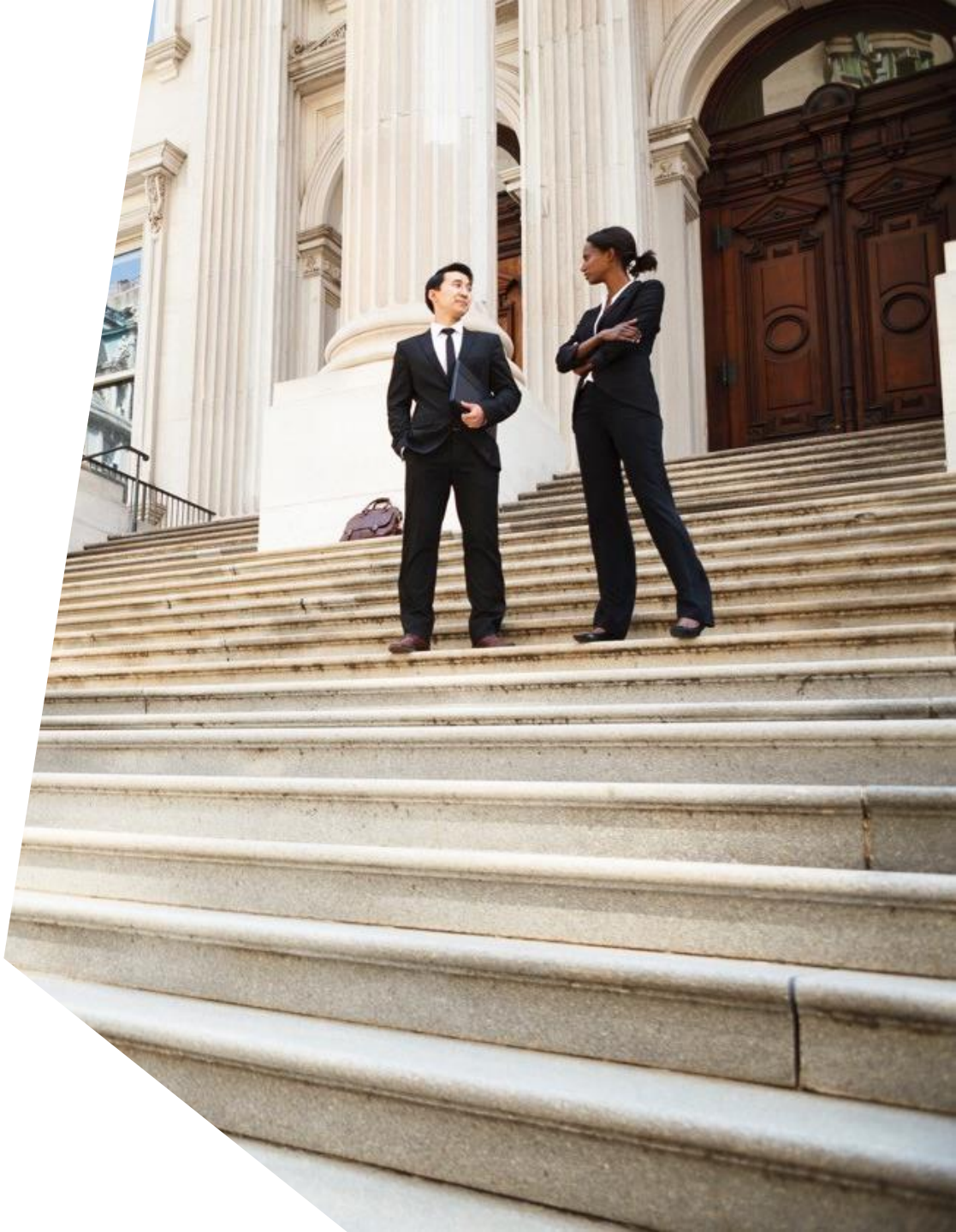
- BsUFA negotiations begin mid-March
- Main topics for BsUFA
  - Improving options for early FDA feedback through enhanced meeting types
  - Postmarket changes: labeling, CMC
  - Regulatory Science
  - Interchangeability
- Trade associations involved in negotiations:
    - PhRMA/BIO
    - Biosimilars Forum
    - Biosimilars Coucil

Recent Legislative Updates and the *GSK v. Teva* Decision

Karin Hessler
Vice President & Deputy General Counsel
Association for Accessible Medicines (AAM)

Why Are Patent Settlements Important?

