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# Biosimilar Therapeutics in Hematology Malignancies — A Contemporary Review

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# Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Ali McBride** - Hospira: Board Member/Advisory Panel; Sandoz: Board Member/Advisory Panel, Grant/Research Support

- **John Valgus -** Amgen: Board Member/Advisory Panel; Sandoz: Board Member/Advisory Panel; Teva: Board Member/Advisory Panel

# Objectives

- Analyze Food and Drug Administration (FDA) guidance documents and discuss the approval process for biosimilars.
- Describe current applications for the use of biosimilars in patients with hematology malignancies.
- Evaluate current clinical practice guidelines for the use of biosimilars in oncology and potential shortcomings.
- Describe desired therapeutic outcomes for biosimilars.

# The Biosimilar Scenario

- As head of your institutional Pharmacy and Therapeutics Committee, you have been tasked to lead your institution through the process of whether or not to add a biosimilar to your formulary

- This will include evaluating contract pricing for each agent evaluated, making decisions on which products will be on formulary, incorporation of these agents into the electronic medical record, and rolling out communication and education for medical staff and patients

- What process will you utilize to lead your team through this process?

# Audience Response Question #1

Which of the following Acts created an abbreviated FDA approval process for biosimilars in the United States?

- A Food, Drug, and Cosmetic Act
- B Public Health Services Act
- C Drug Price Competition and Patent Term Restoration Act
- D Biologics Price Competition and Innovation Act

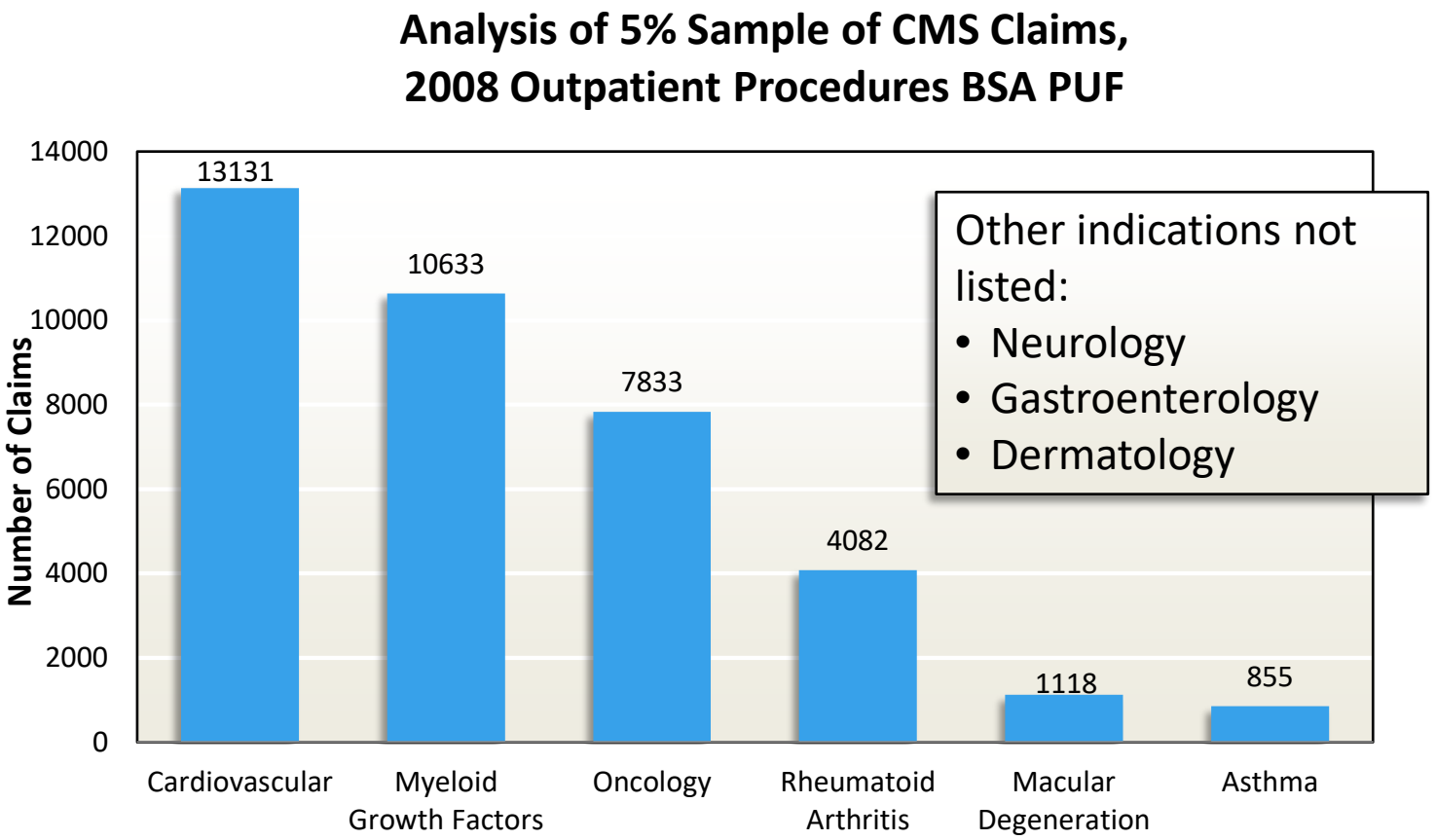
# Why Are Biologics Important?

