

Key Regulatory Issues in Biosimilars

May 4, 2017

John Manthei, Esq. – Moderator
Latham & Watkins LLP

Key Regulatory Issues in Biosimilars

- The abbreviated pathway for U.S. licensure of biosimilars turned 7 years old in March 2017.
 - Established by the Biologics Price Competition and Innovation Act (BPCIA) in 2010 as part of the Affordable Care Act.
 - To date, FDA has approved 5 biosimilar product applications and issued 6 final / 4 draft guidance documents addressing implementation of the BPCIA.
 - As of February 1st, FDA has received meeting requests for biosimilar development programs involving more than 20 different reference biologics.
- Biosimilars are a critical issue with implications for key areas of health policy.
 - Biologics are predicted to account for ~50% of U.S. prescription drug spending by 2018.
 - It is projected that biosimilars could produce \$44-\$250 billion of savings over 10 years.
 - Lower costs may provide opportunities to expand access to biologics for more patients.
- Significant questions regarding the labeling of interchangeable products, reference product exclusivity, “patent dance” mechanics and pharmacy substitution policies – to name just a few – remain outstanding.

Biosimilars—FDA Update

FDLI Annual Conference 2017

Joe Franklin, JD, PhD
Associate Director for Policy
Therapeutic Biologics and Biosimilars Staff
Office of New Drugs
Center for Drug Evaluation and Research, FDA
May 4, 2017

Section 351 of the PHS Act:

Key Concepts



- **Biological product:** § 351(i)(1)
- **§ 351(a) BLA**
- **§ 351(k) BLA:** biosimilar/interchangeable
- **Biosimilar:** § 351(i)(2)
- **Interchangeable:** § 351(i)(3)
- **Reference Product:** § 351(i)(4)
- **Exclusivity:** § 351(k)(6)-(7)

Biosimilars: Approvals and Development Programs



- FDA has approved **5** biosimilars (as of 4/27/2017)
- As of April 1, 2017:
 - **9** companies have publicly announced submission of **14** 351(k) BLAs to FDA.
 - **66** programs were enrolled in the Biosimilar Product Development (BPD) Program.
 - CDER has received meeting requests to discuss the development of biosimilars for **23** different reference products.

Final Guidance Documents



1. **Scientific Considerations** in Demonstrating Biosimilarity to a Reference Product (final, 2015)
2. **Quality Considerations** in Demonstrating Biosimilarity to a Reference Protein Product (final, 2015)
3. **Biosimilars: Questions and Answers** Regarding Implementation of the BPCI Act (final, 2015)
4. **Formal Meetings** Between the FDA and Biosimilar Biological Product Sponsors or Applicants (final, 2015)
5. **Clinical Pharmacology Data** to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)
6. **Nonproprietary Naming** of Biological Products (final, 2017)

Draft & Upcoming Guidance



1. **Reference Product Exclusivity** for Biological Products Filed Under Section 351(a) of the PHS Act (draft)
2. **Biosimilars: Additional Questions and Answers** Regarding Implementation of the BPCI Act (draft)
3. **Labeling** for Biosimilar Products (draft)
4. Considerations in **Demonstrating Interchangeability** With a Reference Product (draft)
5. **Statistical Approaches to Evaluation of Analytical Similarity Data** to Support a Demonstration of Biosimilarity (2017 CDER Guidance Agenda)

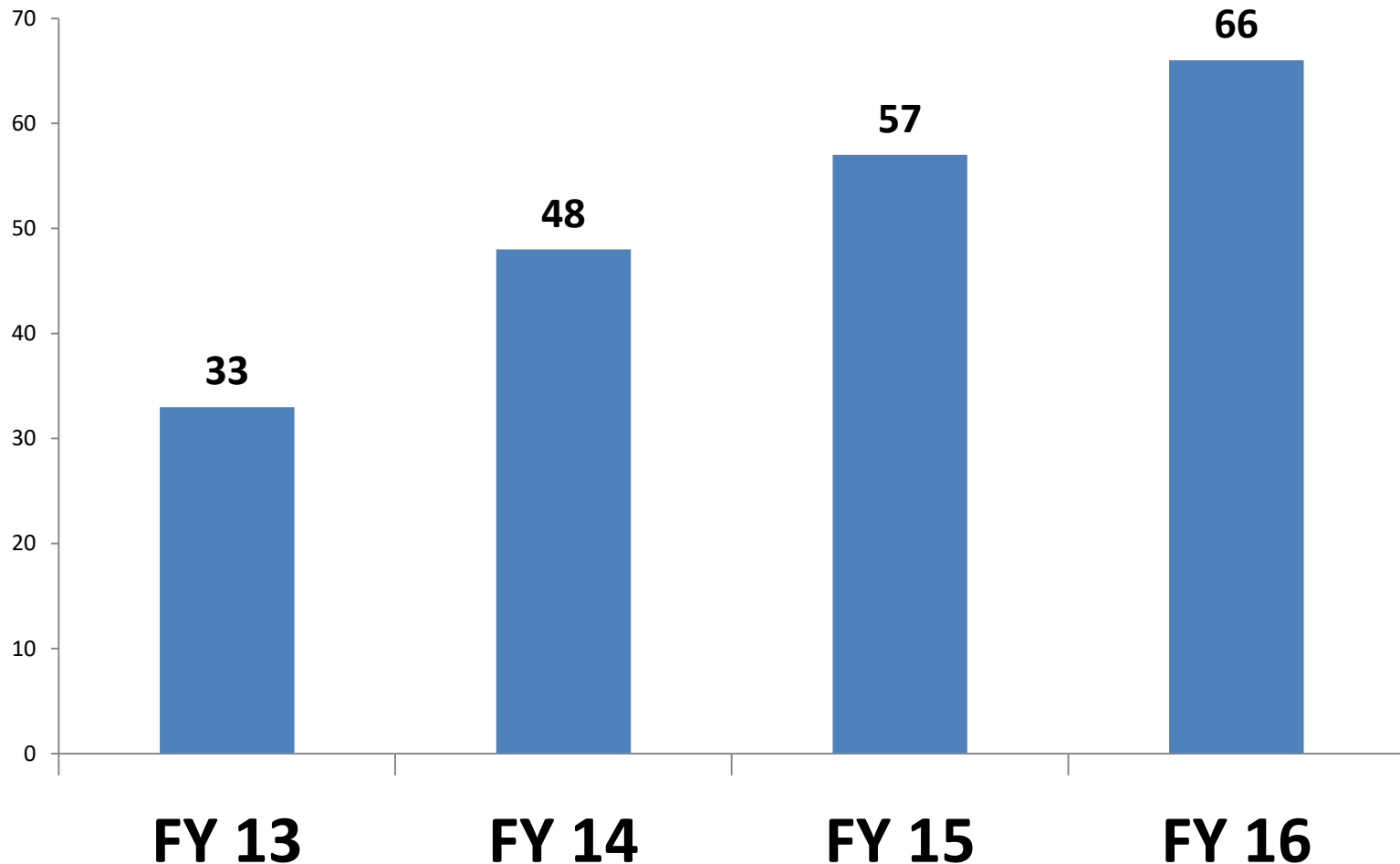
Therapeutic Biologics and Biosimilars Staff (TBBS)