- IMS Study: Settlements accelerate generic entry by as much as ***81 months*** before patent expiration
- Absent settlement, generics and biosimilars would be required to litigate to finality
  - Generics have less than a 50% success rate in Hatch-Waxman litigation
  - If generics lose, they are off-the-market until patent expiration



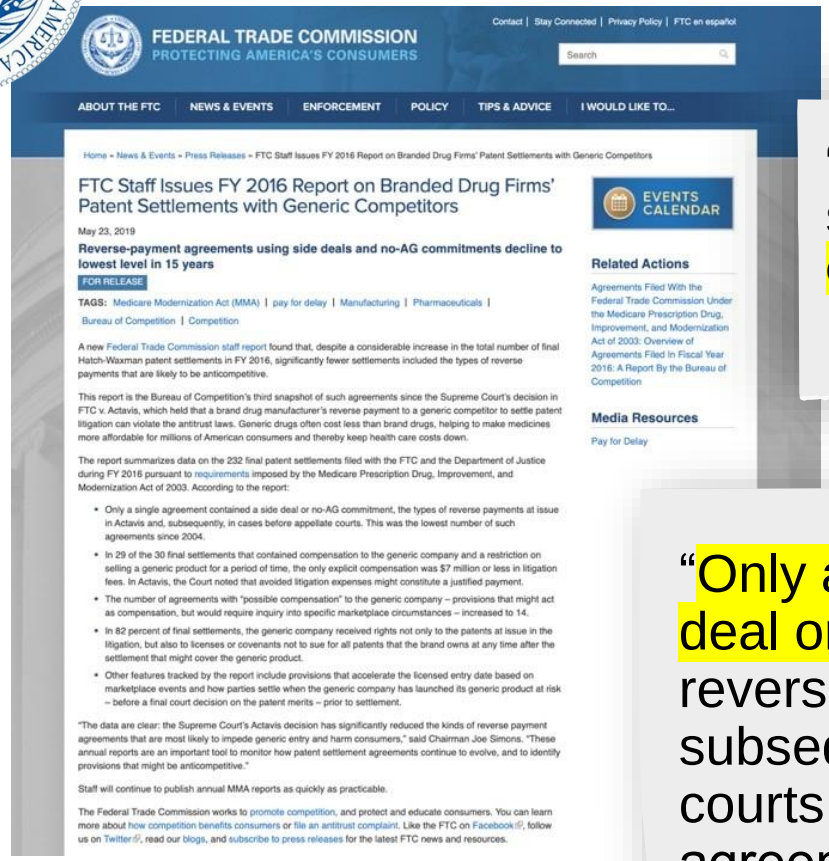
How Are Patent Settlements Regulated?

***FTC v. Actavis*, 570 U.S. 136 (2013)**

- The Supreme Court "decline[d] to hold that reverse payment settlement agreements are presumptively unlawful."
- Instead, the agreements should be carefully analyzed under the antitrust rule of reason
- The Supreme Court recognized that standard settlement terms like "avoided litigation costs or fair value for services" should not give rise to antitrust scrutiny

How Has Actavis Worked?

Federal Trade Commission Report



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FTC Staff Issues FY 2016 Report on Branded Drug Firms' Patent Settlements with Generic Competitors

May 23, 2019

Reverse-payment agreements using side deals and no-AG commitments decline to lowest level in 15 years

FOR RELEASE

TAGS: Medicare Modernization Act (MMA) | pay for delay | Manufacturing | Pharmaceuticals | Bureau of Competition | Competition

A new Federal Trade Commission staff report found that, despite a considerable increase in the total number of final Hatch-Waxman patent settlements in FY 2016, significantly fewer settlements included the types of reverse payments that are likely to be anticompetitive.

This report is the Bureau of Competition's third snapshot of such agreements since the Supreme Court's decision in FTC v. Actavis, which held that a brand drug manufacturer's reverse payment to a generic competitor to settle patent litigation can violate the antitrust laws. Generic drugs often cost less than brand drugs, helping to make medicines more affordable for millions of American consumers and thereby keep health care costs down.

