Biosimilars

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Drug Information Specialist, IU Health
Disclosure statement

• The speaker has nothing to disclose
Objectives

1. Review the history of biosimilars
2. Describe the differentiation from biological products
3. Discuss the development and approval of biosimilars
4. Review state regulations of biosimilars
5. Define the economics of biosimilars
Question

In what century did Congress first address biologic medications?

A. 18th century
B. 19th century
C. 20th century
D. 21st century
1813 – The Vaccine Act (repealed 1822)
• First federal law for any medical substance

1902 – The Biologics Control Act
• Charged Hygienic Laboratory of the Public Health and Marine Hospital Service (pre-NIH) to ensure safety, purity, and potency of vaccines, serums, toxins, anti-toxins, and similar products

1906 – The Federal Food And Drug Act
• Outlawed adulterated/misbranded drugs, no reference made to biologics

www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CBER/default.htm
History of biologics and federal government in US

1938 – The Federal Food, Drug, and Cosmetic Act

• Biologic product is considered a drug,

1944 – The Public Health Service Act

• 1902 Act incorporated into Section 351 of Act, authorization for licensing of biologic products
• Biologic definition: virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, .... Applicable to the prevention, treatment, or cure of a disease or condition of human beings

www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CBER/default.htm
1972 – Regulation of biologics NIH->FDA

1984 – Drug Price Competition and Patent Term Restoration Act
• Expedited pathway for generic drug approval, 505(j)
• Additional pathway for new drug approval, 505 (b)(2)

2009 – Biologics Price Competition and Innovation Act
• Expedited pathway for biosimilar approval, 351(k)
## FDA approval pathways for medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Application</th>
<th>Path</th>
<th>Clinical data</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>NDA</td>
<td>505(b)1</td>
<td>Yes</td>
<td>Full evaluation safety/efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>505(b)2</td>
<td>Yes</td>
<td>Safety/efficacy required but not of the applicant</td>
</tr>
<tr>
<td></td>
<td>ANDA</td>
<td>505(j)</td>
<td>No</td>
<td>Bioequivalence determination</td>
</tr>
<tr>
<td><strong>Biologic</strong></td>
<td>BLA</td>
<td>351(a)</td>
<td>Yes</td>
<td>Full evaluation safety, purity, and potency</td>
</tr>
<tr>
<td></td>
<td>ABLA</td>
<td>351(k)</td>
<td>Likely</td>
<td>Evaluation of safety, purity, and potency, but abbreviated</td>
</tr>
</tbody>
</table>
Which of the following medications have been approved as a biosimilar?
A. Infliximab-dyyb (Inflectra®)
B. Filgrastim-sndz (Zarxio®)
C. Insulin glargine (Basaglar®)
D. A and B
E. A, B, and C
Notes about 505(b)(2) pathway

• Permits FDA to rely on data not developed by applicant for NDA
• Less exclusivity time granted (0-5 years)
• No similar pathway for biologics
• Has historically included naturally derived or recombinant active ingredients (likely will change as of March 23, 2020)

# Biologic products originally via 505 pathway

<table>
<thead>
<tr>
<th>Chorionic gonadotropin</th>
<th>Pegademase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirudin</td>
<td>Pegvisomant</td>
</tr>
<tr>
<td>Follitropin,</td>
<td>Saccrosidase</td>
</tr>
<tr>
<td>urofollitropin,</td>
<td>Somatropin</td>
</tr>
<tr>
<td>menotropin</td>
<td>Taliglucerase alfa</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Velaglucerase alfa</td>
</tr>
<tr>
<td>Imiglucerase</td>
<td>Thyrotropin alfa</td>
</tr>
<tr>
<td><strong>Insulin products</strong></td>
<td><strong>Reclassified as biologics by March 23, 2020</strong></td>
</tr>
<tr>
<td>Mecasermin</td>
<td></td>
</tr>
<tr>
<td>Pancrelipase</td>
<td></td>
</tr>
</tbody>
</table>