Table 4.
Top 15 Drugs by Expenditures in Clinics in 2014

| Drug (Brand Name) | 2013 Expenditures ($ Thousands)[a] | Percent Change in 2013[b] | 2014 Expenditures ($ Thousands)[c] | Percent Change in 2014[d] |
|---|---|---|---|---|
| Infliximab (Remicade) | 2,670,580 | 7.1 | 2,245,189 | 12.8 |
| Pegfilgrastim (Neulasta) | 2,577,038 | 2.4 | 2,044,069 | 4.9 |
| Epoetin alfa (Procrit, Epogen) | 2,598,126 | 5.2 | 2,033,361 | 5.8 |
| Rituximab (Rituxan) | 2,307,286 | 5.1 | 1,779,743 | 3.5 |
| Bevacizumab (Avastin) | 2,097,323 | 2.5 | 1,680,714 | 7.5 |
| Ranibizumab (Lucentis) | 1,707,227 | 15.3 | 1,342,183 | 5.8 |
| Trastuzumab (Herceptin) | 1,538,357 | 4.6 | 1,270,581 | 10.9 |
| Denosumab (Xgeva, Prolia) | 932,431 | 27.2 | 824,607 | 21.7 |
| Pemetrexed (Alimta) | 932,188 | 5.8 | 715,352 | 5.1 |
| Immune globulin[e] | 517,412 | 13.1 | 488,254 | 32.5 |
| Varicella vaccine (Varivax, Zostavax) | 592,886 | –30.7 | 476,574 | 4.1 |
| Influenza virus vaccines[f] | 617,999 | 117.8 | 475,613 | 14.5 |
| Pneumococcal vaccine (Prevnar, Prevnar 13) | 637,430 | 3.4 | 460,824 | –0.2 |
| Natalizumab (Tysabri) | 412,975 | 204.2 | 424,361 | 277.4 |
| HPV vaccine for types 6,11,16,18 (Gardasil) | 523,209 | 14.8 | 420,850 | –0.6 |
| All others | 21,997,663 | 7.0 | 19,335,538 | 20.6 |
| Total | 42,660,130 | 7.6 | 36,017,813 | 15.5 |

Schumock GT et al. *Am J Health Syst Pharm.* 2015;72:717-736.