- Within the CDER's Office of New Drugs (OND) Immediate Office
- **Focused scientific and regulatory policy support for scientific/medical reviewers**
- **Promotes development and consistency of scientific and regulatory approaches for biologics and biosimilars**
- Coordination with other Center and agency components
- Led by Leah Christl, Ph.D.

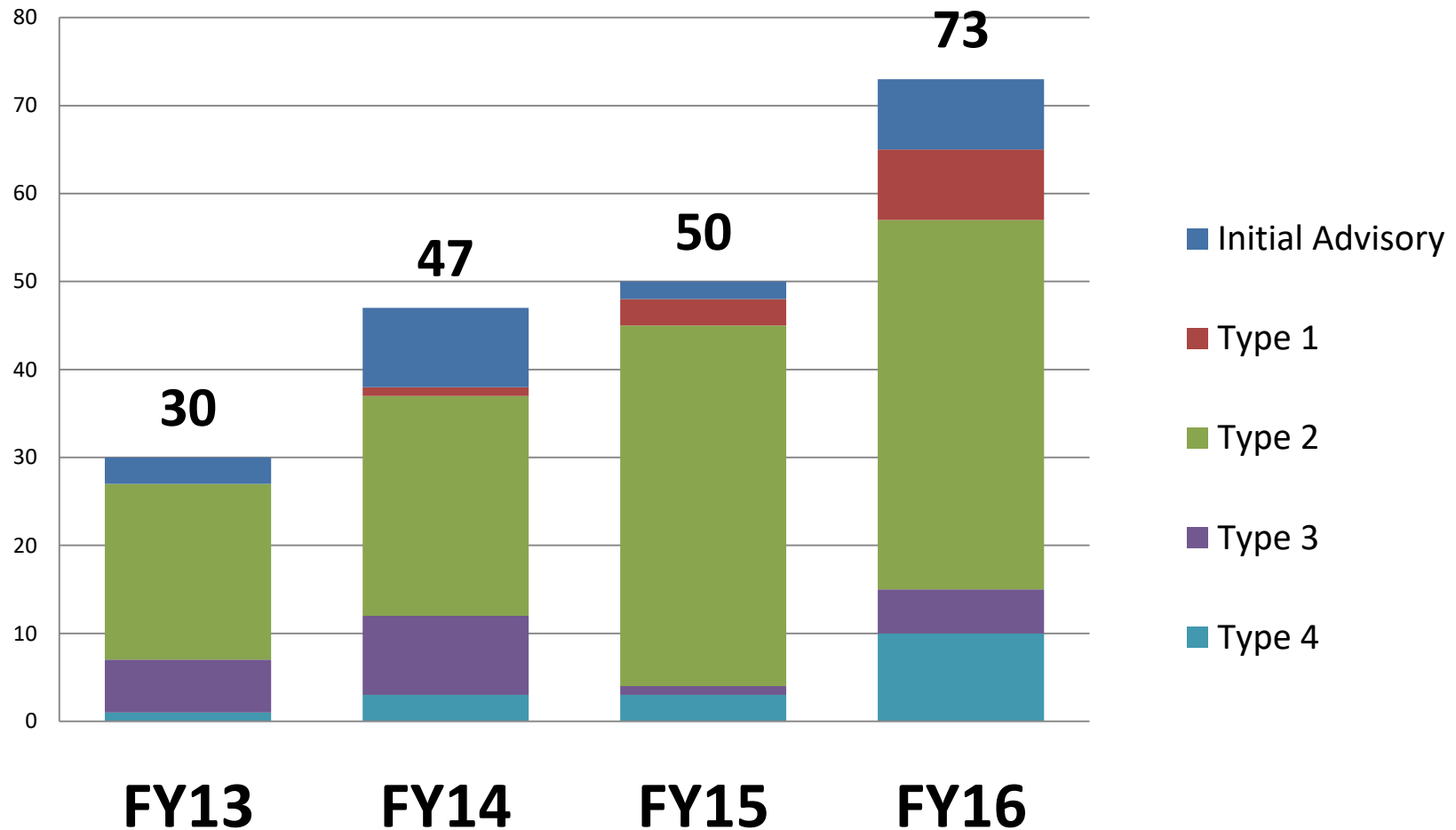
Five Years into BsUFA

- BsUFA I: 2012-2017
- Growth in BPD program; requests for FDA advice from prospective biosimilar applicants
- Growth in 351(k) submissions
- **Development programs and applications generally raise unique scientific and regulatory issues.**

Growth in BPD Enrollment



Scheduled BPD Meetings



Upcoming Issues

Draft & Upcoming Guidance



1. **Reference Product Exclusivity** for Biological Products Filed Under Section 351(a) of the PHS Act (draft)
2. **Biosimilars: Additional Questions and Answers** Regarding Implementation of the BPCI Act (draft)
3. **Labeling** for Biosimilar Products (draft)
4. Considerations in **Demonstrating Interchangeability** With a Reference Product (draft)
5. **Statistical Approaches to Evaluation of Analytical Similarity Data** to Support a Demonstration of Biosimilarity (2017 CDER Guidance Agenda)

Interchangeability

