BOCA RATON REGIONAL HOSPITAL

The Role of Biosimilar Medications in Clinical Practice

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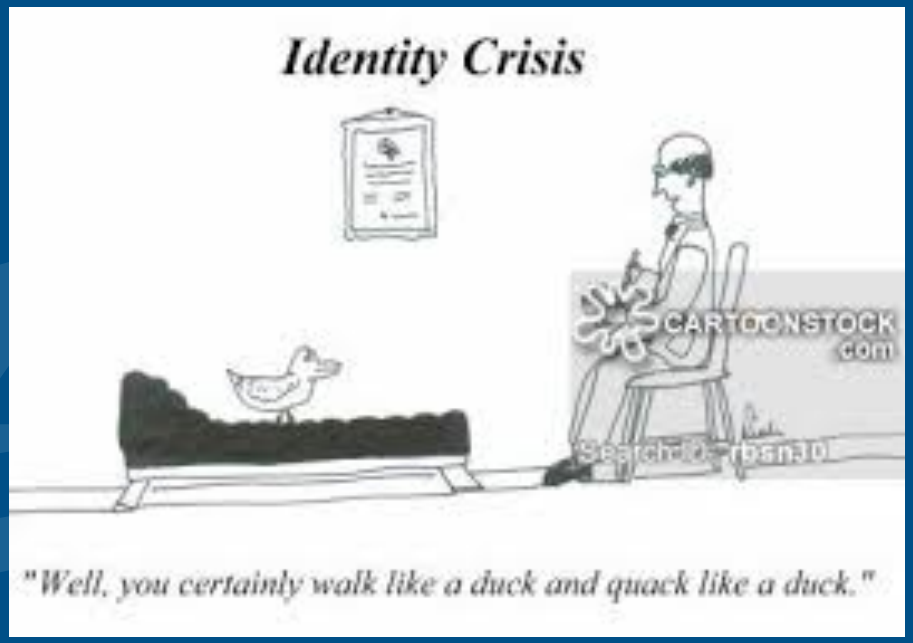

Identity Crisis
CARTOONSTOCK
.com
"Well, you certainly walk like a duck and quack like a duck."

Objectives

- Define what biosimilar medications are
- Compare and contrast different manufacturing techniques between parent drug, generic, and biosimilar medications
- Outline strategies for prescribers and patients regarding biosimilar medications
- Identify future biosimilar medications

What is a Biosimilar?

- A biosimilar is a follow-on biologic that meets **extremely high standards for comparability** to an originator biologic drug and has no clinically meaningful differences in safety, purity, and potency.

mAbs 2011;3:209-217, *Drug Inf J* 2011;45:155-162

What is a Biosimilar?

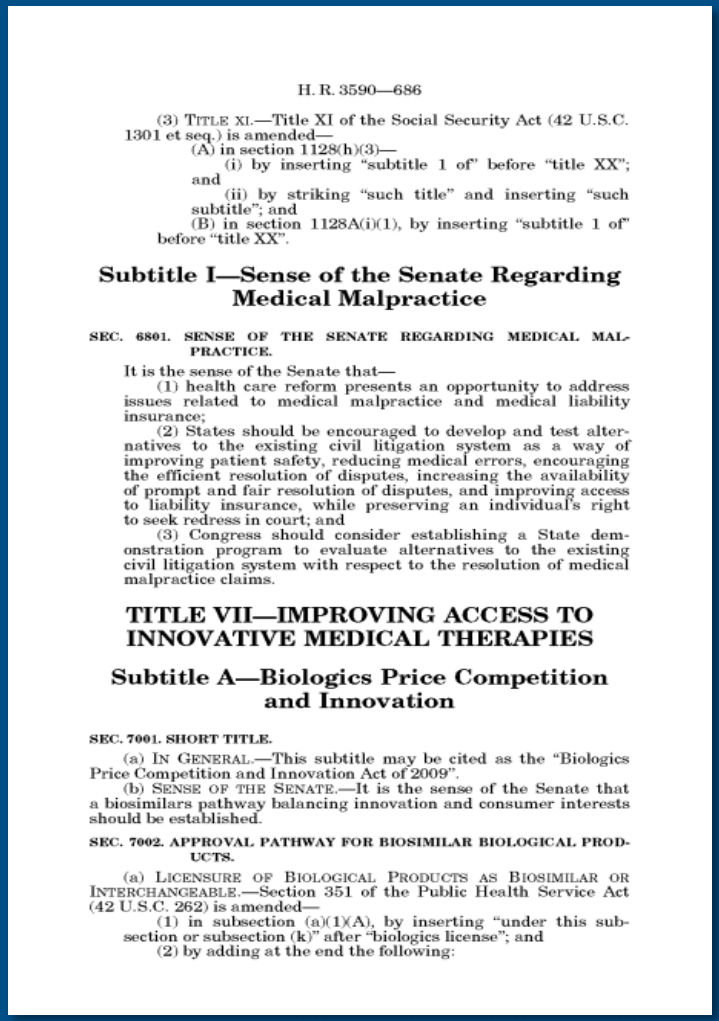
- Biosimilars must be shown to be of a "similar nature in terms of quality, safety, and efficacy" compared with the innovator.
- Biosimilars are NOT generics
    - Different licensing procedure
    - Different requirements of proof of worthiness
- Biosimilars were produced to be price competitive with original compound, but yet maintain patent

European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biologicalmedicinal products. October 30, 2005.

Where Did All of This Come From?

Biologics Price Competition and Innovation Act of 2009

- Signed into law on Mar. 23, 2010
- Created the 351(k) or "biosimilar" pathway
- Granted FDA authority to approve"highly similar" versions of previously approved biologics
- "Abbreviated" process
- Biosimilars must demonstrate safety, purity and potency
- Biosimilar approvals cannot be granted until 12 years after reference (brand) drug is approved (can be filed in 4 yrs)
- Must only have same FDA



H. R. 3590—686

(3) TITLE XI.—Title XI of the Social Security Act (42 U.S.C. 1301 et seq.) is amended—
(A) in section 1128(h)(3)—
(i) by inserting "subtitle 1 of" before "title XX"; and
(ii) by striking "such title" and inserting "such subtitle"; and
(B) in section 1128A(i)(1), by inserting "subtitle 1 of" before "title XX".

Subtitle I—Sense of the Senate Regarding Medical Malpractice

SEC. 6801. SENSE OF THE SENATE REGARDING MEDICAL MALPRACTICE.