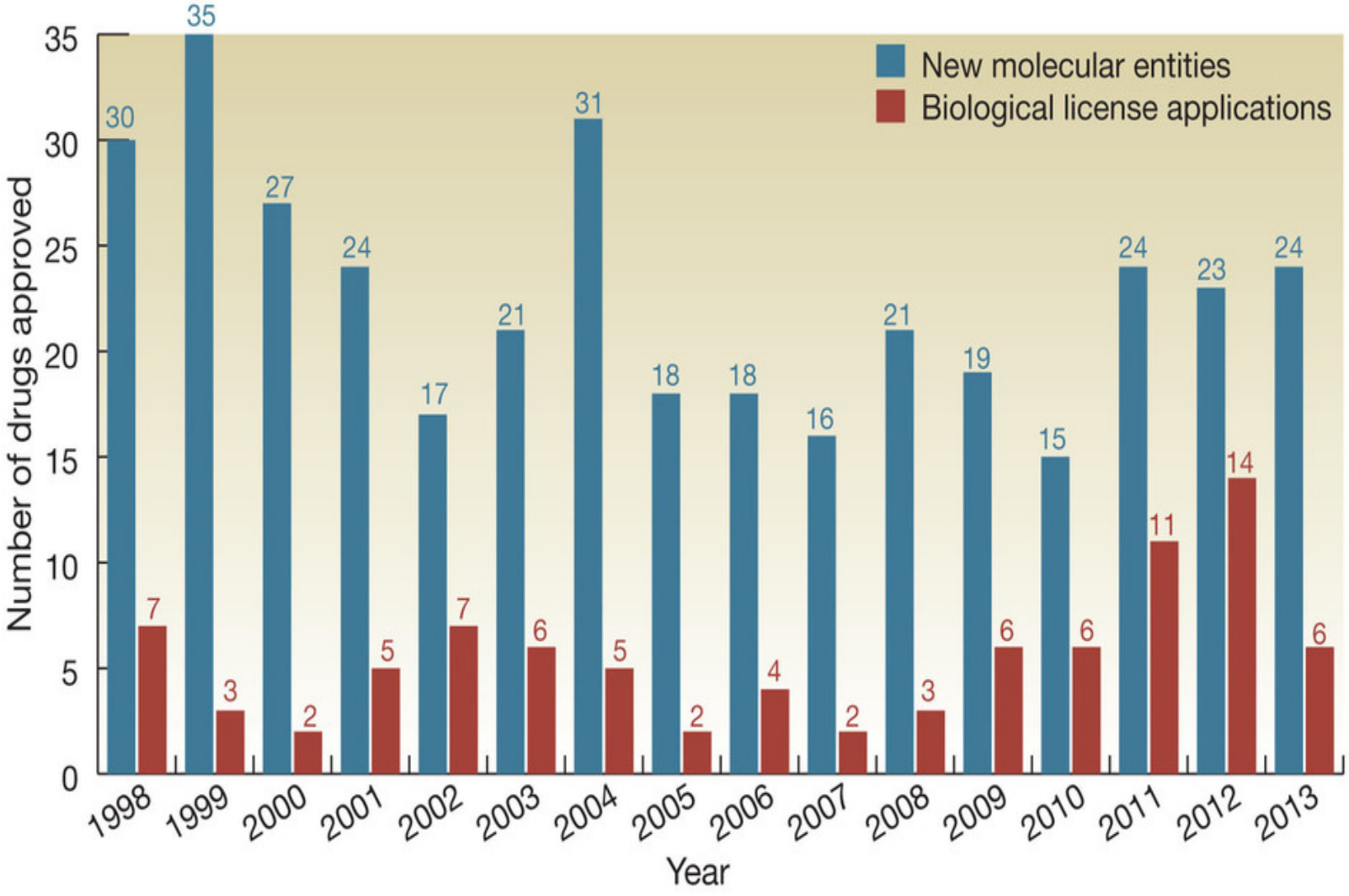
# Therapeutic Uses of Biologics




Excluded: ESAs (1.4 million claims), vaccines, IVIG

"Outpatient_Proc." *BSA Outpatient Procedures PUF*. Centers for Medicare and Medicaid Services, 18 July 2012. Web. 10 Oct. 2016. Data available at: http://cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/BSAPUFS/Outpatient_Proc.html.

# Trends in FDA Approval




Kling J. *Nat Biotechnol*. 2014;32:121-124.

# Rationale for Biosimilars

- The Biologics Price Competition and Innovation Act was enacted to increase competition with biological medications

- Competition will lead to:
  - Decreased prices (or overall expenditures)
  - Increased innovation



Blackstone EA and Joseph PF. *Am Health Drug Benefits*. 2013;6(8):469-78.

# Biological (Biologic) Definition

"Biological product" means:

- A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)
- Applicable to the prevention, treatment, or cure of a disease or condition of human beings (Public Health Service Act Section 351(i))
- Biological products also meet the definition of either a drug or device under Sections 201(g) and (h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

"Classification of Products as Drugs and Devices and Additional Product Classification Issues." *Classification of Products as Drugs and Devices and Additional Product Classification Issues*. Food and Drug Administration, 15 Jan. 2016. Web. 10 Oct. 2016.

# Biologic Definitions

**BIOLOGIC**

- A wide range of products such as vaccines, blood and blood components and recombinant therapeutic proteins derived from living cells or organisms and intended to prevent, treat, or cure a disease.[1,2]

**REFERENCE BIOLOGIC**

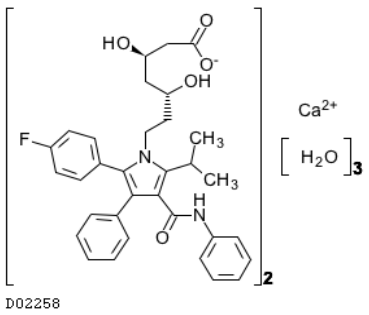
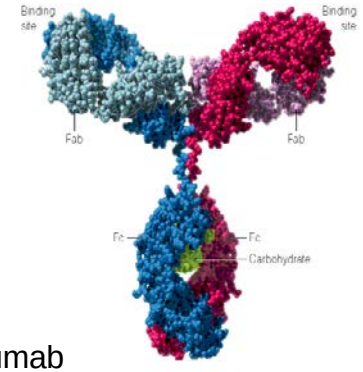
- Originally licensed biologic product used for comparison.[1]

**BIOSIMILAR**

- Biologic that is highly similar to the reference product with no clinically meaningful differences in terms of the safety, purity, and potency.[1]