The report summarizes data on the 232 final patent settlements filed with the FTC and the Department of Justice during FY 2016 pursuant to requirements imposed by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. According to the report:

- Only a single agreement contained a side deal or no-AG commitment, the types of reverse payments at issue in Actavis and, subsequently, in cases before appellate courts. This was the lowest number of such agreements since 2004.
- In 29 of the 30 final settlements that contained compensation to the generic company and a restriction on selling a generic product for a period of time, the only explicit compensation was $7 million or less in litigation fees. In Actavis, the Court noted that avoided litigation expenses might constitute a justified payment.
- The number of agreements with "possible compensation" to the generic company – provisions that might act as compensation, but would require inquiry into specific marketplace circumstances – increased to 14.
- In 82 percent of final settlements, the generic company received rights not only to the patents at issue in the litigation, but also to licenses or covenants not to sue for all patents that the brand owns at any time after the settlement that might cover the generic product.
- Other features tracked by the report include provisions that accelerate the licensed entry date based on marketplace events and how parties settle when the generic company has launched its generic product at risk – before a final court decision on the patent merits – prior to settlement.

"The data are clear: the Supreme Court's Actavis decision has significantly reduced the kinds of reverse payment agreements that are most likely to impede generic entry and harm consumers," said Chairman Joe Simons. "These annual reports are an important tool to monitor how patent settlement agreements continue to evolve, and to identify provisions that might be anticompetitive."

Staff will continue to publish annual MMA reports as quickly as practicable.

The Federal Trade Commission works to promote competition, and protect and educate consumers. You can learn more about how competition benefits consumers or file an antitrust complaint. Like the FTC on Facebook, follow us on Twitter, read our blogs, and subscribe to press releases for the latest FTC news and resources.

EVENTS CALENDAR

Related Actions

Agreements Filed With the Federal Trade Commission Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Overview of Agreements Filed In Fiscal Year 2016: A Report By the Bureau of Competition

Media Resources

Pay for Delay

"Reverse-payment agreements using side deals and no-AG commitments decline to lowest level in 15 years"

"Only a single agreement contained a side deal or no-AG commitment, the types of reverse payments at issue in Actavis and, subsequently, in cases before appellate courts. This was the lowest number of such agreements since 2004."

One Hundred and Twenty-two NYIPLA

How Would the Federal and State Patent Settlement Legislation Work?

Legislation overrules Actavis and imposes presumption of anticompetitive effect if:

- "Anything of value" is given to generic/biosimilar company;
  - Includes "exclusive licenses" *even though those are specifically allowed under federal law*
  - Federal bill includes any type of license
- Delayed generic/biosimilar entry relative to the date of settlement

Accelerators are in doubt under AB 824

AB 824 imposes individual *$20 million penalties per settlement*

AAM v. Becerra: Update

- Case re-filed in September 2020
  - AAM provided supplemental declarations to address the standing issues identified by the Ninth Circuit
  - The Court can now rule on the various constitutional issues. The Court already recognized that:
    - AB 824 likely violates the dormant commerce clause for settlements between non-California companies
    - The $20 million minimum penalty per individual presents Eighth Amendment issues
- The Court cancelled oral argument on October 29 and will issue a decision on the papers
- Decision expected shortly

Cornyn-Blumenthal (S. 1416)

- Caps brands at **20 patents** if BSA complies with patent dance
  - 10 patents can be later-issuing patents
- Number of patents **outside the cap:**
  - Method of treatment patents
  - Device patents
  - Patents with actual filing dates before and up to 4 years after BLA approval
- Brand can seek **additional patents** if:
  - Section 2(a) manufacturing information not sufficiently provided
  - PTO delays
  - Material change in biosimilar product or process