Draft Guidance



Includes recommendations related to:

- “alternating or switching,” § 351(k)(4)(B):
- “same clinical result as the reference product in any given patient,” § 351(k)(4)(A)(ii)
- Use of US-licensed reference product in studies
- Product presentations considerations

Interchangeability

Draft Guidance



NOA (82 FR 5579) invited comment on:

- Draft guidance
- Regulation of post-approval manufacturing changes of interchangeable products
- Conditions of use that are licensed for the RP after an interchangeable has been licensed

Comment period ends on 5/19/17 (82 FR 13819)

Draft & Upcoming Guidance



Other draft guidance to note:

- Implementation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 (draft)



Key Regulatory Issues in Biosimilars

An Update on the BPCIA and the “Patent Dance”

Chad A. Landmon

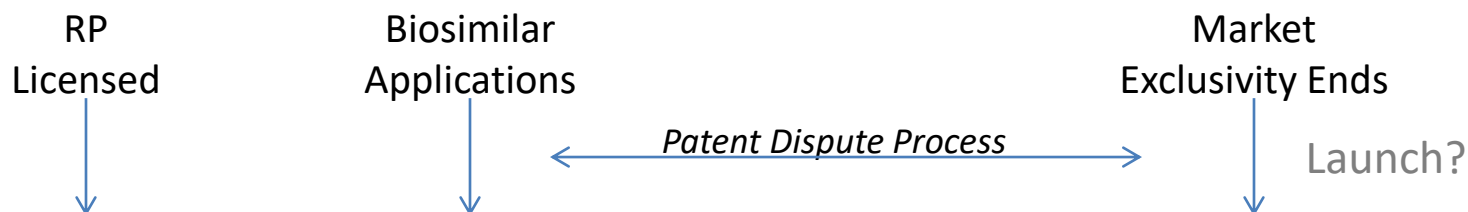
Partner

Axinn, Veltrop & Harkrider LLP

clandmon@axinn.com

Biologics Price Competition & Innovation Act

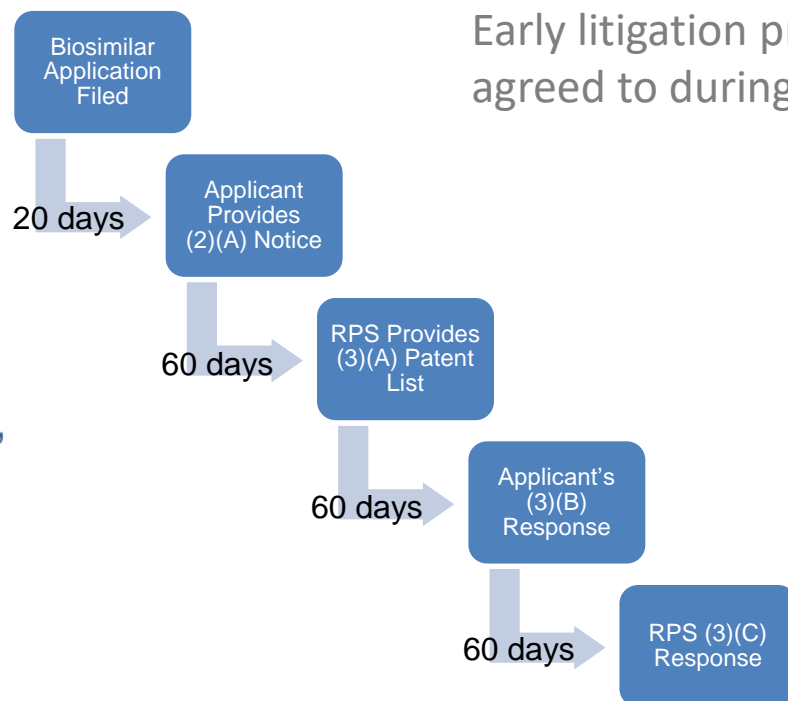
- Abbreviated pathway to FDA licensure for follow-on alternatives to biologics
- Timing
 - Applications may not be submitted until 4 years after RP licensed
 - Licenses “may not be made effective” until 12 years after RP licensed