It is the sense of the Senate that—
(1) health care reform presents an opportunity to address issues related to medical malpractice and medical liability insurance;
(2) States should be encouraged to develop and test alternatives to the existing civil litigation system as a way of improving patient safety, reducing medical errors, encouraging the efficient resolution of disputes, increasing the availability of prompt and fair resolution of disputes, and improving access to liability insurance, while preserving an individual's right to seek redress in court; and
(3) Congress should consider establishing a State demonstration program to evaluate alternatives to the existing civil litigation system with respect to the resolution of medical malpractice claims.

TITLE VII—IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES

Subtitle A—Biologics Price Competition and Innovation

SEC. 7001. SHORT TITLE.

(a) IN GENERAL.—This subtitle may be cited as the "Biologics Price Competition and Innovation Act of 2009".
(b) SENSE OF THE SENATE.—It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—
(1) in subsection (a)(1)(A), by inserting "under this subsection or subsection (k)" after "biologics license"; and
(2) by adding at the end the following:

FDA Goals

- These goals include targets for FDA to review 70% of applications for biosimilars within 10 months of receipt in fiscal years 2013 and 2014, 80% in fiscal year 2015, 85% in fiscal year 2016 and 90% in fiscal year 2017

Approval Process

Approval Pathways (Biologics)

Product type	Application type	Application pathway	Clinical studies	Application requirements
Biologic (Public Health Service Act)	Biologics License Application (BLA)	351(a)	Yes	Full evaluation of purity, safety and potency
	Biosimilar Application (established 2010)	351(k)	Yes	Yes, but abbreviated process (one clinical trial)

Lucio SD, et al. Am J Health-Syst Pharm. 2013;70:2004-2017.

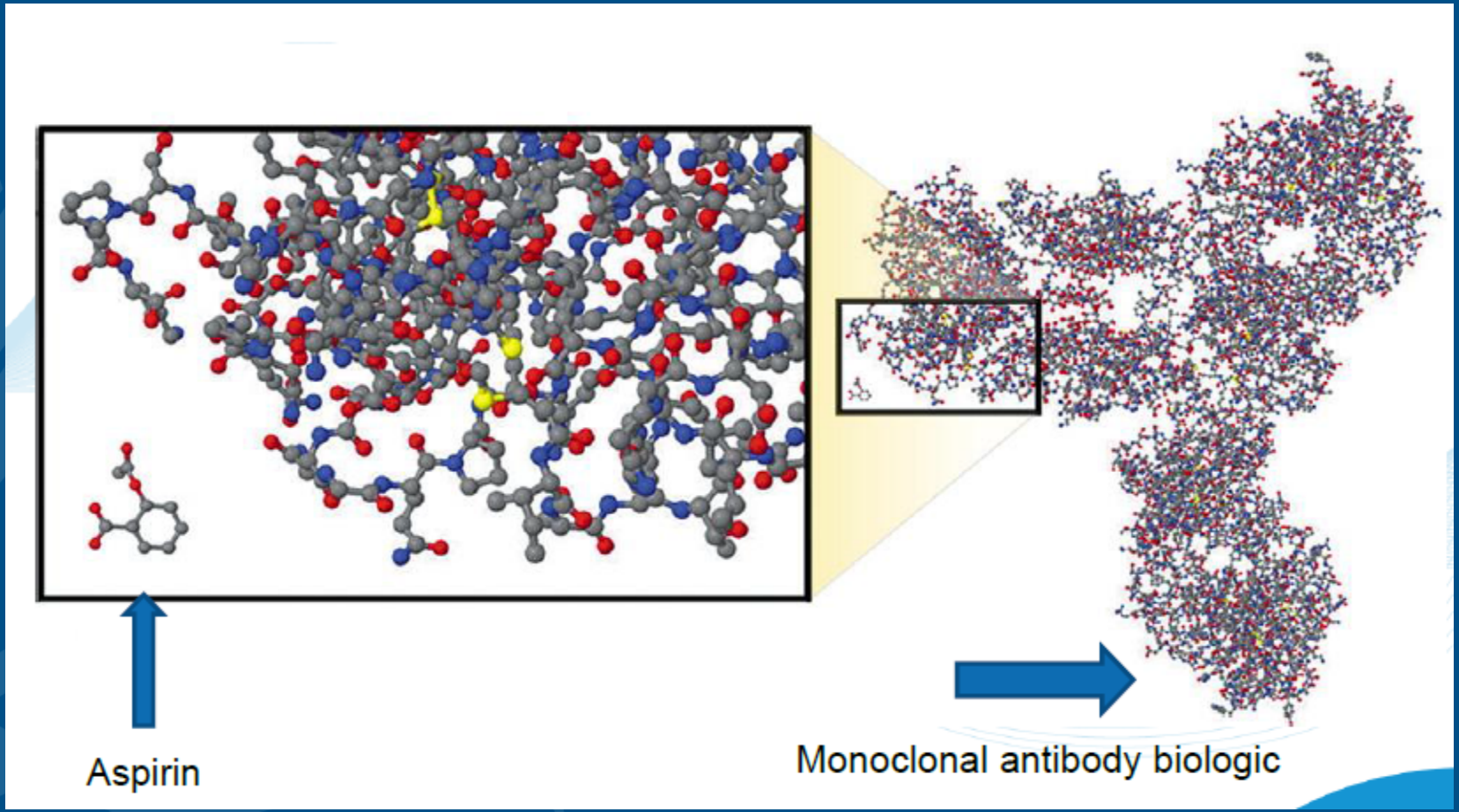
What Areas of Therapy are Biosimilars Impacting?

- Rheumatoid arthritis
- Cancer
- Multiple sclerosis
- Anemia
- Psoriasis
- Inflammatory bowel disease

First You Have to Know What Biological Medications Are

- Biological products, or biologics, are medical products.
- Biological products could be made of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.
- Like drugs, biological products are used to either:
  - treat or cure diseases and medical conditions,
  - prevent diseases, or
  - diagnose diseases
- Biological products are made from a variety of natural sources.