"42 U.S.C. 262 - Regulation of Biological Products." *42 U.S.C. 262 - Regulation of Biological Products*. U.S. Government Publishing Office, 2010. Web. 10 Oct. 2016.
Weise M, et al. Blood. 2012;120:5111-5117

# Small Molecules vs. Biologics

| | Small Molecule Drugs | Biologics |
|---|---|---|
| Size (MW) | Small (<1,000 Daltons) | Large (>10,000 Daltons) |
| Source | Chemical synthesis | Cultures of living cells |
| Structure | Simple, well defined, independent of manufacturing process | Complex (heterogeneous), defined by the exact manufacturing process |
| Characterization | Easy to characterize | Cannot be characterized completely |
| Immunogenicity | Mostly non-immunogenic | Immunogenic |
| Example | Atorvastatin   Atorvastatin MW = 558.64 | Trastuzumab   Trastuzumab MW = 185,000 |

Declerck PJ. *GaBI J.* 2012; 1:13-6.

# Evolution of Biosimilar Approval Pathway in U.S.

Two federal laws for the approval of pharmaceuticals in the United States

- Food, Drug, and Cosmetic Act (FDCA)
  - New drug application (NDA)
  - Abbreviated NDA (ANDA)
- Public Health Service Act (PHSA)
  - Biologics license application (BLA)

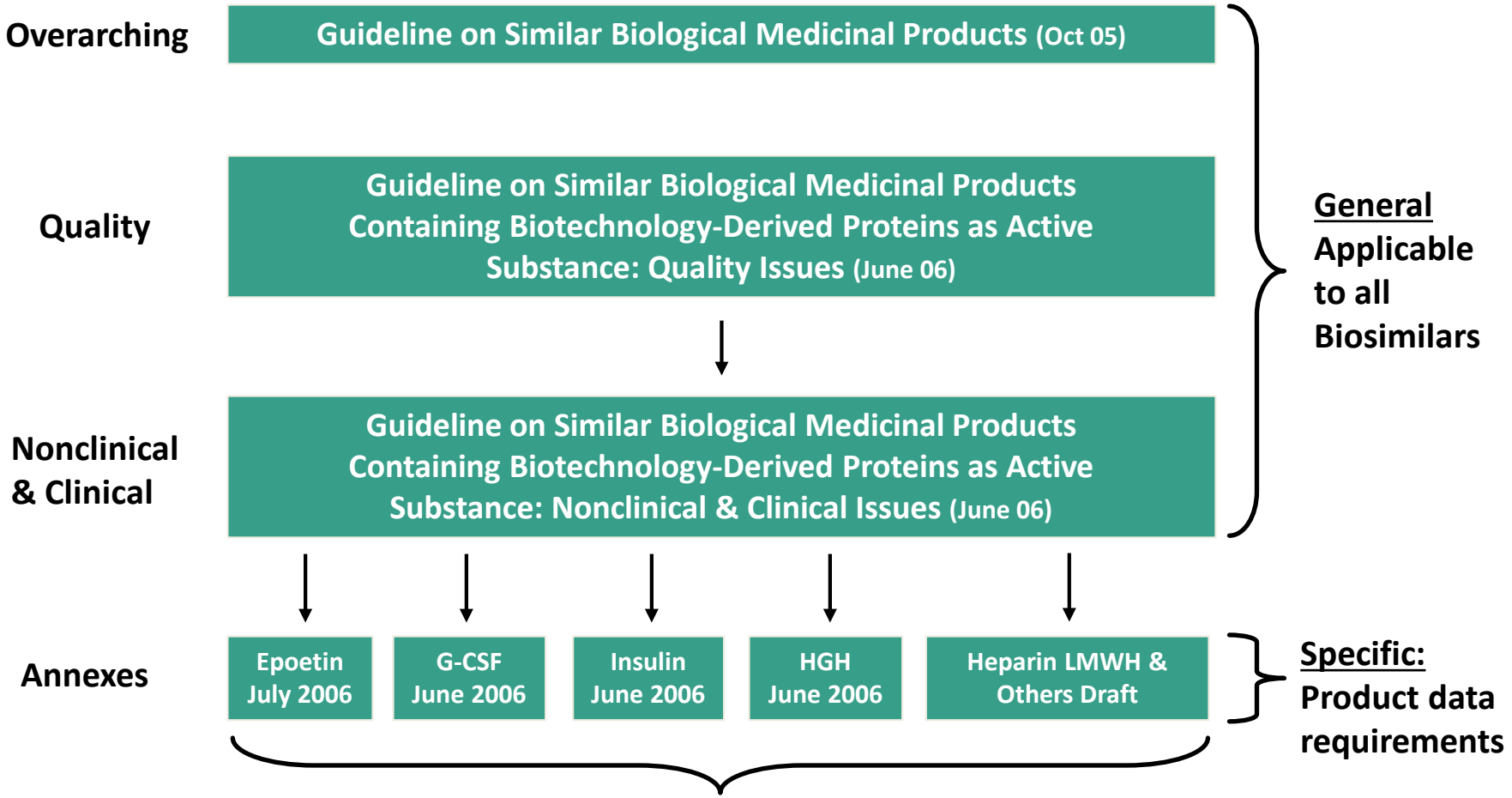
Most biologics approved under PHSA

- Drug Price Competition and Patent Term Restoration Act (aka Hatch Waxman Act) of 1984 does not apply
- Biologics Price Competition and Innovation Act (BPCI) of 2009 created an abbreviated FDA approval pathway for biosimilars
  - Full interpretation and implementation still pending