Patent Dispute Process

Early Phase Litigation

“Patent Dance”



Early litigation proceeds on patents agreed to during negotiations

Negotiation

If parties disagree, Applicant selects number of patents at issue

A selection of 0 means that RPS may choose 1 patent

Patent Dispute Process

- Applicant provides **Notice of Commercial Marketing**. (42 U.S.C. § 262 (l)(8)(A))
- Late litigation: Before the first commercial marketing, the reference product sponsor (“RPS”) may seek **a preliminary injunction** prohibiting the commercial manufacture or sale of the biosimilar product until the court decides issues of patent validity, enforcement, and infringement.

Late litigation can proceed on any patent included on one of the initial “lists” provided by the RPS or Applicant that is not included on the early phase negotiated lists

Notice of Commercial Marketing

- The subsection (k) applicant ***shall provide*** notice to the reference product sponsor (RPS) not later than 180 days before the date of the first commercial marketing of the biological product ***licensed under subsection (k)***.
- Failure to Provide Notice of Commercial Marketing
 - RPS may bring Declaratory Judgment action for patent infringement, validity or enforceability (42 U.S.C. § 262(l)(9)(B))

Amgen Inc. v. Sandoz Inc., No. 2015-1499 (Fed. Cir. July 23, 2015) (Neupogen®)

- Complying with 42 U.S.C. § 262 (l)(2)(A) (providing aBLA and manufacturing process) is not mandatory because BPCIA provides a remedy.
- The Applicant can provide effective notice of commercial marketing only **after** the FDA has licensed (approved) the biosimilar product.
- Where the Applicant fails to provide its aBLA and manufacturing information, the 180-day notice of commercial marketing is mandatory; in this case, Sandoz may not market Zarxio before 180 days from March 6, 2015, *i.e.*, September 2, 2015.
- If Applicant provides the aBLA and manufacturing information but fails to provide Notice of Commercial Marketing - RPS can seek a declaratory judgment. (42 U.S.C. § 262(l)(9)(B))

Amgen Inc. v. Sandoz Inc.

- After petition for *en banc* rehearing denied, Sandoz petitions Supreme Court (Feb. 16, 2016).
- Questions presented:
 - Whether **notice of commercial marketing given before FDA licensure is effective?**
 - Whether treating **Section 262(l)(8)(A)** as a **standalone requirement and creating an injunctive remedy** that delays all biosimilars by 180 days after approval is improper?
- Federal Circuit erred by holding “than an applicant ‘may only give effective notice of commercial marketing *after* the FDA has licensed its product.”
- Federal Circuit erred by “creating a new remedy . . . an injunction against commercial marketing until 180 days after post-approval notice is given.”

Amgen Inc. v. Sandoz Inc.

- Amgen opposes petition for certiorari
 - Amgen argues that the Federal Circuit was correct – “notice of commercial marketing is effective only after FDA licensure of the Applicant’s product under subsection (k).”
- Amgen files conditional cross-petition in March 2016 to introduce other “patent dance” questions into appeal
 - Is an Applicant required by 42 U.S.C. § 262(l)(2)(A) to provide the Sponsor with [a copy of its biologics license application and related manufacturing information](#), which the statute says the Applicant “shall provide,” and, where an Applicant fails to provide that required information, is the Sponsor’s [sole recourse](#) to commence a declaratory-judgment action under 42 U.S.C. § 262(l)(9)(C) and/or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii)?

Amgen Inc. v. Sandoz Inc.

- Supreme Court deferred decision on cert and sought Solicitor General input.
 - Solicitor General: Supreme Court should review and decide in Sandoz's favor on questions presented by the parties' cross-petitions for certiorari.
- On January 13, 2017, Supreme Court granted Sandoz's petition and Amgen's cross-petition, consolidating case nos. 15-1039 and 15-1195.
- Represents first time Supreme Court will interpret BPCIA
- On April 13, 2017, Supreme Court granted Acting Solicitor General's motion to participate in oral argument
- Oral argument held on **April 26, 2017**

“Tentative” License for Biosimilars?

- Federal Circuit doubled down on post-licensure notice of commercial marketing in *Amgen v. Apotex* (Neulasta®), No. 2016-1308 (Fed. Cir. July 5, 2016).
- Attempted to address the criticism of *Amgen v. Sandoz*, that requiring notice post-licensure effectively extends by 180 days the 12-year exclusivity term of the RP:

“[W]e have been pointed to no reason that the FDA may not issue a license before the 11.5-year mark and deem the license to take effect on the 12-year date—a possibility suggested by § 262(k)(7)(A)’s language about when the FDA approval may ‘be made effective.’”

“Tentative” Licensure for Biosimilars?