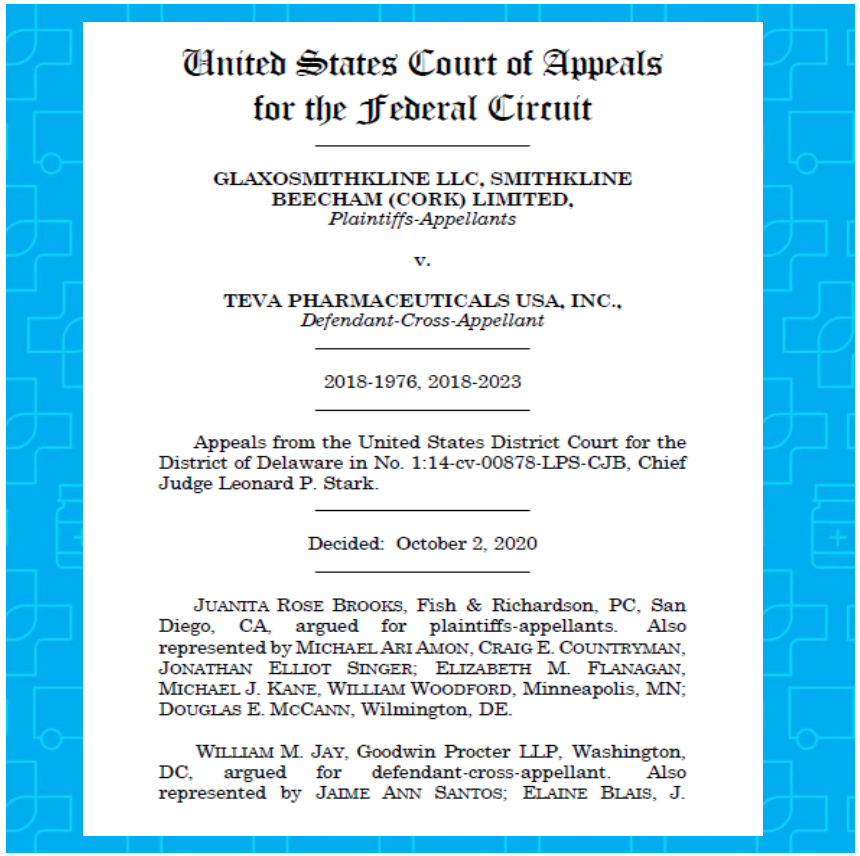
GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.

- Recent decision allows a brand company with a patent on only one use of a product to block competition on every use of that product
  - Even when the patented use has been carved-out of the labeling for the follow-on product
- Far from being limited to A-rated generic drugs, the case has significant negative implications:
  - Interchangeable biosimilar sponsors
  - Non-interchangeable biosimilar sponsors
  - Marketplace communications on biosimilars
  - FDA and industry educational efforts
  - Patients needing access to generics and biosimilars

Factual Background

- Coreg® (carvedilol) is approved for three indications, including the patented use for the treatment of CHF
- Teva carved out that indication
- GSK nevertheless claimed that Teva induced infringement via press releases, the product catalog, the A-rating, and failure to caution against the drug's use for the indication
- The trial made clear that prescribers did not rely on any Teva conduct – switching occurred at the pharmacy
- GSK contended that if Teva promoted its product as a generic, causation and induced infringement could be inferred
- GSK also argued that a use (left ventricular dysfunction following myocardial infarction) that it did not tell FDA was patented was covered by its patent

Outcome of the Case



United States Court of Appeals
for the Federal Circuit

GLAXOSMITHKLINE LLC, SMITHKLINE BEECHAM (CORK) LIMITED,
Plaintiffs-Appellants

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Cross-Appellant

2018-1976, 2018-2023

Appeals from the United States District Court for the District of Delaware in No. 1:14-cv-00878-LPS-CJB, Chief Judge Leonard P. Stark.

Decided: October 2, 2020

JUANITA ROSE BROOKS, Fish & Richardson, PC, San Diego, CA, argued for plaintiffs-appellants. Also represented by MICHAEL ARI AMON, CRAIG E. COUNTRYMAN, JONATHAN ELLIOT SINGER; ELIZABETH M. FLANAGAN, MICHAEL J. KANE, WILLIAM WOODFORD, Minneapolis, MN; DOUGLAS E. MCCANN, Wilmington, DE.

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for defendant-cross-appellant. Also represented by JAIME ANN SANTOS; ELAINE BLAIS, J.

- A divided panel of the Federal Circuit found that there was substantial evidence of induced infringement.
- Chief Judge Prost authored a lengthy dissent, noting that the opinion “nullifies Congress’s provision for skinny labels”
- Patent law allowed GSK to lie in wait from 2007 until 2014, then sue for lost profits – $234MM – which far exceeded Teva’s revenue, creating a disincentive
- The panel reheard the case on February 23. The sole issue involved in the rehearing was whether there was substantial evidence of inducement during the carve-out period.

What Does This Mean for Biosimilars?