According to the FDA, “drugs” are different from “biologics”

Zelenetz AD et al. *J Natl Compr Canc Netw.* 2011; 9(Suppl 4):S1–S22.

# EMA Model: Biosimilar Regulations

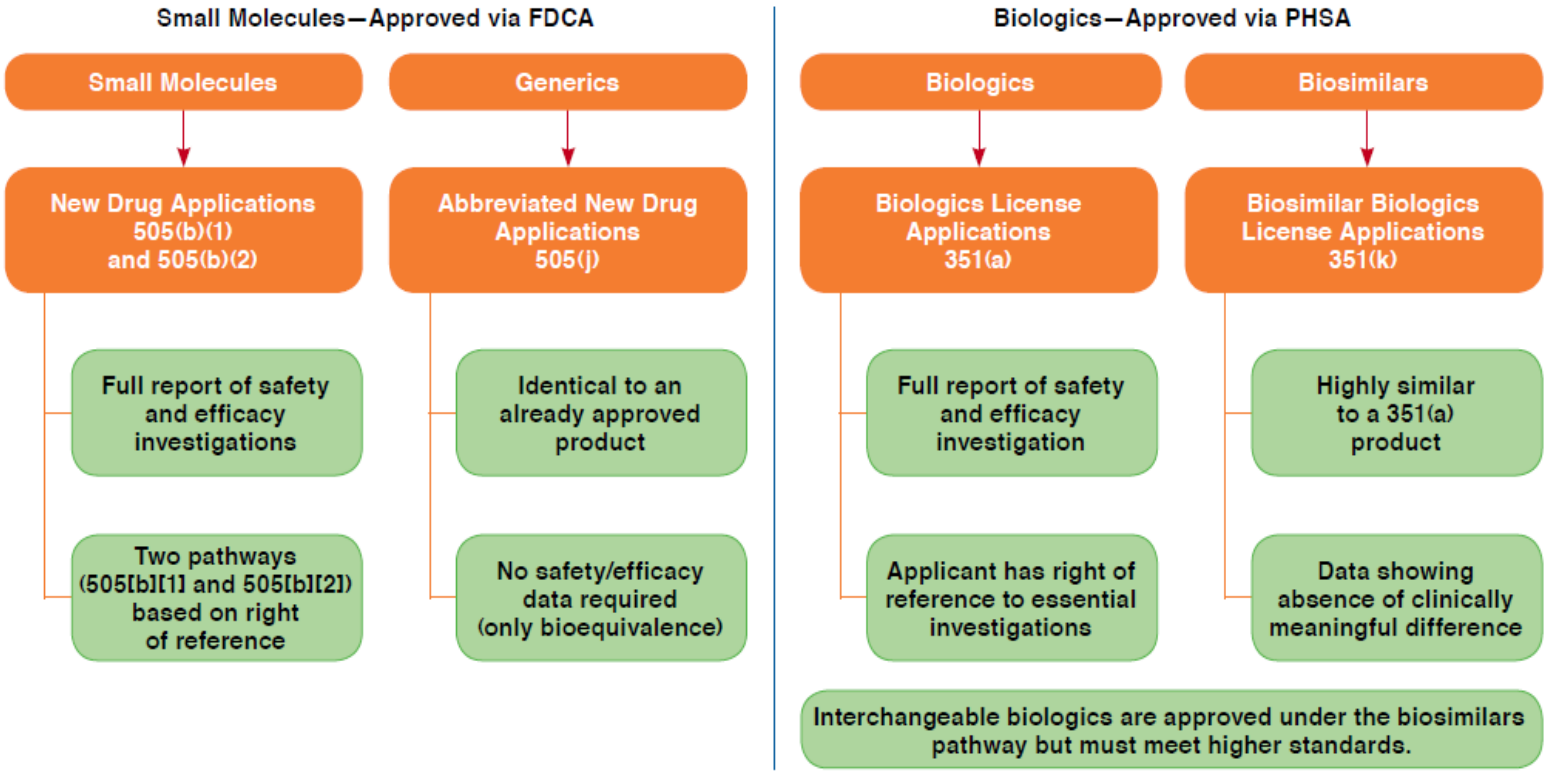



***26 biosimilar marketing authorizations have been granted***

EMA=European Medicines Agency

"Multidisciplinary: Biosimilar." *European Medicines Agency*. N.p., n.d. Web. 10 Oct. 2016.