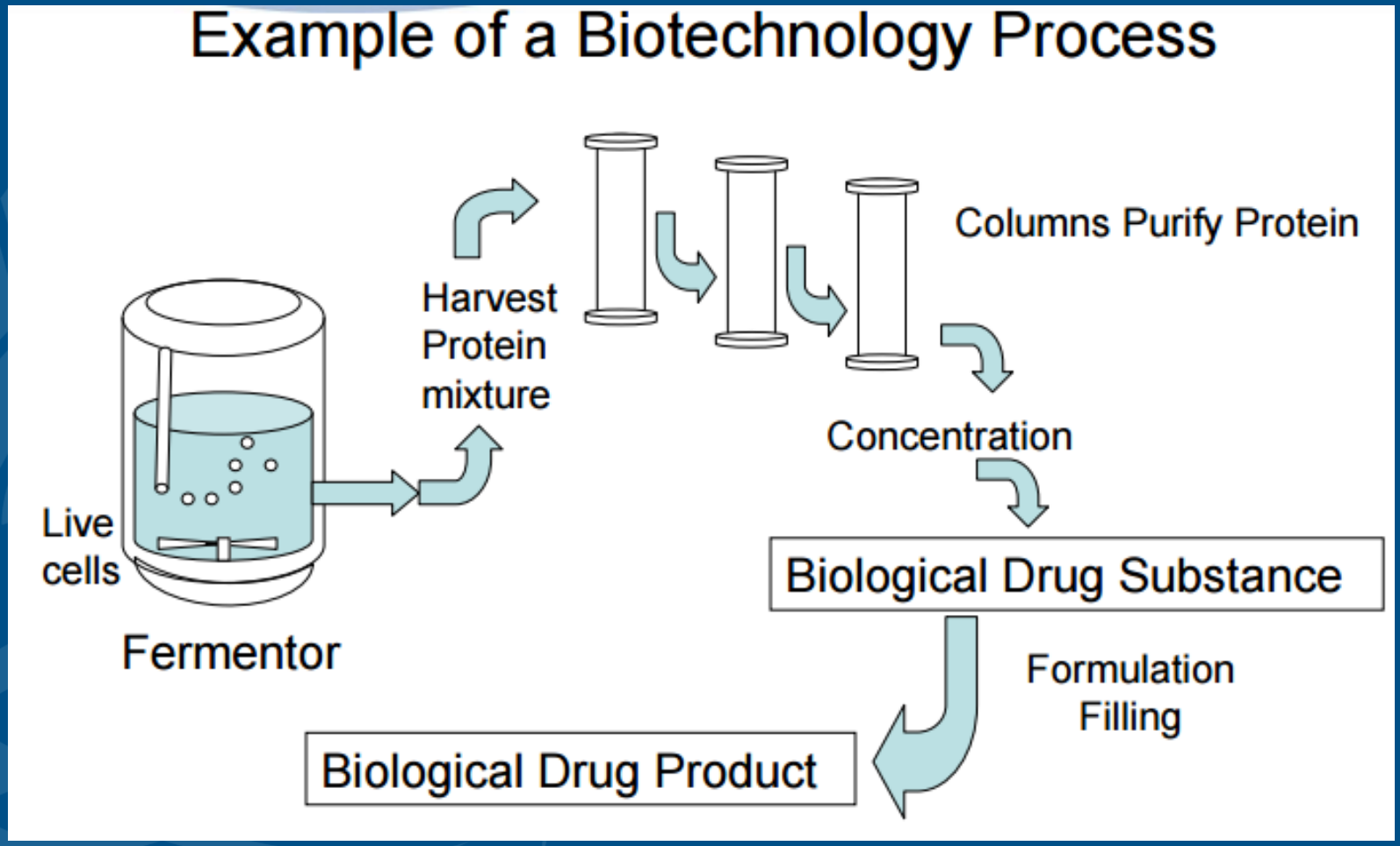
Biosimilars Replicate Large, Complex Biological Medications



N Engl J Med 2011;365:385-388.

Biological Medication Manufacturing

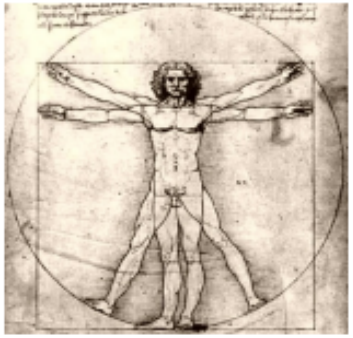
First You Have to Know What Biological Medications Are



First You Have to Know What Biological Medications Are

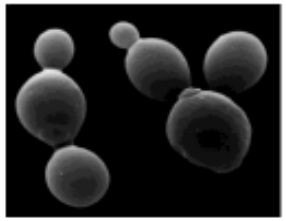
Source Materials

Mammalian cell-culture



Humans

Avian cell-culture



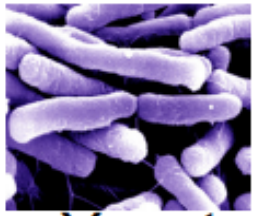
Bacteria

Mice

Transgenics

Plant cell-culture

Insect cell-culture



Yeast

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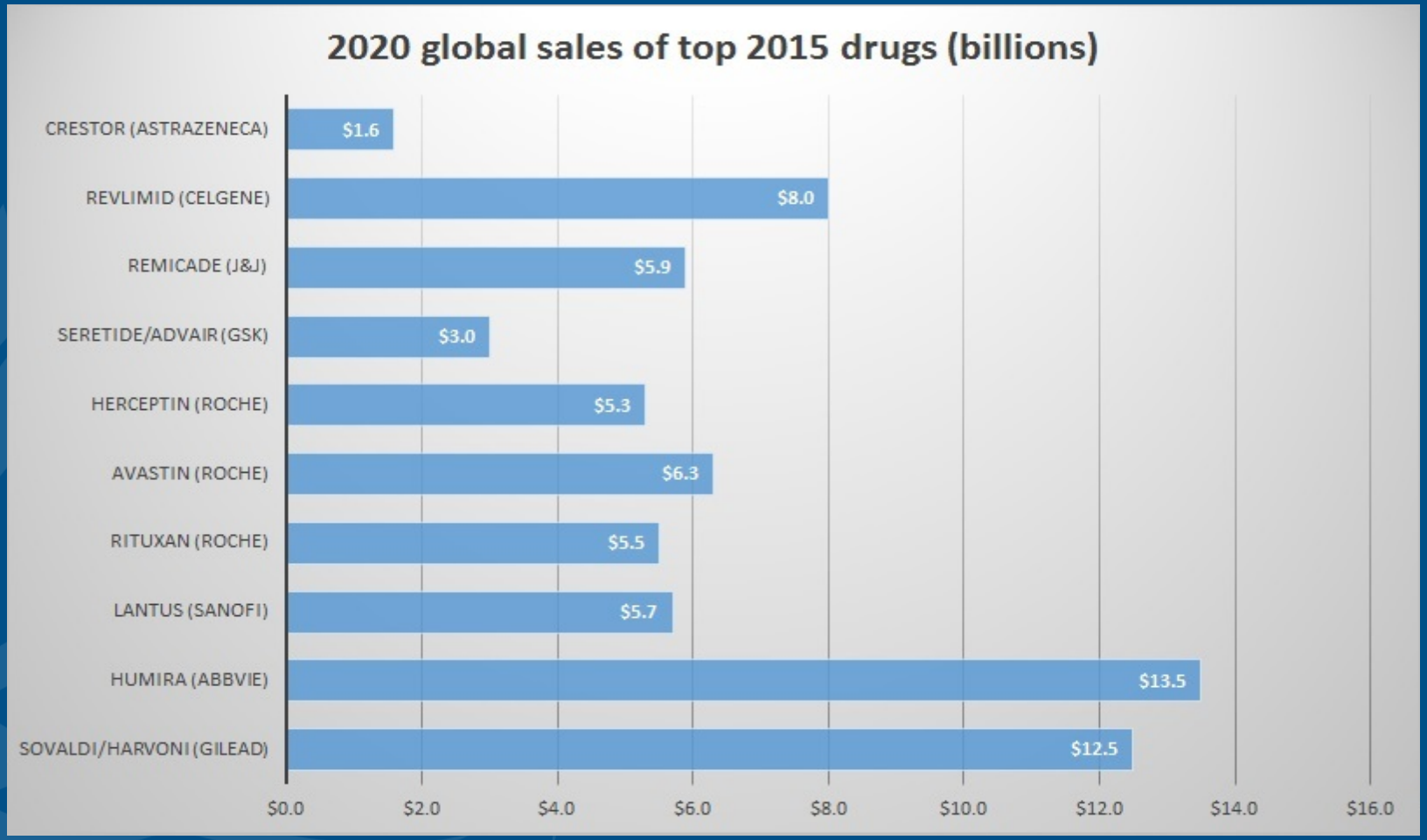
Biologics Facts