## Biologics vs Drugs

<table>
<thead>
<tr>
<th>General features</th>
<th>Biologics</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Structure</td>
<td>Complex</td>
<td>Simple</td>
</tr>
<tr>
<td>Degradation</td>
<td>Complex</td>
<td>Precise and known</td>
</tr>
<tr>
<td>Variability</td>
<td>Heterogeneous</td>
<td>Single, defined structure</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Cell bank, unlikely to achieve identical copy</td>
<td>Predictable chemical and reagent reaction, identical copy can be made</td>
</tr>
<tr>
<td>Characterization</td>
<td>Difficult to fully characterize</td>
<td>Easy to fully characterize</td>
</tr>
<tr>
<td>Stability</td>
<td>Sensitive to storage/handling</td>
<td>Less sensitive to storage and handling</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Higher potential</td>
<td>Lower potential</td>
</tr>
</tbody>
</table>
Biologics Price Competition and Innovation Act

- Signed into law – March 23, 2010
- Created an *abbreviated* licensure pathway, 351(k)
- Created 12-year exclusivity period for reference products
- 1-year exclusivity period for first interchangeable biosimilar

Biologics Price Competition and Innovation Act

• Amended the definition of biological product to include “protein (except any chemically synthesized polypeptide)
  – Protein: >40 amino acids in size
  – Chemically synthesized polypeptide: made entirely from chemical synthesis and <100 amino acids in size

• Transition period for biologics approved via 505 pathway under FDCA

Which of the following elements are required for biosimilar approval?

A. All indications of reference product
B. Same mechanism of action
C. All dosage forms of reference product
D. All of the above
General requirements of 351(k) pathway

• Biosimilar to reference product
• Same mechanism of action as reference product
• Proposed condition(s) of use same as reference product
• Same route, formulation, and strength as reference product
• Facilities meet standards to assure safety, purity, and potency
April 2015: scientific considerations in demonstrating biosimilarity

April 2015: quality considerations in demonstrating biosimilarity of protein product

December 2016: clinical pharmacology studies to support biosimilarity

- describes role of fingerprint-like analysis algorithms to characterize PK & PD data

January 2017: nonproprietary naming
August 2014: reference product exclusivity for biologics

January 2017: considerations in demonstrating interchangeability
  • Describes approaches to totality of evidence and design characteristics of switch studies

September 2017: statistical approaches to evaluate analytic similarity
What is biosimilarity?

• Biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

• There are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product

www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm290967.htm
# Generic vs Biosimilars

<table>
<thead>
<tr>
<th>Features</th>
<th>Generics</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval requirements</td>
<td>No clinical trials; bioequivalence needed</td>
<td>Abbreviated process but ≥ 1 clinical study required</td>
</tr>
<tr>
<td>Indications</td>
<td>Same as originator</td>
<td>May/may not be extrapolated</td>
</tr>
<tr>
<td>Nonproprietary name</td>
<td>Same as originator</td>
<td>???????</td>
</tr>
<tr>
<td>Interchangeability</td>
<td>At approval (Orange Book)</td>
<td>Possible, but unlikely (Purple Book)</td>
</tr>
<tr>
<td>Cost to develop</td>
<td>$1- 4 million</td>
<td>$100 – 250 million</td>
</tr>
<tr>
<td>Price relative to originator</td>
<td>Often 80-90% less</td>
<td>??? 20-30% less??</td>
</tr>
</tbody>
</table>
The majority of studies in a biosimilar application focus on:
A. Analytic characterization
B. Animal studies
C. Pharmacokinetic studies
D. Clinical effectiveness
Key concept #1 – goals of stand-alone and biosimilar development are different

351 (k) pathway – biosimilars
GOAL: to demonstrate biosimilarity (or possibly interchangeability) to reference

351(a) pathway – new biologics
GOAL: establish safety and efficacy

<table>
<thead>
<tr>
<th>Clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK &amp; PD</td>
</tr>
<tr>
<td>Analytical</td>
</tr>
</tbody>
</table>

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561565.pdf
Key concept #2: Stepwise Approach

Evaluation of residual uncertainty at each step of development

- Analytical studies → animal studies → clinical PK & PD studies → immunogenicity assessment → additional clinical studies (as needed)

There is not a one pivotal study that will demonstrate biosimilarity (*Totality-of-the-evidence approach*)