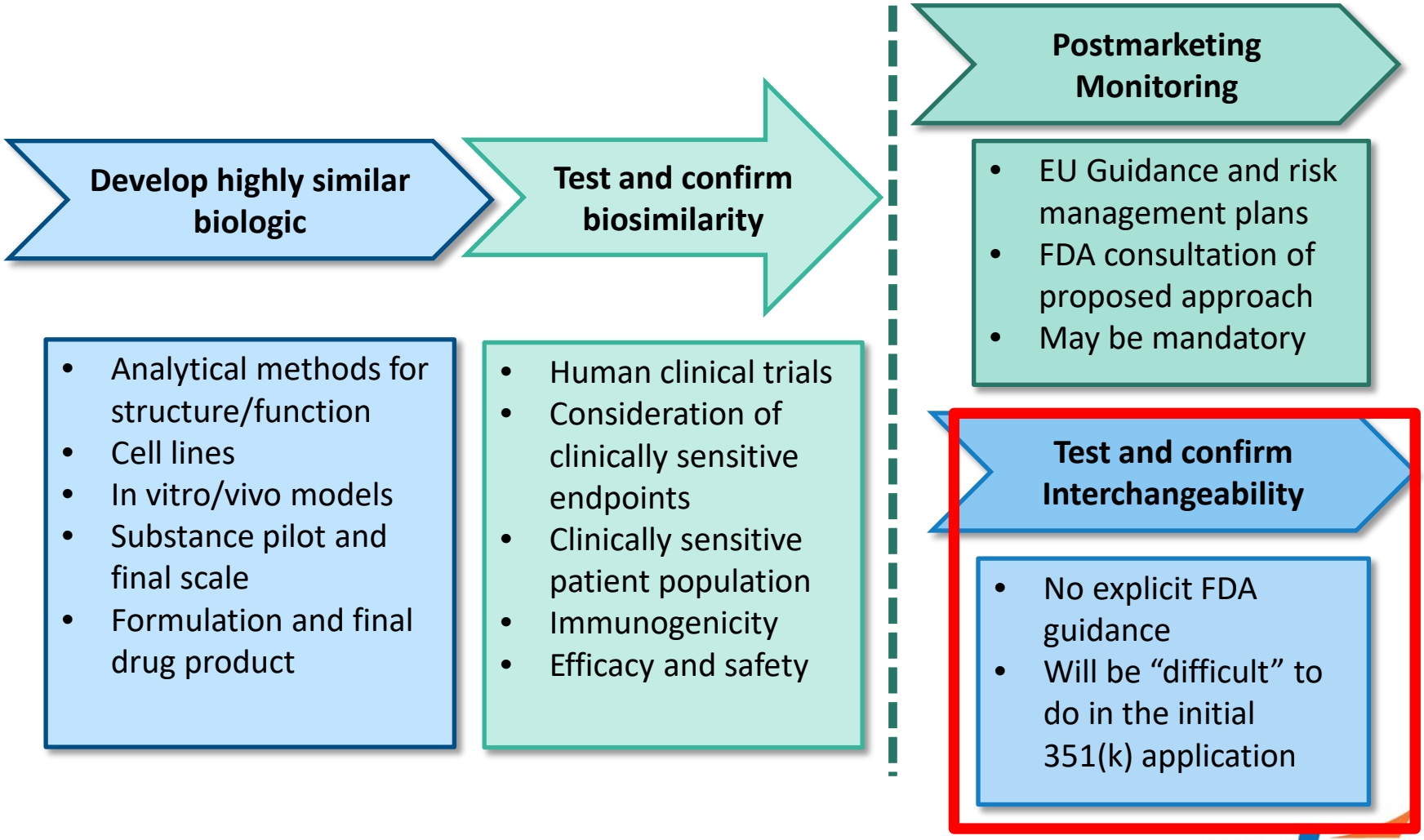
# Regulatory Pathways for Drugs and Biologics




*Note: For historical reasons, a few biological products are currently approved under the FDCA. However, under the BPCI Act, all biological products will be approved under the PHSA beginning in 2020.*
*BPCI Act=Biologics Price Competition and Innovation Act; FDCA=Food, Drug, and Cosmetic Act; PHSA=Public Health Service Act.*

Li EC, et al. *J Manag Care Spec Pharm*. 2015;21(7):532-39

# Biosimilar Development Approach Implementation




McCamish M & Woollett G. *Clin Pharmacol Ther*. 2012;91:405-17.
"Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." *Food and Drug Administration* (n.d.): n. pag. May 2015. Web. 10 Oct. 2016.