- ✓ Account for <1% of all prescriptions
- ✓ Constitute 28% of prescription drug spending
- ✓ Will increase in production by 20% rate per year
- ✓ By 2025, more than 70% of new drug approvals will be biologics

1. Saparwari et al, Progress and hurdles for follow-on biologics, NEJM, 2015; 2380-2382
2. Center for Drug Evaluation and Research 2014
3. Erickson BE, Untangling Biosimilars; Chem Eng News 2010: 25-27

Biological Medications Among Top Projected Sales



Why The Need for Biosimilars Anyway?

- High cost of R&D leads to high cost to patients
- Many patients subsidized by federal and state programs (taxpayers pay)
- Incentive for price control in the marketplace BEFORE patents expire

Generics Vs. Biosimilars

Key Attributes	Generics	Biosimilars
Molecular Complexity/ Manufacturing	Simple Products via Chemical Means, Made EXACT Same Way as Brand	Highly Complex Products by Living Cells, May Vary in Purification from Brand
Immunogenicity	None	YES
Approval	None, just show bioequivalence	YES, Must Conduct at Least 1 Clinical Trial for toxicity, immunogenicity, PK, analytical studies
Same Generic Name	YES	NO, May Have Different
Indications	Same as Brand	**May** Not Have Same as Brand
Interchangeability	YES	Not Automatically
Price Discounts	50%-90% of Brand	15%-30% of Brand
Role of Originator	None	Prominent

Where Did it Begin?

Europe's Action

- European Union introduced biosimilar legislation in 2004
- •Approval process managed by European Medicines Agency (EMA)
- •Product specific class guidance documents available for:
  - Insulin
  - Human growth hormone
  - G-CSFs
  - Erythropoietins
  - Interferons
  - Low molecular weight heparins
  - Monoclonal antibodies
- •Two applications for biosimilar infliximab filed with EMA

European Biosimilars

Biosimilar Trade Name	Marketer	Active Substance	Reference Drug	Year of Approval
Epoteins				
Abseamed	Medice	epoetin alfa	Eprex/Erypo	2007
Binocrit	Sandoz	epotein alfa	Eprex/Erypo	2007
Epoetin Alfa Hexal	Hexal	epotein alfa	Eprex/Erypo	2007
Retacrit (2)	Hospira	epotein zeta	Eprex/Erypo	2007
Silapo	Stada	epotein zeta	Eprex/Erypo	2007
Filgrastims				
Accofil	Accord	filgrastim	Neupogen	2014
Biograstim	AbZ-Pharma	filgrastim	Neupogen	2008
Filgrastim Hexal	Hexal	filgrastim	Neupogen	2009
Grastofil	Apotex	filgrastim	Neupogen	2013
Nivestim	Hospira	filgrastim	Neupogen	2010
Ratiograstim	Ratiopharm	filgrastim	Neupogen	2008
Tevagrastim	Teva	filgrastim	Neupogen	2008
Zarzio (3)	Sandoz	filgrastim	Neupogen	2009

http://www.biologicsblog.com/blog/ten-years-of-biosimilars-in-europe/

European Biosimilars

Growth Hormones				
Omnitrope (4)	Sandoz	somatropin	Genotropin	2006
Insulins				
Abasaglar (5)	Eli Lilly	insulin glargine	Lantus	2014
Monoclonal Antibodies				
Inflectra	Hospira	infliximab	Remicade	2013
Remsima	Celltrion	infliximab	Remicade	2013

http://www.biologicsblog.com/blog/ten-years-of-biosimilars-in-europe/

Biosimilars in the U.S.

- Only one true biosimilar is available in the U.S. – ZARXIO (filgrastim-SNDZ), made by Sandoz

- Granix (TBO-filgrastim) was not filed under the same pathway as the biosimilar pathway

- Both compete with filgrastim (Neupogen)