Key concept #3 - Analytics

Extensive characterization

Structural: Primary amino acid sequence, modifications (e.g. glycosylation), protein folding and protein-protein interactions
- Sensitive to formulation and environmental conditions
- Impurities (product or process-related)
- NOTE: manufacturers must show comparability with process changes

Functional: pharmacological activities of compound
- In vitro assays: biological or binding assays, enzyme kinetics
- In vivo assays: animal models that exhibit disease or symptom

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561565.pdf
Possible outcomes of analytic assessments

• Insufficient analytic similarity – unlikely to continue via 351(k) pathway without significant changes

• Analytic similarity with residual uncertainty – likely to require more downstream studies to rule out concerns

• Tentative analytic similarity – appropriate to proceed

• Fingerprint-like analytic similarity – may possibly require less studies
Key concept #4 – role of clinical studies

Residual uncertainty from analytics and PK/PD studies drives nature and scope of clinical studies

• A PK and PD comparison with reference product is required
• At least 1 clinical study comparing immunogenicity is expected
• A comparative clinical study is necessary if there are residual uncertainties

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561565.pdf
Comparative PK and PD studies

Considered most sensitive clinical study/assay to assess differences between products

- Pharmacokinetics: demonstrate similarity in an adequately sensitive population to detect differences
- Pharmacodynamics: similar PD measures that reflect mechanism of action or biologic effects of drug
- For short (<5 days) half-lives, rapid PD responses, and low immunogenicity a crossover design is sufficient, otherwise a parallel design recommended

Similarity supports assumption that similar exposure & response will provide similar efficacy and safety

Clinical immunogenicity studies

Establish that there are no clinically meaningful differences in immune responses with reference product

Studies should consider:
- Nature of immune response
- Clinical relevance and severity of consequences
- Incidence
- Population being studied

Recommended duration of follow-up of 1 year for chronic dosing

FDA considers a naïve-population to be most sensitive design
Comparative clinical study

Investigates clinical meaningful differences in safety and efficacy with reference product

Population, endpoints, sample size and duration should be sensitive to detect differences

• Endpoints may be different (e.g. PD measures more sensitive to change than clinical endpoints)

Equivalence designs are most common

Assess safety and immunogenicity

Which of the following factors would NOT preclude extrapolation of indications?

A. Differences in indications
B. Differences in mechanism of action
C. Differences in immunogenicity
D. Differences in pharmacokinetics
**Key concept #5 - Extrapolation**

*Potentially*, extrapolation can be used for approval of $\geq 1$ indication

- Scientific justification is required
- Differences between indications (e.g. IBD and RA) does not preclude extrapolation
- FDA guidance notes factors to consider are:
  - MOA in each condition of use
  - PK in different patient populations
  - Immunogenicity in different patient populations
  - Differences in expected toxicities in each condition of use and population

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561565.pdf
Per BPCI Act, requirements are:

- Meet all requirements to be biosimilar PLUS can be expected to produce the same clinical result in any given patient. In addition, for products given more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use is not greater than risk of using reference product without alteration or switch.

- IMPACT: interchangeable product may be substituted for reference product without intervention of prescriber

Current guidance on switching studies

Endpoints should be biologically relevant (e.g. PD measures)
Switching should incorporate at least two separate exposure periods to each of the two products (i.e. at least 3 switches with each switch crossing over to alternate product)
In general, must use patients with condition(s) of interest, as opposed to healthy patients
In contrast to biosimilarity studies, FDA advice against using non-US-licensed comparators (i.e. bridging studies are not sufficient)
Dose formulation should be similar to comparator

True or False – the package insert of a biosimilar agent will incorporate reference product labeling

• True
• False
Labeling

Approved prescribing information summarizes essential information needed by practitioners for safe and effective use of drug

FDA recommends biosimilar applicants to incorporate reference product labeling, with appropriate product-specific modifications

Guidance on post-approval new conditions of use for biosimilar or reference product unclear (e.g. Neupogen/Amgen)

### Biologics – proposed nonproprietary naming

**Guidance released January 2017**
Nonproprietary name = core name plus FDA-designated suffix
Suffices are **devoid of meaning** and **unique, four-letter lowercase letters**