# Extrapolation

- From “Biosimilars: what clinicians should know”
  - “Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.”

Weise M et al. *Blood.* 2012;120(26):5111-5117.

# Extrapolation Review

| Extrapolation difficulty | MOAs | Measures of effectiveness | Examples |
|---|---|---|---|
| Difficult | Very complex<br>Not well understood | Mortality<br>Progression free survival | Trastuzumab |
| Intermediate | Multiple mechanisms<br>Not as well understood | Clinical measures of disease activity (CDAI in IBD) | Infliximab |
| Easy | Simple<br>Well understood | PD or surrogate markers (hemoglobin) | Epoetin |

Agarwal AB, McBride A. Crit Rev Oncol Hematol. 2016;104:98-107.

# Audience Response Question #2

Which if to following definitions accurately describes the current FDA view on biosimilar interchangeability?

A. Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same pharmacodynamic result as the reference product in any given patient

B. Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same pharmacokinetic result as the reference product in any given patient

C. Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same immunogenicity result as the reference product in any given patient

D. Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient

# Interchangeability Definition

- Interchangeability definition
  - "Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient."
  - "For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch"

"H.R.3590 Patient Protection and Affordable Care Act (Enrolled Bill [Final as Passed Both House and Senate] - ENR." *Food and Drug Administration*(n.d.): n. pag. Food and Drug Administration. Web. 10 Oct. 2016. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf>.

# Interchangeability

- Safety standards for determining interchangeability
  - Major risk is immunogenicity
  - Residual questions about diminished efficacy or increased immune-related reactions

- Will be “difficult” in the initial 351(k) application due to the sequential nature of the assessment
  - Immune reactions are highly variable and sensitive to many different factors
  - Data package to be submitted will generally not be sufficiently sensitive to detect rare/serious adverse events

"H.R.3590 Patient Protection and Affordable Care Act (Enrolled Bill [Final as Passed Both House and Senate] - ENR." *Food and Drug Administration*(n.d.): n. pag. Food and Drug Administration. Web. 10 Oct. 2016. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf>.

# FDA Purple Book

- Lists biological products approved by FDA and dates of approval
- Lists approval pathway: e.g., 351(a), 351(k)
- Lists if a biosimilar is interchangeable
- Defines exclusivity period

"Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations." *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*. Food and Drug Administration, 27 Sept. 2016. Web. 10 Oct. 2016.

# Biosimilar Implications in Hematology

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# Audience Response Question #3

Which of the following reference biologics has an approved biosimilar available currently in the United States?

A. Filgrastim
B. Pegfilgrastim
C. Trastuzumab
D. Rituximab

# European Biosimilars Experience

| Active Substance | Products | Approval |
|---|---|---|
| Epoetin alfa | Abseamed<br>Binocrit<br>Epoetin Alfa Hexal | 8/2007<br>8/2007<br>8/2007 |
| Epoetin zeta | Retacrit<br>Silapo | 12/2007<br>12/2007 |
| Filgrastim | Accofil<br>Biograstim<br>Filgrastim Hexal<br>Grastofil<br>Nivestim<br>Ratiograstim<br>Tevagrastim<br>Zarzio | 9/2014<br>9/2008<br>2/2009<br>10/2013<br>6/2010<br>9/2008<br>9/2008<br>2/2009 |
| Follitropin alfa | Bemfola<br>Ovaleap | 3/2014<br>9/2013 |
| Infliximab | Inflectra<br>Remsima | 9/2013<br>9/2013 |
| Insulin glargine | Abasaglar/Abasria | 9/2014 |
| Somatropin | Omnitrope | 4/2006 |

"European Public Assessment Reports." *European Medicines Agency Biosimilar Medicinal Prducts*. European Medicines Agency, n.d. Web. 10 Oct. 2016. <http://www.ema.europa.eu/ema/index.>.

# Biosimilars Market Uptake in Europe


"Assessing Biosimilar Uptake and Competition in European Markets." (2014): n. pag. Oct. 2014. Web. 11 Oct. 2016. <https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Assessing_biosimilar_uptake_and_competition_in_European_markets.pdf>.

# Biosimilars in the US

| Brand Name | INN | Manufacturer | aBLA submitted |
|---|---|---|---|
| Zarxio™ | filgrastim-sndz | Sandoz | 7/2014 |
| | Pegfilgrastim-sndz | Sandoz | 11/18/2015 |
| Remsima® | infliximab | Celltrion Inc. | 8/2014 |
| | pegfilgrastim | Apotex Inc. | 12/2014 |
| Retacrit™ | epoetin zeta | Hospira | 1/2015 |
| Grastofil™ | filgrastim | Apotex Inc. | 2/2015 |

"Biosimilar News." *Home*. GaBi Online, n.d. Web. 11 Oct. 2016. <http://www.gabionline.net/Biosimilars/News>.