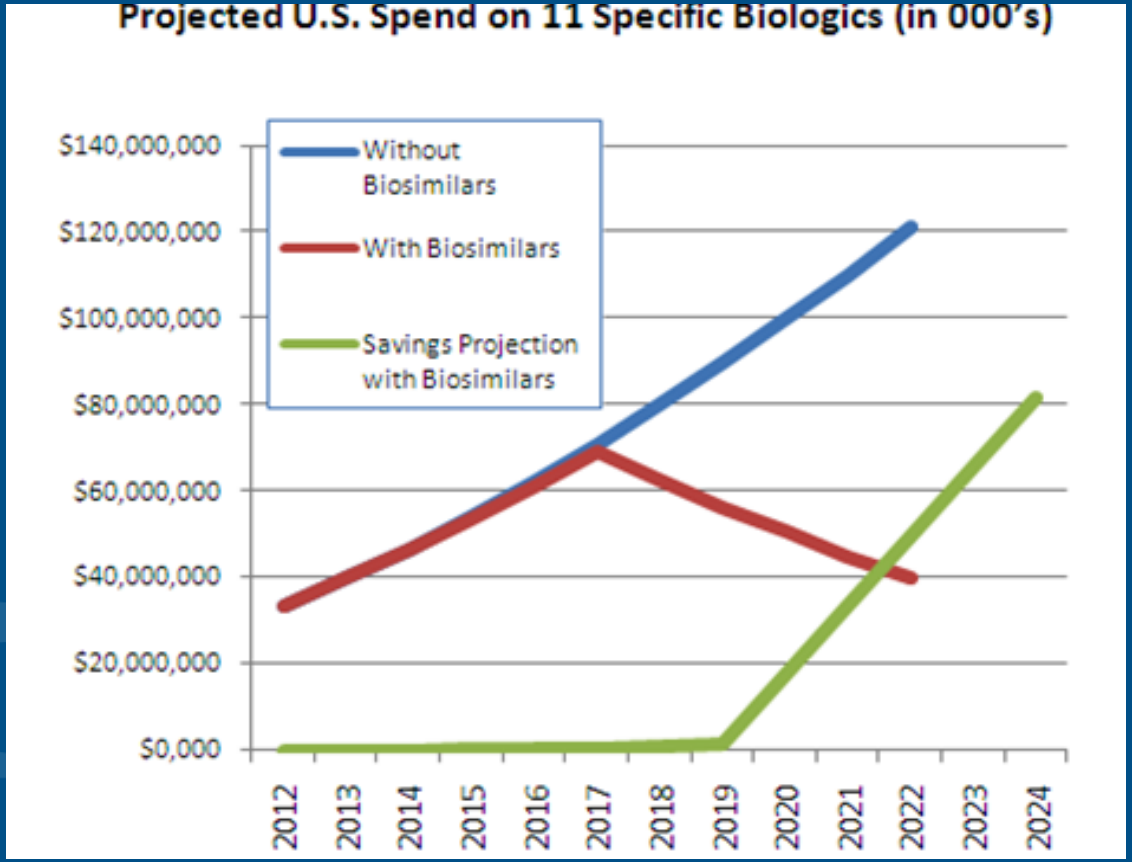
Biosimilars in the U.S.

Biosimilar	Approved?	Available?
Zarxio (filgrastim-sdz) *Neupogen**	Yes	Yes
Inflectra (infliximab-dyyb) *Remicade**	Yes	No
Erelzi (etanercept) *Embrel**	Yes	No
Amjevita (adalimumab-atto) *Humira**	Yes	No

US Pharmacist, Octber 2016

Expected Savings With Biosimilars

- **Projected Savings per Express Scripts**
  - **250 Billion in Projected Savings from just 11 biosimilars**



Source: Express Scripts

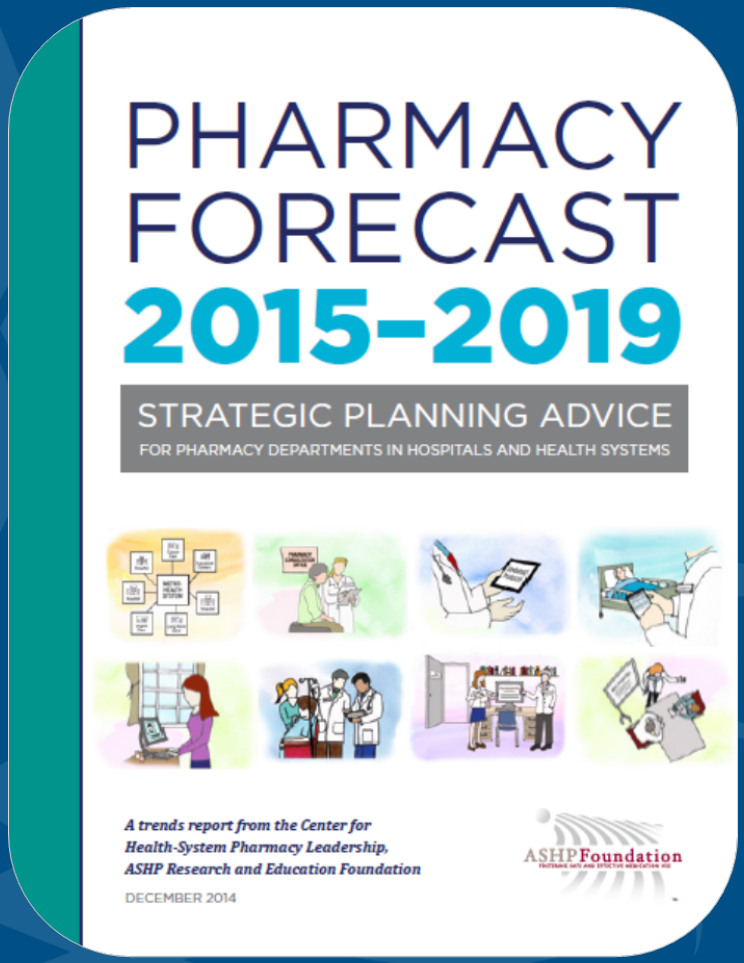
Legislature

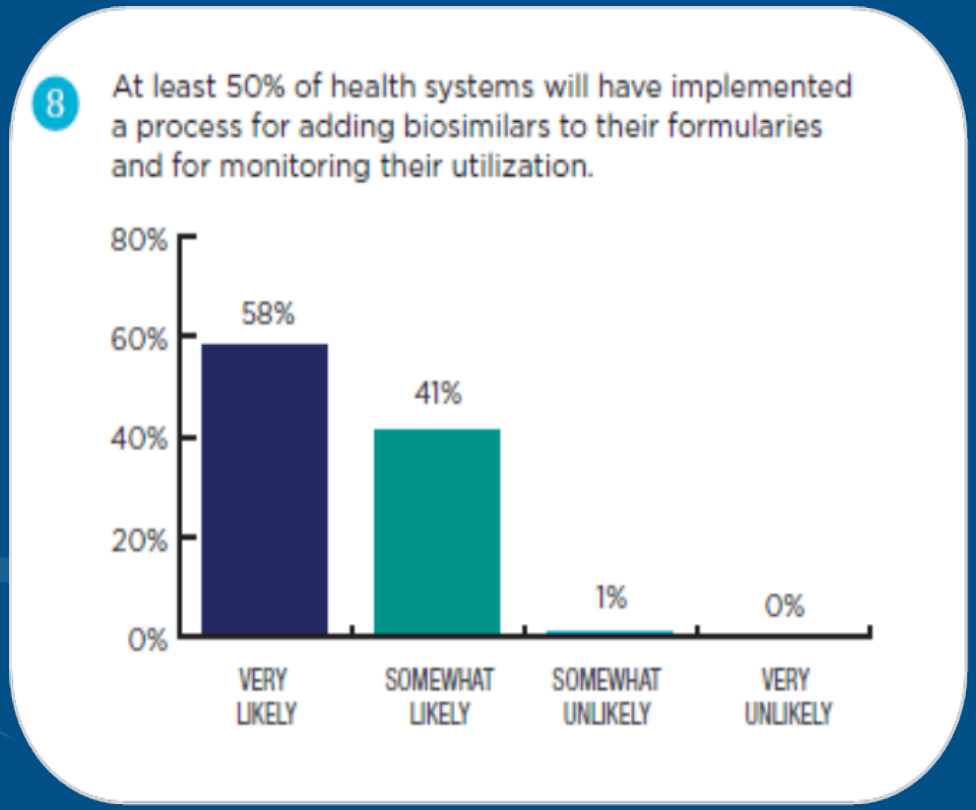
1. **Nearly a dozen makers of biosimilars**---including leading manufacturers like **Hospira/Pfizer**, **Samsung**, and **Sandoz**---have collectively formed the **Biosimilars Forum**, a nonprofit group that will lobby for how biosimilars are used in the United States.