- The complexity of innovator patent estates makes labeling carve-outs critical to biosimilar sponsors' ability to gain approval and launch products
  - Amgen's Enbrel® (etanercept) has many indications, including psoriatic arthritis and plaque psoriasis; Sandoz carved these out to avoid patent litigation
  - Merck's Keytruda® (pembrolizumab) currently has >18 indications
- Whether to avoid litigation altogether or as part of a staged launch based on a settlement, with different indications being licensed over time, this ability it vital to biosimilar market access
- The Federal Circuit's decision disrupts this ability, chilling future launches, putting the past 6 years of launches at risk, and potentially even preventing future settlements

Potential impact goes far beyond interchangeable biosimilars – and communications will be key

1

Industry and FDA are working hard to educate the market that these products are “highly similar,” with “no clinically meaningful differences”

2

In the biosimilar market, uptake depends on active promotion and education by sponsors to providers and purchasers – not true for generics, where there is usually no promotional activity

3

Based on FDA policy, biosimilar labeling is “generic” labeling – the only data is from the innovator – providers ask about broader uses, and disclaimers may not even work

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The Bottom Line

- In GSK, truthful statements only regarding the A-rating, combined with knowledge that the drug may be used for the protected use, led to a verdict of hundreds of millions of dollars in damages

- What does this mean for skinny-labeled biosimilars that are promoted as having “no meaningful differences” from brand products? How are we to communicate about them? How are we to avoid patent litigation and launch them?

Chief Judge Prost's Dissent

- "The Supreme Court has explained that one of Congress's essential purposes in designing a procedure for generic approval was to 'speed the introduction of low-cost generic drugs to the market.' *Caraco Pharm*., 566 U.S. at 405. The **Majority's holding undermines this purpose by creating infringement liability for any generic entering the market with a skinny label**, and by permitting infringement liability for a broader label that itself did not actually cause any direct infringement. Congress did not intend either of these consequences.

- Indeed, far from 'speed[ing] the introduction of low cost generic drugs,' this result discourages generics from entering the market in the first instance. **Teva did everything right—using a skinny label, taking care not to encourage infringing uses—and yet, given today's result, it was ultimately more costly for Teva to sell an unpatented drug for unpatented uses than it would have been to stay out of the market altogether**: Teva only sold $74 million worth of carvedilol during the allegedly infringing period (mostly for unpatented uses) but now owes $234 million in damages for sales made for a single indication. **This irony reflects the fact that Teva's product was dramatically less expensive—costing less than 4 cents per pill as compared with Coreg®'s price of at least $1.50 per pill."**

Looking Ahead

- Anyone with an interest in developing the market for biosimilars should be concerned about the recent *GSK* decision
- The threat of inducement liability – totaling more than six years of a brand's lost profits – is something any biosimilar company will have to consider if it plans to use a carve-out
- And without the ability to carve out, biosimilars will be delayed again and again, as brands obtain more and more patents on particular methods of use

Exclusivity of Gene Therapies Under Orphan Drug Regulations

Margareta Sorenson
Senior Director of Intellectual Property
Amicus Therapeutics

Orphan Drugs

Orphan drug - a drug intended for use in a *rare disease or condition*…

Rare disease or condition: any disease or condition which:

(a) affects less than 200,000 persons in the United States, or

(b) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales …

See sections 526 of the FD&C Act, 21 U.S.C. §360bb; *see also* 21 CFR Part 316(C).

7-year exclusivity provision:

…if the Secretary—(1) approves an application …, or (2) issues a license … for a drug … for a rare disease or condition, the Secretary may not approve another application under section 355 of this title or issue another license under section 262 of title 42 for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. …

See section 527 of the FD&C Act, 21 U.S.C. 360cc; *see also* 21 CFR 316.3(b)(12) and 21 CFR Part 316(D).