- Federal Circuit suggests that text of BPCIA provides statutory authority to FDA to provide an alternative solution in the form of pre-effective date approvals.
 - FDA can tentatively license a biosimilar any time after the aBLA is submitted and still comply with § 262(k)(7)(A), which provides that biosimilar approval “**may not be made effective** . . . until the date that is 12 years after the date on which the reference product was first licensed.”
- The court stated that it “read 8(A) as allowing the 180-day notice of commercial marketing to be sent as soon as the license issues, even if it is not yet effective, because it is at the time of the license that ‘the product, its therapeutic uses, and its manufacturing processes are fixed.’”
- Effectively invites FDA to create a process akin to the “tentative approval” process for generic drugs under the Hatch-Waxman Act.

“Tentative” Licensure for Biosimilars?

- Does BPCIA provide FDA with adequate statutory authority to issue tentative aBLA licenses?
- Will the Applicant be able to provide proper notice of commercial marketing that meets the requirement under § 262(l)(8)(A) upon receiving such tentative licensure?
- Would FDA want to grant tentative licenses without finalized regulations covering such an approach under the BPCIA?
- FDA’s position on tentative licenses for aBLAs is currently unknown.
 - In the absence of such a position, possibility of CP to force the question, or possibly litigation by an Applicant?

Current Status

- Pending Supreme Court decision in *Amgen v. Sandoz*, Applicant **must** provide notice of commercial marketing **after** receiving FDA approval and 180 days prior to first commercial sales, effectively extending 12-year exclusivity period.

Outcomes on Notice and Market Entry

- Notice can only be provided post-licensure → Effectively provides RPS with a 180-day injunction beyond 12-year exclusivity period; further subject to preliminary or permanent injunction
- Notice can be given before licensure → Applicants can strategically time when to provide notice; notice triggers second wave before FDA licensure; potential for earlier market formation, subject to injunctions

Questions?

Key Regulatory Issues in Biosimilars

Ensuring Patient Access

Christine M. Simmon
Senior Vice President Policy & Strategic Alliances
Executive Director, Biosimilars Council



Your Generics & Biosimilars Industry



The Biosimilars Council

- Launched in April, 2015
- **Mission:** The Biosimilars Council, a division of the Association of Accessible Medicines (formerly known as the Generic Pharmaceutical Association (GPhA)), works to support the broad components of the biosimilar industry, and enable patients increased access to safe, effective and affordable biosimilar medicines.
- See www.biosimilarscouncil.org



Biosimilars Council Member Companies

APOTEX
ADVANCING GENERICS

 **biorasi**[™]
CLINICAL RESEARCH OPTIMIZED[™]
Powered by ProAct+[™]

 **Mylan**


AmerisourceBergen[®]