2. This development comes as the FDA has a number of biosimilars currently under consideration.

Palmer E. Biosimilar manufacturers form group to influence market in U.S. May 7, 2015: *Fierce Pharma Marketing.* Available at http://www.fiercepharmamanufacturing.com/story/biosimilar-manufacturers-form-group-influence-market-us/2015-05-07. Accessed October 5, 2015.

By 2019……..


PHARMACY FORECAST 2015–2019
STRATEGIC PLANNING ADVICE
FOR PHARMACY DEPARTMENTS IN HOSPITALS AND HEALTH SYSTEMS
A trends report from the Center for Health-System Pharmacy Leadership, ASHP Research and Education Foundation
DECEMBER 2014
ASHPFoundation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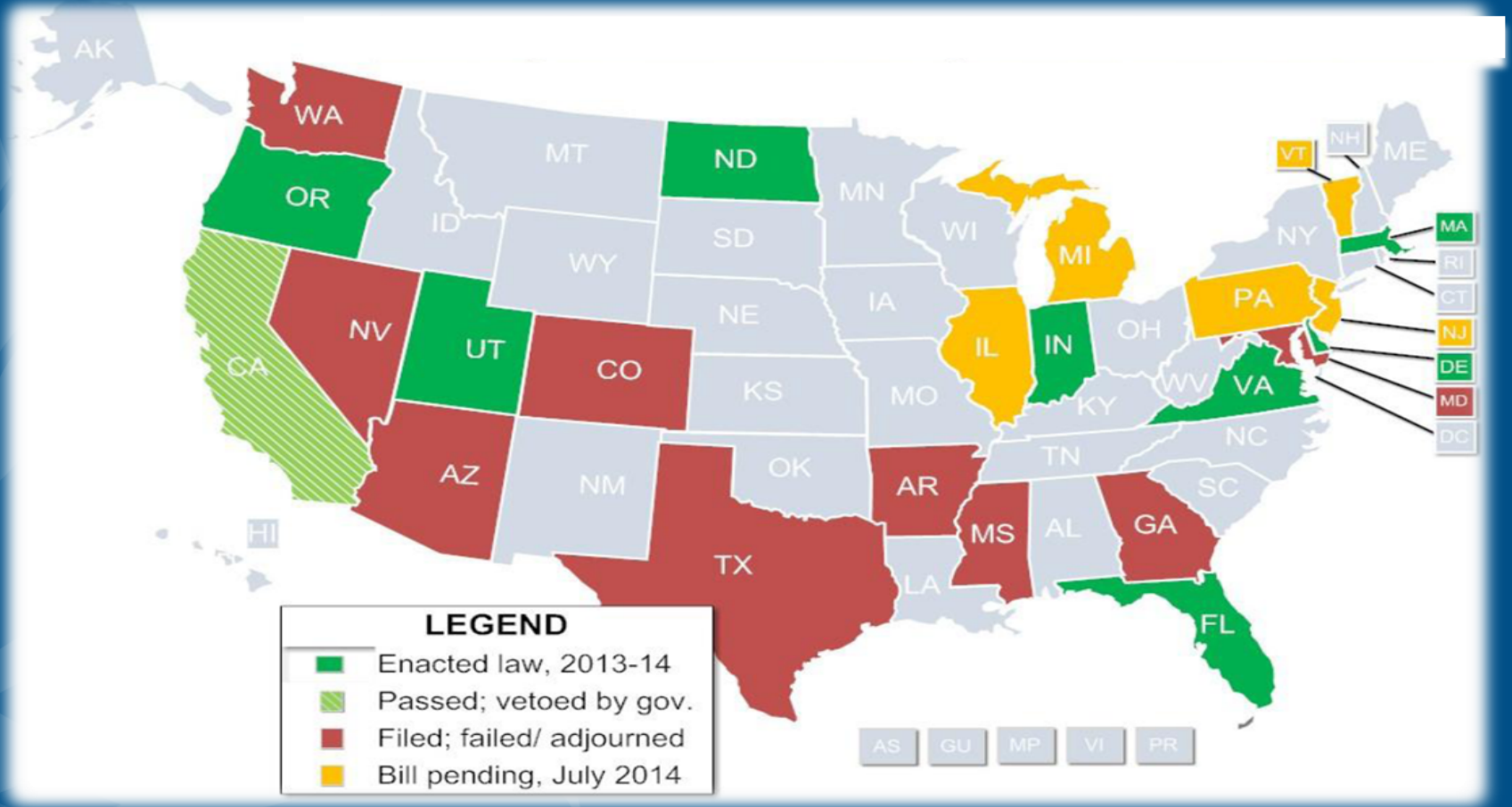
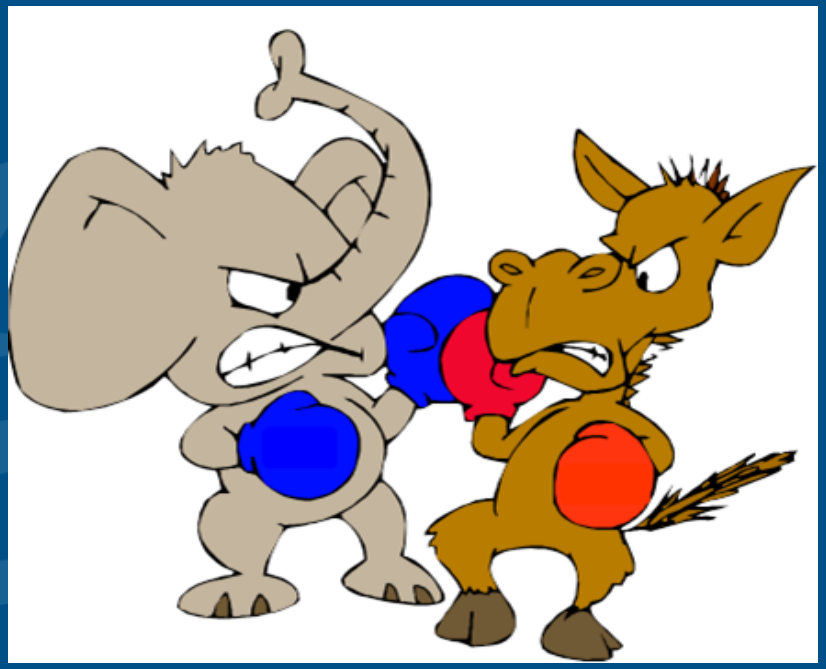
At least 50% of health systems will have implemented a process for adding biosimilars to their formularies and for monitoring their utilization.
80%
60%
40%
20%
0%
58%
41%
1%
0%
VERY LIKELY
SOMEWHAT LIKELY
SOMEWHAT UNLIKELY
VERY UNLIKELY