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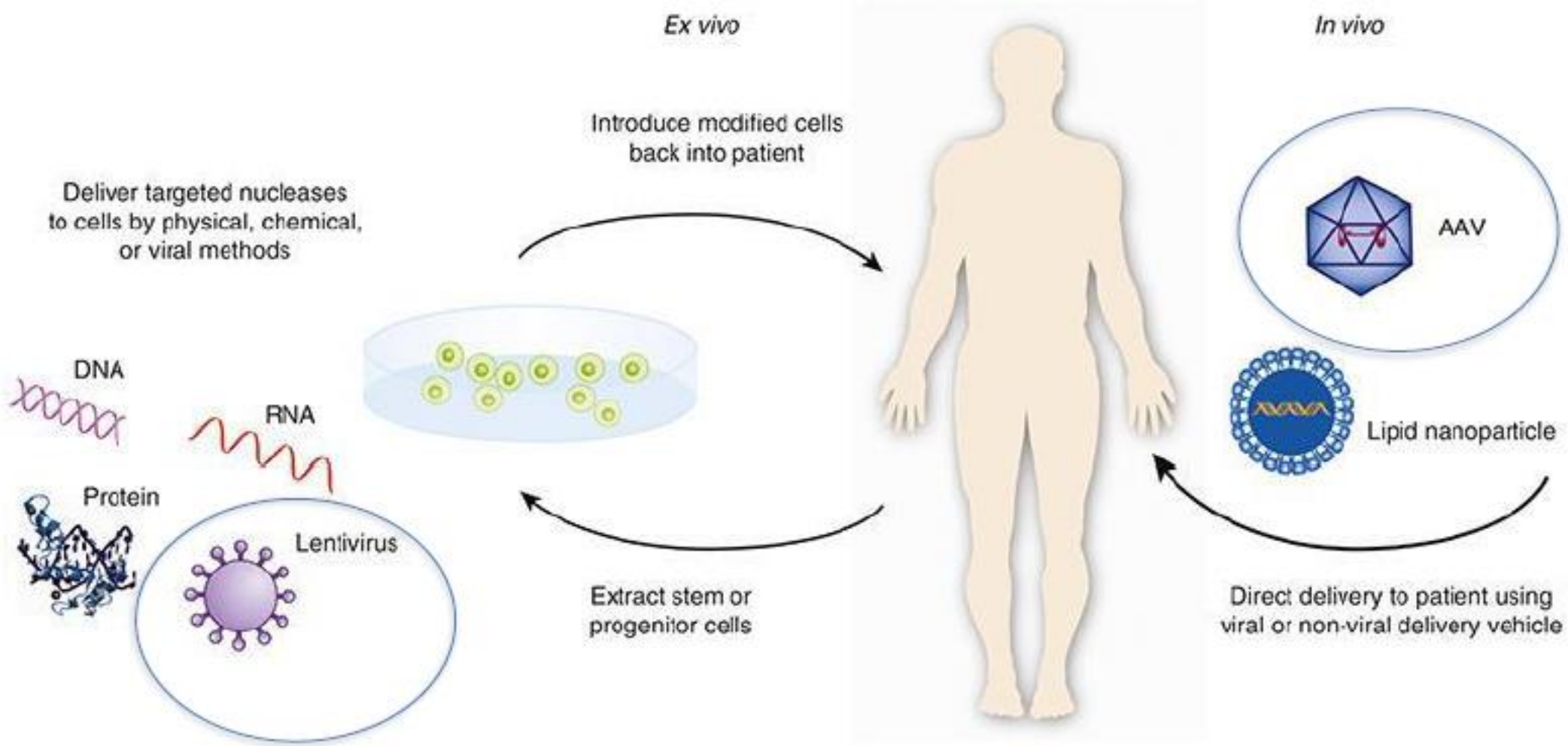
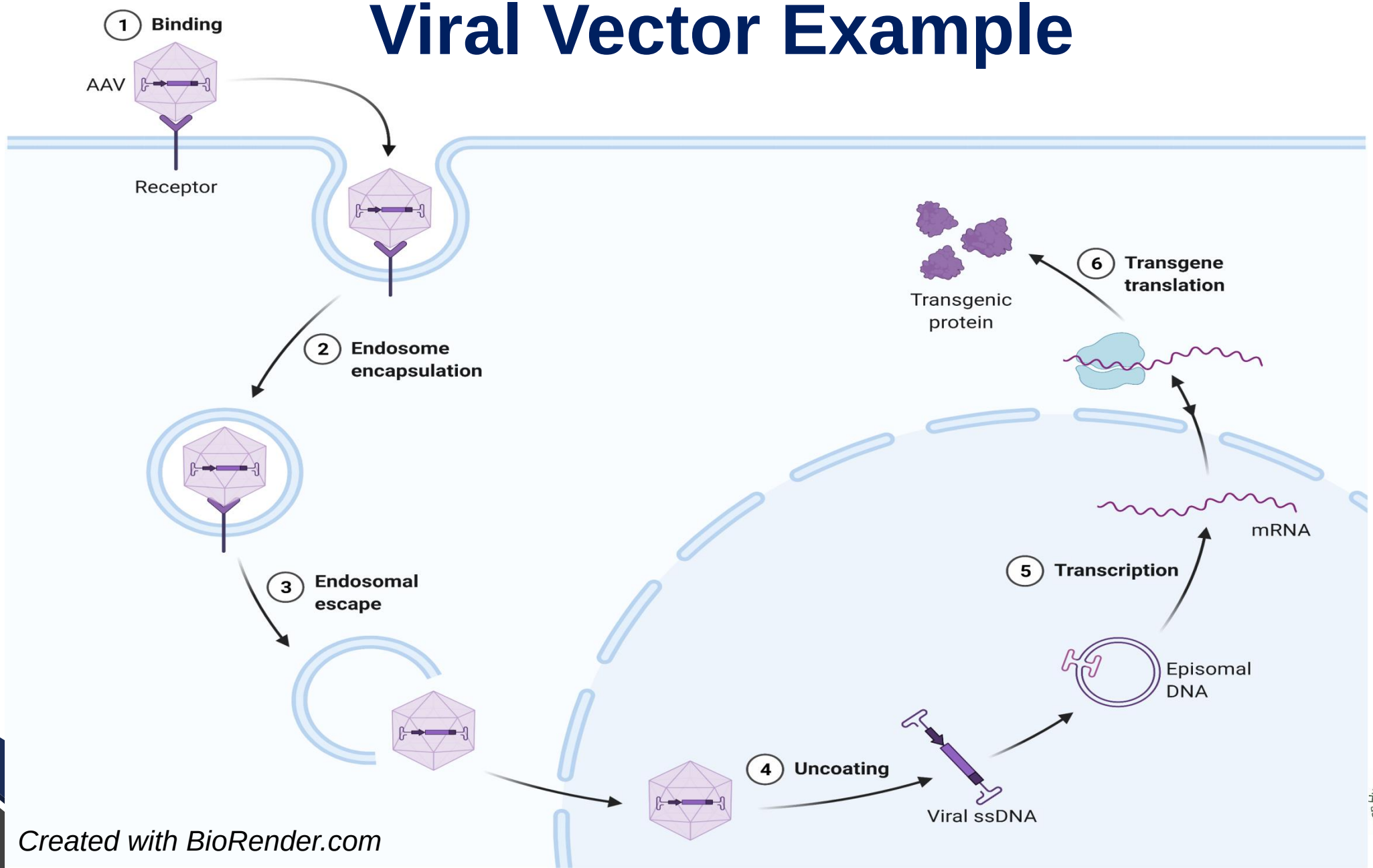
Gene Therapy Overview