PFE*nex*


amneal
PHARMACEUTICALS

 **DR. REDDY'S**

 **SANDOZ**
a Novartis company

 **Biocon**

 **LUPIN**
PHARMACEUTICALS, INC.

TEVA

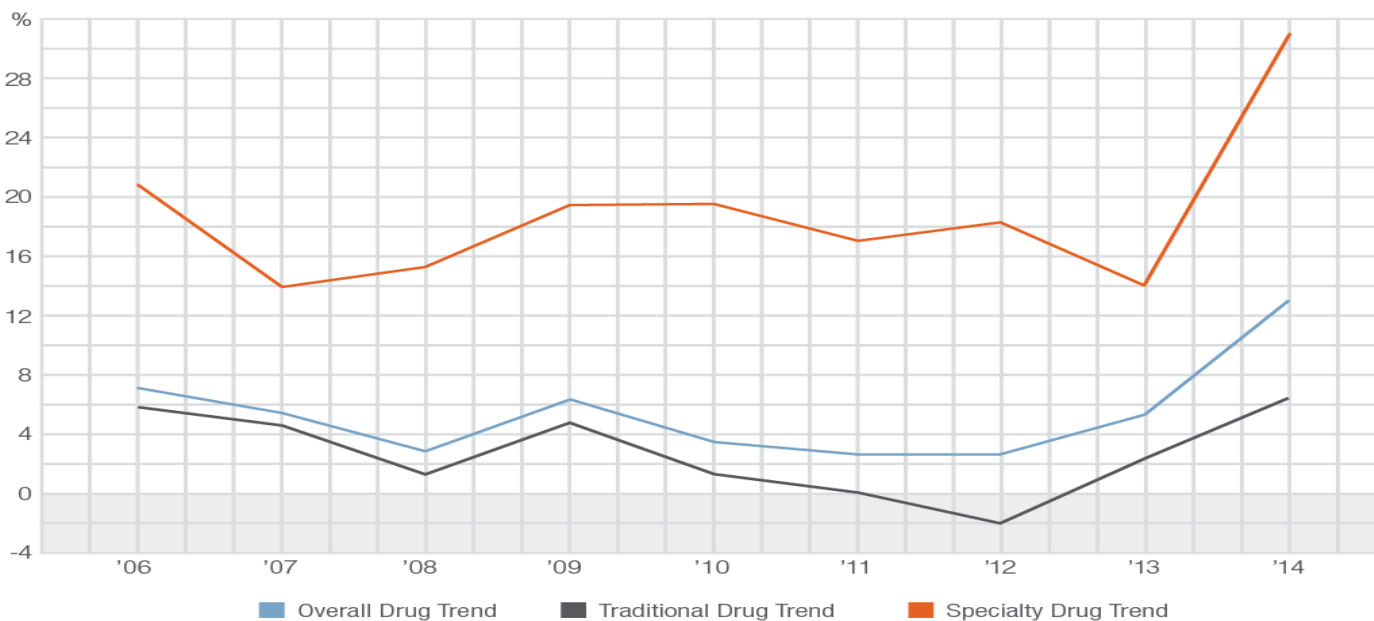
MOMENTA 

ZYDUS
PHARMACEUTICALS
A GLOBAL GENERIC PHARMACEUTICAL COMPANY

Specialty Drug Spending is Rising Unsustainably

COMPONENTS OF OVERALL DRUG TREND

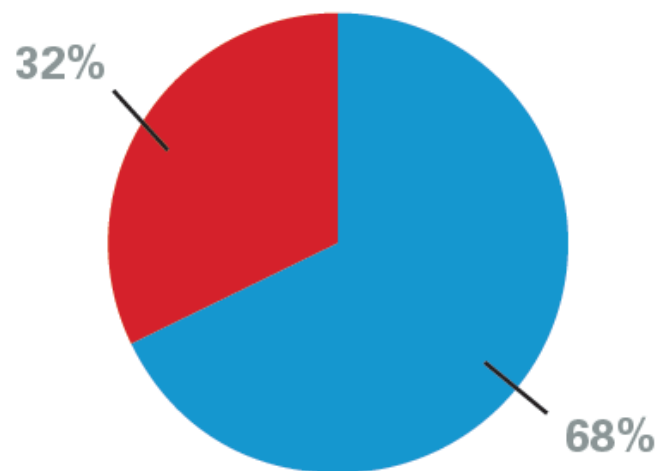
EXPRESS SCRIPTS 2006-2014



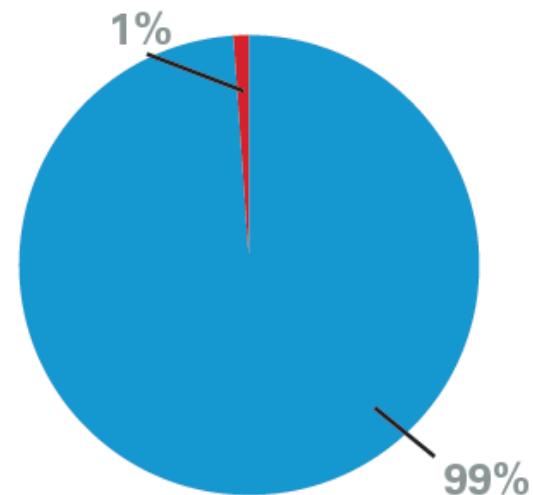
Specialty Drug Costs Are the Real Threat to Sustainability of the Health Care System

Figure 1: U.S. Spending on Prescription Drugs, 2014

Prescription Drug Spending in 2014



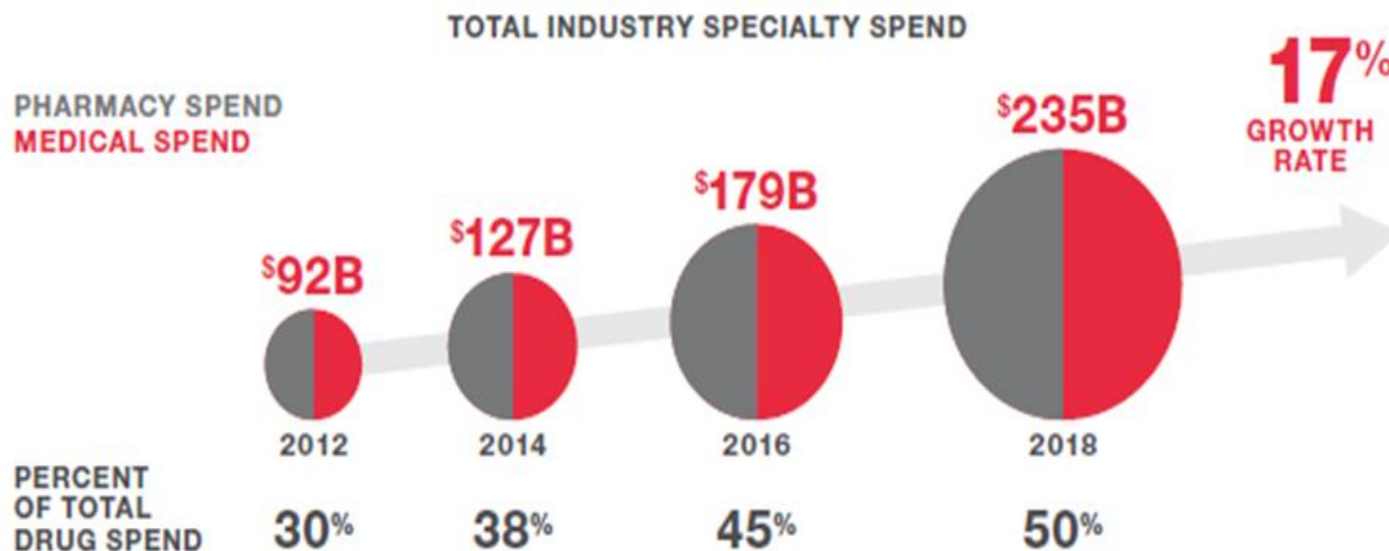
Prescriptions Written in 2014



Source: The Express Scripts 2014 Drug Trend Report. March 2015. Available at: <http://lab.express-scripts.com/drug-trend-report/>