#### Timeline for *retroactive* naming of biologic products???

<table>
<thead>
<tr>
<th>Current generic name</th>
<th>Trade name</th>
<th>Proposed generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sndz</td>
<td>Zarxio®</td>
<td>Filgrastim-bflm</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen®</td>
<td>Filgrastim-jcwp</td>
</tr>
<tr>
<td>Tbo-filgrastim</td>
<td>Granix®</td>
<td>Filgrastim-vkzt</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Neulasta®</td>
<td>Pegfilgrastim-ljfd</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epogen®/Procrit®</td>
<td>Epoetin alfa-cgkn</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade®</td>
<td>Infliximab-hjmt</td>
</tr>
</tbody>
</table>

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**August 28, 2015  80 FR 52224**

[Butler University](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation)
Nonproprietary naming

Enhancing biologic product pharmacovigilance
  • Proprietary name, proper name, manufacturer, NDC number, lot number, billing codes
  • Some change over time
Ensuring safe use – preventing inadvertent substitution
  • Note guidance on interchangeable naming not published
Advancing appropriate practices and perceptions regarding biologics
  • Requiring all biologics to have suffix
### Biosimilars approved to date in USA

<table>
<thead>
<tr>
<th>Biosimilar product FDA approval date</th>
<th>Reference product FDA Approval date</th>
<th>Biosimilar status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sndz/Zarxio® Sandoz, Mar 2015</td>
<td>Filgrastim / Neupogen® Amgen, Feb 1991</td>
<td>On market, all indications granted at approval*</td>
</tr>
<tr>
<td>Infliximab-dyyb/Inflectra® Hospira, Apr 2016</td>
<td>Infliximab/Remicade® Janssen, Aug 1998</td>
<td>On market, all indications but orphan uses</td>
</tr>
<tr>
<td>Etanercept-szzs/Erelzi™ Sandoz, Aug 2016</td>
<td>Etanercept/Enbrel® Amgen, Nov 1998</td>
<td>Not on market, all indications granted*</td>
</tr>
<tr>
<td>Adalimumab-atto/Amjevita® Amgen, Sept 2016</td>
<td>Adalimumab/Humira® AbbVie, Dec 2002</td>
<td>Not on market, all indications but orphan uses</td>
</tr>
<tr>
<td>Infliximab-abda/Renflexis™ Merck, Apr 2017</td>
<td>Infliximab/Remicade® Janssen, Aug 1998</td>
<td>On market, all indications but orphan uses</td>
</tr>
<tr>
<td>Adalimumab-adbm/Cyltezo™ Boehringer, Sept 2017</td>
<td>Adalimumab/Humira® AbbVie, Dec 2002</td>
<td>Not on market, all indications but orphan uses</td>
</tr>
<tr>
<td>Bevacizumab-awwb/Mvasi™ Amgen, Sept 2017</td>
<td>Bevacizumab/Avastin® Genentech, Feb 2004</td>
<td>Not on market, all indication but orphan uses</td>
</tr>
</tbody>
</table>

* reference product has new indication since biosimilar approval
## Biosimilar reviews (not approved) in 2017

<table>
<thead>
<tr>
<th>Biosimilar product FDA review date</th>
<th>Reference product FDA Approval date</th>
<th>Biosimilar status in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin – Hospira May 2017</td>
<td>Epoetin / Epogen/Procrit® Amgen, Feb 1991</td>
<td>Advisory vote: 14-1 Not approved</td>
</tr>
<tr>
<td>CHS-1701 – Coherus June 2017</td>
<td>Pegfilgrastim / Neulasta® Amgen, Jan 2002</td>
<td>Advisory vote: n/a Not approved</td>
</tr>
</tbody>
</table>

www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/default.htm
<table>
<thead>
<tr>
<th>Active substance</th>
<th># biosimilars</th>
<th>Year first approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>3</td>
<td>2017</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>2</td>
<td>2016</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>3</td>
<td>2007</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>2</td>
<td>2007</td>
</tr>
<tr>
<td>Etanercept</td>
<td>2</td>
<td>2016</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>7</td>
<td>2008</td>
</tr>
<tr>
<td>Follitropin alfa</td>
<td>2</td>
<td>2013</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3</td>
<td>2013</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2</td>
<td>2014</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6</td>
<td>2017</td>
</tr>
<tr>
<td>Somatropin</td>
<td>1</td>
<td>2006</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>2</td>
<td>2017</td>
</tr>
</tbody>
</table>