www.fda.gov

Viral Vector Example



Created with BioRender.com

FDA Draft Guidance

"*Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*" (January 2020)

- **Same drug** means:

  (i) If it is a drug composed of small molecules, a drug that contains the same active moiety … and is intended for the same use as the previously approved drug, ...

  (ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug.

  21 CFR 316.3(b)(14)

FDA Draft Guidance (cont'd)

- **Examples** from Guidance:
  - If different transgenes → different drugs
  - If vectors of different viral class (e.g., gammaretrovirus vs. adeno-associated virus (AAV) → different drugs
  - If same transgene and same viral class (e.g. AAV2 vs. AAV5) … sameness will be determined on a case-by-case basis.
  - If there are only minor differences between transgenes and/or vectors → **NOT** different drugs
  - Sameness… may also depend on additional features … that can contribute to the therapeutic effect (e.g., regulatory elements, cell type that is transduced)

Draft Guidance at 3-4.

FDA Draft Guidance (cont'd)

Are Two Gene Therapy Products the Same or Different?

	Different
	Different
	Different
	Depends

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FDA Draft Guidance – Public Comments

- Scope of the guidance—*i.e*. whether it applies to oncolytic viruses, genome editing and mRNA-based therapies
- Clarity on "**minor differences**" and "**additional features**"
- What factors will be considered in "**case-by-case**" determinations
- Criteria and types of data that the FDA will consider

See, e.g. comments by PhRMA, Biomarin, BIO, ASGCT

FDA Draft Guidance – Public Comments (cont'd)

- Consider therapies based on viruses of the same class but different serotypes → **different** drugs, given differences in tropism, immunogenicity and infectivity

See, e.g., comments by Regeneron & Pfizer

- Consider therapies using different manufacturing systems and technologies → **different** drugs

See, e.g., comments by CSL Behring, Freeline Therapeutics

Summary and Future Direction

- ***The draft guidance***:
  - Applies “sameness” broadly to encompass vectors of the same viral class, and transgenes expressing the same enzyme.
  - Leaves uncertain what differences will be sufficient, and what data and criteria will be applied in a “case-by-case” analysis.
  - Creates potential for litigation over these issues.
- Although a manufacturer can avoid “sameness” by showing clinical superiority, this is challenging, given the small patient numbers and high cost of manufacturing.
- While orphan exclusivity provides a useful incentive, it can discourage drug development if applied too broadly.
- Having more clear and balanced guidance will reduce cost, decrease litigation, and benefit patients with rare diseases.