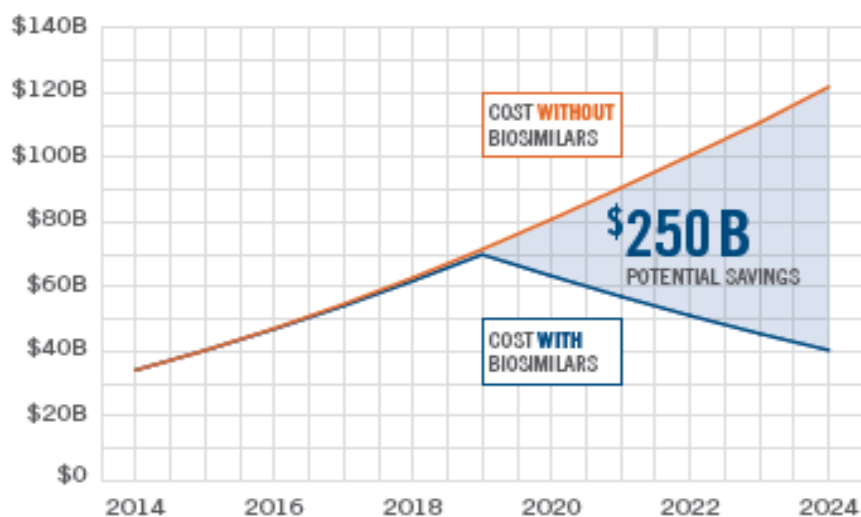
Specialty Meds Will See Continued Growth

SPECIALTY IS GROWING IN ABSOLUTE DOLLARS AND PERCENT OF DRUG SPEND⁴



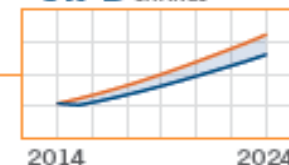
Biosimilars Offer Significant Opportunities for Savings

\$250 BILLION COULD BE SAVED IN THE NEXT DECADE IF THESE 11 BIOSIMILARS ARE APPROVED

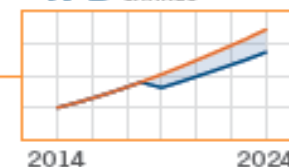


Avastin[®] (bevacizumab)
 Epogen[®] (epoetin alfa)
 Herceptin[®] (trastuzumab)
 Humira[®] (adalimumab)
 Intron A[®] (interferon alfa-2a)
 Neulasta[®] (pegfilgrastim)
 Neupogen[®] (filgrastim)*
 Pegintron[®] (peginterferon alfa-2b)
 Procrit[®] (epoetin alfa)
 Remicade[®] (infliximab)*
 Rituxan[®] (rituximab)

\$5.7 B POTENTIAL SAVINGS



\$17 B POTENTIAL SAVINGS



*Awaiting FDA approval.

Numerous Outstanding Policy Issues Remain

- **Legislative:**
 - Federal:
 - BSUFA II
 - Ensuring no barriers to accessing samples
 - Inter Partes Review
 - State: Continue to pass legislation to allow pharmacy level substitution
- **Regulatory:**
 - Interchangeability
 - Extrapolation of additional indications
 - Reimbursement

Legislative - Federal

BSUFA II Enhancements

- Application review extended to 12 months (from 10 months) but with increased FDA-sponsor communication;
- Meeting management enhanced;
 - FDA feedback in advance of meetings
 - Timing for various meetings was adjusted
- FDA committed to complete guidances by specific dates;
- User fee adjustments;
 - To be based solely on biosimilar program costs (BsUFA 1 was tied to PDUFA)
 - No establishment or supplement fees
- FDA commits to hiring staff to work on biosimilars;
 - 15 dedicated to biosimilar coordination and policy
 - Additional review staff
- Modernization of FDA resource tracking spent on biosimilars;
- Annual meeting to review status of BsUFA finances.