[EMA biosimilar status to date](http://www.ema.europa.eu/ema/)
Notable biosimilars in other markets

- Abciximab
- Bevacizumab and trastuzumab
- Chorionic gonadotropin
- Darbepoetin alfa
- Interferon alfa-2b & 1a (also PEG versions)
- Ranibizumab
- Rasburicase
- Reteplase and streptokinase
## Biologics that are biosimilars in other countries

<table>
<thead>
<tr>
<th>351 pathway – not biosimilar</th>
<th>505(b)(2) pathway – not generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tbo-filgrastim / Granix®, Teva - Aug 2008</td>
<td>Insulin glargine / Basaglar®, Eli Lilly - Dec 2015</td>
</tr>
<tr>
<td>• Tevagrastim (Europe)</td>
<td>• Abasaglar (Europe)</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine / Lusduna®, Merck - July 2017</td>
</tr>
<tr>
<td></td>
<td>• Lusduna (Europe)</td>
</tr>
<tr>
<td></td>
<td>Insulin lispro / Admelog®, Sanofi-Aventis – Sept 2017</td>
</tr>
<tr>
<td></td>
<td>• Under review</td>
</tr>
</tbody>
</table>
### Filgrastim example

<table>
<thead>
<tr>
<th>Proprietary name</th>
<th>Neupogen®</th>
<th>Granix®</th>
<th>Zarxio®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonproprietary</td>
<td>Filgrastim</td>
<td>Tbo-filgrastim</td>
<td>Filgrastim-sndz</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Amgen</td>
<td>Teva</td>
<td>Sandoz</td>
</tr>
<tr>
<td>Pathway</td>
<td>351(a) – BLA</td>
<td>351(a) – BLA</td>
<td>351(k) – biosimilar</td>
</tr>
<tr>
<td>Ingredient</td>
<td>R-metHuG-CSF</td>
<td>R-metHuG-CSF</td>
<td>R-metHuG-CSF</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>18,800 Da</td>
<td>18,800 Da</td>
<td>18,800 Da</td>
</tr>
<tr>
<td>Protein length</td>
<td>175 amino acids</td>
<td>175 amino acid</td>
<td>175 amino acid</td>
</tr>
<tr>
<td>Expression system</td>
<td>E. Coli</td>
<td>E. Coli</td>
<td>E. Coli</td>
</tr>
<tr>
<td>Dosages</td>
<td>300, 480 mcg</td>
<td>300, 480 mcg</td>
<td>300, 480 mcg</td>
</tr>
<tr>
<td>Dosage forms</td>
<td>Vial, syringe</td>
<td>Syringe</td>
<td>Syringe</td>
</tr>
<tr>
<td>Routes</td>
<td>Subcut, IV</td>
<td>Subcut</td>
<td>Subcut, IV</td>
</tr>
<tr>
<td># Indications</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Approval/Available</td>
<td>1991/Yes</td>
<td>2012/Yes</td>
<td>2015/Yes</td>
</tr>
</tbody>
</table>

www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Comparative clinical studies in a biosimilar application will most commonly be testing for which of the below?

A. Noninferiority
B. Superiority
C. Equivalence
Rheumatoid arthritis (PLANETRA)

ACR 20 response at week 30

- Infliximab/Hospira: 73.4%
- Infliximab/Janssen: 69.7%
- Difference 4% (95%CI -4 to 12%)

No difference in treatment-emergent AE, antibody development, or PK/PD measures
Plaque psoriasis (EGALITY)

- PASI 75 at 12 weeks
  - Etanercept/Sandoz 75.7%
  - Etanercept/Amgen 73.4%
  - Difference -2.3% (95%CI -9.85 to 5.30%)

- Switching treatments at 6 wk intervals out to week 30 did not impact 52-week efficacy, safety, or immunogenicity
Adalimumab-atto (Amjevita®; Amgen)