Interpreting State Legislation Related to Biologics and Biosimilar Substitution



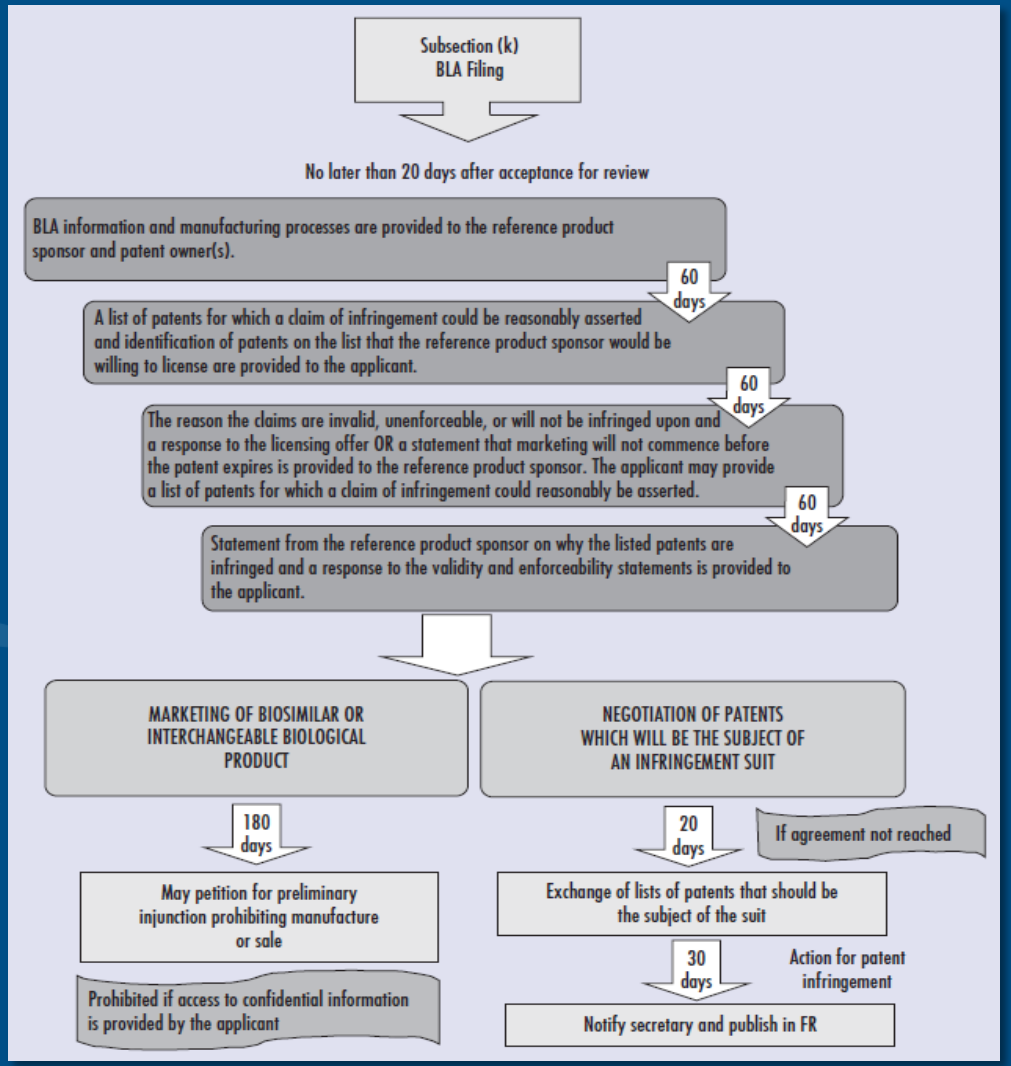
http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Accessed Nov. 25, 2014.

It’s a Fight to the End!



Litigation

Within 20 days of FDA accepting a biosimilar application for review, access to BLA information and manufacturing processes must be provided to the reference product sponsor and patent owner.



Sensabaugh SM. *Drug Inf J.* 2011;45:155-162

Litigation

- Current Lawsuits:

MYLAN FILES AMICUS BRIEF IN SUPPORT OF *CERTIORARI* IN *AMGEN V. APOTEX*

October 25, 2016 • Posted by Big Molecule Watch

Amgen v. Apotex (pegfilgrastim) • BPCIA and Related U.S. Statutes • U.S. Biosimilar Litigation News

***JANSSEN V. CELLTRION*: JANSSEN APPEALS JUDGMENT INVALIDATING THE '471 PATENT**

October 24, 2016 • Posted by Big Molecule Watch

Approved Biosimilar Products • Janssen v. Celltrion (infliximab) • U.S. Biosimilar Litigation News • U.S. District Court Decisions

Litigation

AMGEN V. HOSPIRA (EPOETIN ALFA): DISTRICT COURT LETS IN NEW INFRINGEMENT THEORIES, NOT NEW DEFENDANTS

October 14, 2016 • Posted by Big Molecule Watch

Amgen v. Hospira (epoetin alfa) • U.S. Biosimilar Litigation News • U.S. District Court Decisions

LITIGATION UPDATE IN *ABBVIE V. AMGEN*: ABBVIE'S ANSWER FILED IN RESPONSE TO AMGEN'S COUNTERCLAIMS

October 12, 2016 • Posted by Big Molecule Watch

AbbVie v. Amgen (adalimumab) • U.S. Biosimilar Litigation News

Litigation

SANOFI SUES MERCK OVER PROPOSED INSULIN GLARGINE BIOSIMILAR

September 22, 2016 • Posted by Big Molecule Watch

U.S. Biosimilar Litigation News

Formulary Management: Key Questions

- Will the biosimilar product be endorsed only for labeled indications or for off-label indications as well?
- What is the existing level of adverse events with the originator product?
  - How will you ensure appropriate pharmacovigilance with the biosimilar?

Lucio SD, et al. Am J Health-Syst Pharm. 2013;70:2004-2017.