Recent Case Developments

Notice Requirement Development

Genentech, Inc. v. Immunex Rhode Island Corp.,
964 F.3d 1109 (Fed. Cir. 2020)

- **Facts and procedural history –** Genentech manufactured Avastin; Amgen filed aBLA to market biosimilar version, called Mvasi; Amgen sent § 262(l)(8)(A) letter notifying Genentech of its intent to commercially market Mvasi; Amgen filed two supplements to its application and, in August 2018, third supplement adding manufacturing facility and fourth supplement changing its drug label; in July 8, 2019, Amgen was ready to commercially launch Mvasi; Genentech filed motions based on Amgen's alleged failure to comply with notice requirement under § 262(l)(8)(A); D. Del. denied motions; Genentech appealed. *See id.* at 1110-11.
- **Question –** Whether Amgen's initial letter or later supplementations trigger 180-day waiting period under § 262(l)(8)(A). *See id.* at 1111.
- **Rationale –** "The statute makes clear that the biosimilar applicant must provide notice to the reference product sponsor prior to commercially marketing *the* ***biological product***." *Id.* (emphasis in original). § 262(l)(8)(A) states, "The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)."
- **Holding –** Affirmed. "Amgen notified Genentech of its intent to commercially market its biological product, Mvasi, on October 6, 2017. Despite its later supplements . . . Mvasi did not change. Genentech, therefore, had notice of Amgen's intent to commercially market Mvasi as required under Section 262(l)(8)(A) as early as October 6, 2017." *Id.*

Venue Development

Valeant Pharms. N. Am. LLC v. Mylan Pharms. Inc.,
978 F.3d 1374 (Fed. Cir. 2020)

- **Facts and procedural history –** Mylan submitted Paragraph IV certification for Valeant's Jublia Orange-Book-listed patents; Valeant filed complaint in D.N.J. alleging Mylan infringed Orange-Book-listed patents pursuant to Hatch-Waxman Act; Mylan moved to dismiss for improper venue and under 12(b)(6); D.N.J. dismissed complaint based on improper venue; Valeant appealed. *See id.* at 1376-77.
- **Question –** "[W]here 'acts of infringement' under § 1400(b) occurred with respect to infringement claims brought pursuant to the Hatch-Waxman Act." *Id.* at 1375 (footnote omitted).
- **Rationale –**
  - "[H]as committed acts of infringement" [in § 1400(b)], a present perfect phrase, counsels that the acts accused o infringement must have already occurred." *Id.* at 1381.
  - "A plain language reading of th[e] [Hatch-Waxman Act] directs us to the conclusion that it is the submission of the ANDA, and only the submission, that constitutes an act of infringement in this context." *Id.*
- **Holding –** Affirmed on this issue. "[I]n Hatch-Waxman cases, venue is not proper in all judicial districts where a generic product specified in an ANDA is likely to be distributed. It is proper only in those districts that are sufficiently related to the ANDA submission—in those districts where acts occurred that would suffice to categorize those taking them as a 'submitter' under § 271(e)." *Id.* at 1384.

Written Description/Enablement Development

Amgen Inc. v. Sanofi, Aventisub LLC,
987 F.3d 1080 (Fed. Cir. 2021)

- **Facts and procedural history –** Amgen filed complaint against Sanofi alleging infringement of two patents; Amgen and Sanofi stipulated to infringement of select claims and tried issues of validity to jury; D. Del. granted JMOL of nonobviousness and no willful infringement; jury found Sanofi failed to prove invalidity based on lack of enablement and written description; Sanofi appealed; Federal Circuit held D. Del. erred in its evidentiary rulings and jury instructions regarding Sanofi's defenses of lack of enablement and written description and remanded; parties tried written description and enablement to jury; jury found Sanofi failed to prove invalidity; D. Del. granted JMOL for lack of enablement and denied JMOL for lack of written description; Amgen appealed. *See id.*
- **Question –** Whether claims directed to genus of monoclonal antibodies were enabled. *See id.*
- **Rationale –** "Here, the evidence showed that the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations." *Id.*
- **Holding –** Affirmed. "The functional limitations here are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude under these facts that anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments." *Id.*

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Thank you!