Plaque psoriasis
% improvement in PASI at wk 16
• Adalimumab/Amgen: 80.9%
• Adalimumab/Abbvie: 83.1%
• Difference -2.18% (95%CI -7.39 to 3.02%)
No impact on safety or immunogenicity after a single switch
Rheumatoid arthritis
ACR 20 response at week 30
• Infliximab/Merck: 64.1%
• Infliximab/Janssen: 66.0%
• Difference -1.88% (95%CI -10.26 to 6.51%)

No difference in treatment-emergent AE, antibody development, or PK/PD measures
Rheumatoid arthritis

% ACR 20 at wk 12 and 24

- Adalimumab/Boehringer: 80.9%
- Adalimumab/Abbvie: 83.1%
- Difference -2.18% (95%CI -7.39 to 3.02%)

No impact on safety or immunogenicity after a single switch
Bevacizumab (Mvasi™, Amgen)

Non-small cell lung cancer

ORR [up to 19 weeks]
- Bevacizumab/Amgen: 39.0%
- Bevacizumab/Genentech: 41.7%
- Risk ratio (90%CI): 0.90 (0.80 to 1.09)

No difference in treatment-emergent AE, antibody development, or PK/PD measures
Breast Cancer

ORR at week 24

- Trastuzumab/Mylan: 69.6%
- Trastuzumab/Genentech: 64.0%
- Difference 5.53% (95%CI -3.08 to 14.04%)

No difference in treatment-emergent AE, antibody development, or PK/PD measures
Chronic kidney disease on hemodialysis (2 studies – IV & Subcut)
Mean weekly Hb level last 4 weeks of study
• Epoetin/Hospira: 10.2 g/dL
• Epoetin/Amgen: 10.1 g/dL
Difference: 0.04 (95%CI -0.13 to 0.21)

No difference in treatment-emergent AE, antibody development, or PK/PD measures
State legislation on biosimilars

Legislation on Biologics and Biosimilar Substitution, 2013-2017

LEGEND
- Enacted law, 2013-17
- Filed; failed/adjourned 2013-17 (most recent action)
- Other regulation: step therapy enacted law

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See NCSL reports for details at www.ncsl.org
* = NY enacted bill on governor's desk as of 6/30/17
Which of the following FDA resources does Indiana rely on to determine interchangeability of biosimilar?

A. Orange Book
B. Green Book
C. Yellow Book
D. Purple Book
Similarities between state legislation on interchangeability

- FDA approval as interchangeable
- Prescriber decision (i.e. DAW)
- Notification vs Communication
- Patient notification
- Record keeping
- Immunity
- Web lists
- Cost or Pricing

www.ncsl.org
Figure 1. Potential Cost Savings Across Biologic Classes

- Anti-TNF products, 21%
- Long-acting insulins, 15%
- Monoclonal antibody antineoplastics, 13%
- Fast-acting insulins, 11%
- Colony-stimulating factors, 6%
- Interferons, 6%
- Erythropoietin products, 6%
- Growth hormones, 3%
- Immunostimulants excl. Interferons, 5%
- Ocular antivascular products, 3%
- Miscellaneous antirheumatic agents, 2%
- Miscellaneous immunosuppressants, 2%
- Bone calcium regulators, 2%
- Antipsoriasis products, 1%
- Anti-asthma and COPD, 1%
- All other classes, 2%

www.rand.org/pubs/perspectives/PE127.readonline.html
Private pay: exclusions, step therapy, prior authorization

Medicare Part B
• Biosimilars share common ASP limit and HCPCS code (use modifiers for mftr)

Medicare Part D
• Coverage Gap Discount Program excludes generic and biosimilar products – donut?
Common payment arrangements for biologics

- Self-administered, pharmacy-dispensed
- Biologics used in inpatient vs outpatient facilities
- Biologics administered in physician offices

<table>
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<th>Beware the rebate trap?</th>
<th>Pre-biosimilar</th>
<th>50% of patients switch to biosimilar</th>
<th>100% of patients switch to biosimilar</th>
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</table>

Adapted from JAMA 2017;317:2163-2164
Pharmacists needs

• Bidirectional EHR communication
• Standard identification across settings
• Consistent terminology
• Clear roles and responsibilities
• Lessons learned from Europe
• EDUCATION on biologics
  – Health care professionals & consumers
Questions?