Formulary Management: Key Questions

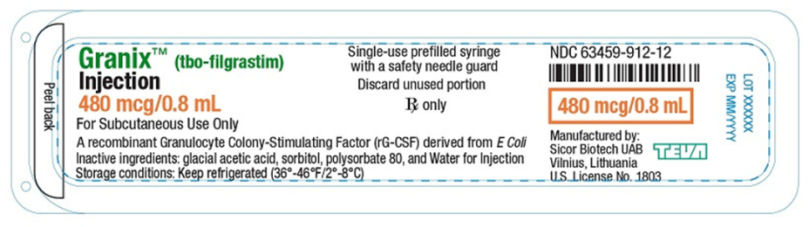
- What was the approval history of the biosimilar?
- What information is available concerning the clinical efficacy and safety of the biosimilar?
  - E.g., FDA review document, published trials, European data, expert organization guidelines

BRRH Approach

- Pharmacy and Therapeutics Committee had to evaluate the following regarding biosimilars:
  - Clinical trials
  - Safety
  - Interchangeability
  - Cost
  - Reimbursement

BRRH Approach

- Tbo-filgrastim (Granix) was approved after a full drug review with interchange from Neupogen in late 2013



- Biosimilars presented at Pharmacy & Therapeutics Committee in March of 2015, approved all biosimilars as interchanged, approved by Medical Staff

BRRH Approach

- Vizient (contracting) sent out bids for Granix, Neupogen, and newly biosimilar drug Zarxio for award
- Award granted to Sandoz, maker of Zarxio
- BRRH implemented interchange of Granix and Neupogen to Zarxio (Zarxio only option in CPOE) in July of 2016

Where are the Other Biosimilars?

Projected US Patent Expiration Dates

Brand Name	Potential Biosimilar Entry
Neupogen	2013
Epogen/Procrit	2014
Neulasta	2015
Synagis	2015
Rituxan	2016
Erbitux	2016
Humira	2016
Remicade	2018
Herceptin	2019
Avastin	2019
Aranesp	2024
Enbrel	2028

The Pink Sheet, Pending Biosimilar FDA Performance Tracker, accessed September 24, 2015; *The Pink Sheet*, "Biosimilar Application Reviews May Be Growing More Challenging,"September 28, 2015

The Future……..

Table 1. Selected Biosimilars Under Investigation

Reference Product (Brand, Manufacturer)	Est. Patent Expiration (U.S.)	Indication	Biosimilar	Manufacturer	Published Data
Adalimumab (Humira, AbbVie)	2022	RA, psoriatic arthritis, AS, UC, Crohn's disease, psoriasis, HS, JIA	GP2017 PF-06410293 BCD-057	Sandoz Pfizer Biocad	Phase III trial under way Phase I trial under way Phase III (2017)
Bevacizumab (Avastin, Genentech)	2019	Colorectal, lung, and renal cancers	BCD-021 PF-06439535 ABP 215	Biocad Pfizer Amgen	Phase III trial completed Preclinical/phase I trials completed Phase III trials under way
Cetuximab (Erbitux, Eli Lilly)	Expired (2016)	Colorectal, head and neck cancers	ABP 494	Amgen	Phase III trial under way
Darbepoetin alfa (Aranesp, Amgen)	2018	Anemia due to CKD or chemotherapy	BCD-066	Biocad	Phase III trials under way (2017)
Enoxaparin (Lovenox, Sanofi-Aventis)	Expired (2010)	DVT, VTE	BCD-060	Biocad	Phase III trials under way (2016)
Epoetin alfa (Epogen, Amgen)	Expired (2015)	Anemia due to CKD or chemotherapy	HX575	Sandoz	Phase III trial completed
Glatiramer acetate (Copaxone, Teva)	Expired (2014)	Multiple sclerosis	BDC-063	Biocad	Phase III trials under way (2016)
Infliximab (Remicade, Janssen Biotech)	September 2018	Autoimmune diseases including RA, psoriasis, UC, Crohn's disease	GP 1111 PF-06438179 ABP 710 BCD-055	Sandoz Pfizer Amgen Biocad	Phase III trial under way Phase III trial under way No data available Phase III (2017)
Pegfilgrastim (Neulasta, Amgen)	Expired (October 2015)	Chemotherapy-induced neutropenia	LA-2006	Sandoz	File accepted by FDA at the end of 2015
Rituximab (Rituxan, Genentech)	September 2016	Lymphoma	GP2013 BCD-020 PF-05280586 CT-P10 RTXM83 ABP 798	Sandoz Biocad Pfizer Celltrion mAbxience Amgen	Phase II and III trials under way Phase III trials completed Preclinical/phase I trials completed Phase III trials completed Phase III trials completed No data available
Trastuzumab (Herceptin, Genentech)	June 2019	Breast cancer	BCD-022 PF-05280014 ABP 980 CT-P6	Biocad Pfizer Amgen Celltrion	Successful phase I trials Preclinical/phase I trials completed Phase III trials under way Phase III trials completed

AS: ankylosing spondylitis; CKD: chronic kidney disease; DVT: deep venous thrombosis; est: estimated; HS: hidradenitis suppurativa; JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; UC: ulcerative colitis; VTE: venous thromboembolism. Source: References 17-22.

US Pharmacist, October 2016

The Future……..

Brand Product	FDA Did Not Accept BLA Before…..	FDA Will Not Approve BLA Before…..
Canakinumab (Ilaris) (Periodic fever symptoms, juvenile idiopathic arthritis)	June 2013	June 2021
Eculizumab (Soliris) (Atypical hemolytic uremic syndrome, Paroxysmal nocturnal hemoglobinuria)	March 2011	March 2019
Natalizumab (Tysabri) MS	November 2008	November 2016
Ranibizumab (Lucentis) (Diabetic retinopathy, Macular diseases)	June 2010	June 2018
Ustekinumab (Stelara) (Crohn's/Psoriasis)	September 2013	September 2021

White Paper Outlook on US Biosimilar Competition, Drug Today; 399-410

Impact on Physicians

- Must know the process and **feel confident** in prescribing biosimilars
- Understand hospital formulary decision making when it comes to biosimilars
- Insurance companies will likely favor biosimilars if there is no generic available
- Hospitals will have in CPOE systems the biosimilar name and not the original brand name

Summary

- Biosimilars are here to stay and be bigger players in the biologics market
- Florida has demed biosimilars interchangeable
- Physicians will have to understand role biosimilars will play in their practice
- Hospital pharmacies will determine which form of the drug to have, either brand, generic, biosimilar and chose based on:
    - Safety
    - Efficacy
    - Reimbursement


THE END

BOCA RATON REGIONAL HOSPITAL