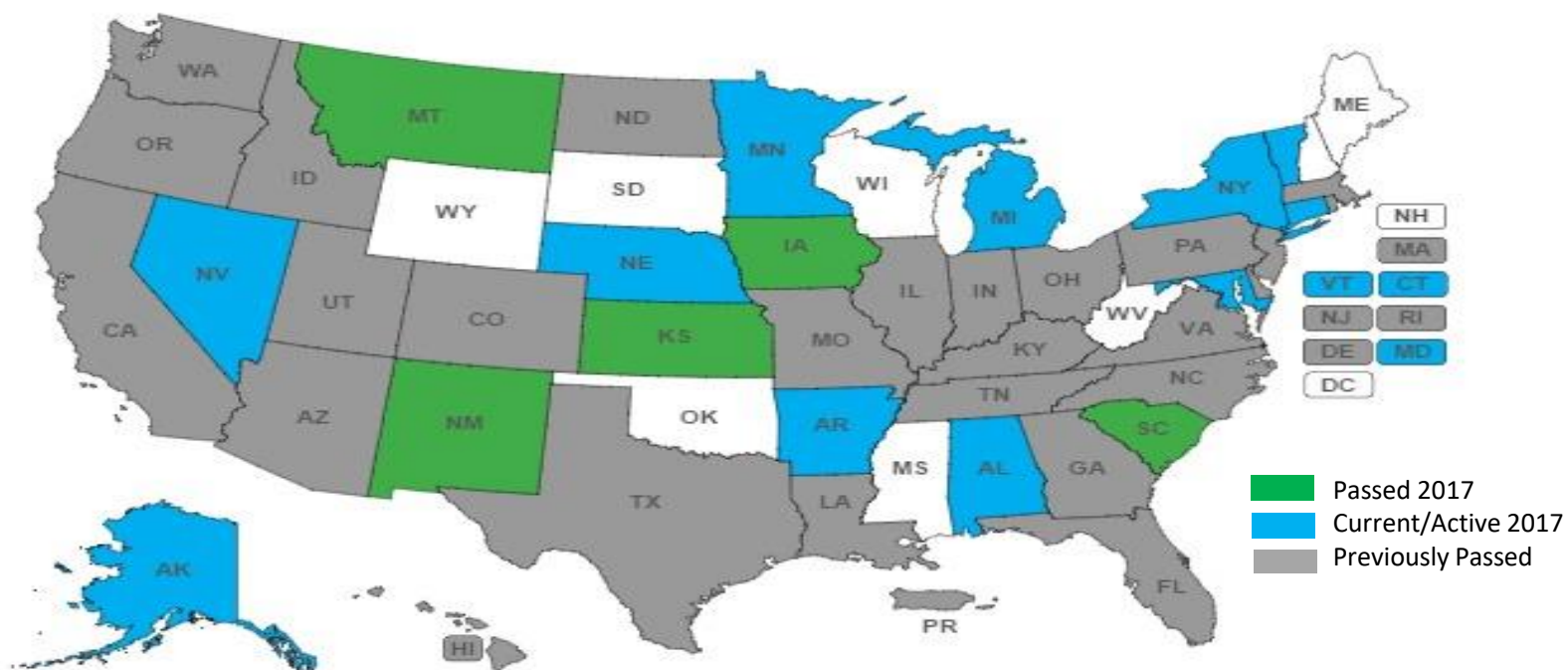
Legislative - Federal

- Anticompetitive abuse of Risk Evaluation and Mitigation Strategy (REMS) and restricted distribution systems affect approximately 120 products that total \$30 Billion per year in costs
- “**Creating and Restoring Equal Access to Equivalent Samples Act of 2017**” (CREATES) was introduced by bi-partisan Senate & House members.
- Addresses REMS abuses that deny the product samples and also those that deny access into to an FDA approved single-shared REMS program.
- Empowers courts to award damages that would incentivize good-faith dealing.
- Ensures patient safety by requiring authorization from FDA for sample recipients.
- CBO scored it as a \$3.3 billion saver.

Legislative - Federal

- Some advocates have called to exempt pharmaceutical patents from the IPR process.
- This exemption is unnecessary, and would ultimately cost patients and payers more by delaying competition and increasing the cost to develop a competitor:
 - The cost of an exemption would be over \$X.X to the federal government alone;
 - Only a small fraction of IPRs instituted are for pharmaceutical patents, around 8%;
 - There is no evidence that pharmaceutical patents are overturned at IPR more often than any others;
 - The IPR process has been proven to be a more efficient process for the review of patents than traditional district court litigation, and is subject to judicial review after a decision has been rendered.

Legislative - State Interchangeable Biologic Substitution



Regulatory - Extrapolation

- Biosimilar applicants are not required to provide clinical data for every indication of the reference product.
 - Clinical data in applications is focused on showing biosimilarity rather than individual safety and efficacy profiles for each indication
- Some groups have requested individual Advisory Committee votes for each indication, which would be a departure from how FDA has approached extrapolation so far, as well as from the generics market.
- To date, all biosimilar products approved have been extrapolated for all indications.
- FDA is expected to put out guidance titled “Statistical approaches to evaluation of analytical similarity data to support a demonstration of biosimilarity” which will expand upon the types of evidence biosimilar applicants can rely on.

Regulatory -- Interchangeability

- The FDA issued draft guidance Jan. 12, 2017.
- The Council still developing comments, and is generally supportive.
- Potential areas of concern:
 - The statute does not prescribe the type or amount of information required to make any of the specific showings required for an interchangeability determination but instead leaves it to FDA's discretion to determine whether the "information" submitted is "sufficient" on a case-by-case basis depending upon the specific product in question.
 - Complexity of biological products varies widely, and this affects the type and amount of data required to demonstrate both biosimilarity and interchangeability.
 - Too much testing to demonstrate interchangeability could approach or even exceed that required to obtain approval of a full BLA. This, in turn, would erect significant barriers to the development of interchangeable biological products that, as a practical matter, would serve as an effective deterrent to applicants seeking to use this important licensure pathway.

Reimbursement Roundup

Federal payment policy on biosimilars is inconsistent across programs.

When a biosimilar comes to market, relevant determinations will follow conventions similar to...	Innovator Biologic	Generic Drug	Unique Biosimilar
Medicare Part B			
Coverage	✓		
Coding			✓
Payment			✓
Medicare Part D			
Transition Fills	✓		
P&T Committee Formulary Review Timeline	✓		
USP Coverage Requirements		✓	
LIS Cost Sharing	✓		
Coverage Gap Discount Program		✓	
Mid-Year Formulary Changes	✓		
Protected Classes		Unknown	
Medicaid			
Rebates	✓		

Questions?