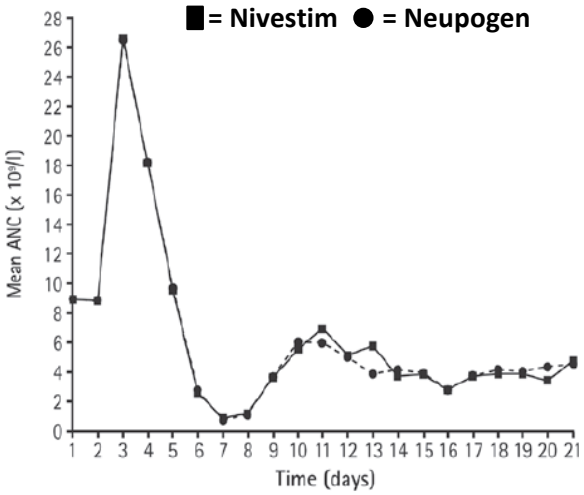
# Filgrastim (Tevagrastim) in Europe

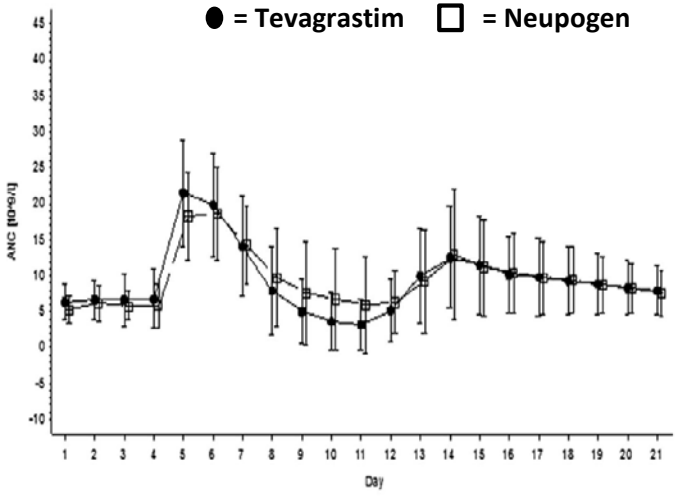
- Recombinant human G-CSF produced via E. coli
- Two Phase I studies compared it to reference product
- Clinical efficacy comparison to reference product in patients receiving up to 4 cycles of chemotherapy
  - Comparable efficacy
  - No immunogenicity findings
- Safety evaluations found no clinically meaningful differences in adverse effect profile

Gascon P. *Target Oncol*. 2012;7(Suppl 1):S29-S34.

# Head-to-Head Oncology Trials

**Absolute Neutrophil Count**




- Nivestim vs Neupogen[1]
- 279 patients (2:1)
- Breast cancer chemotherapy

- Tevagrastim vs Neupogen[2]
- 240 patients (2:1)
- Lung cancer chemotherapy


1. Waller CF, et al. *Oncologie*. 2010;33(10):504-511.
2. Gatzemeier U, et al. *J Thorac Oncol*. 2009;4(6):736-740.

# Available G-CSFs in the US and Approved Indications

| | Filgrastim | Tbo-filgrastim | Filgrastim-sndz | Pegfilgrastim |
|---|---|---|---|---|
| **Approval Pathway** | BLA | BLA | Biosimilar 351(k) | BLA |
| **Reference Product** | None | None | Filgrastim | none |
| **Cancer patients receiving myelosuppressive chemotherapy** | ✓ | ✓ | ✓ | ✓ |
| **Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy** | ✓ | --- | ✓ | --- |
| **Cancer patients receiving bone marrow transplant** | ✓ | --- | ✓ | --- |
| **Patients undergoing peripheral blood progenitor cell collection and therapy** | ✓ | --- | ✓ | --- |
| **Patients with severe chronic neutropenia** | ✓ | --- | ✓ | --- |

# Tbo-Filgrastim: US Approval

- Filed as a Biologic License Application rather than the biosimilar pathway
- Approved in US in 2012 as tbo-filgrastim
- Included in 2014 NCCN Guidelines for Myeloid Growth Factors
- Dosing and duration considered to be same as for filgrastim
- Indicated for decreasing duration of SN in nonmyeloid malignancies receiving myelosuppressive chemotherapy
- No indication in BMT/SCM

"Drugs@FDA: FDA Approved Drug Products." *Drugs@FDA: FDA Approved Drug Products*. Food and Drug Administration, 2012. Web. 11 Oct. 2016. <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.
National Comprehensive Cancer Network (NCCN).
Myeloid growth factors version 2.2014. 2014 Feb 2; National Comprehensive Cancer Network.

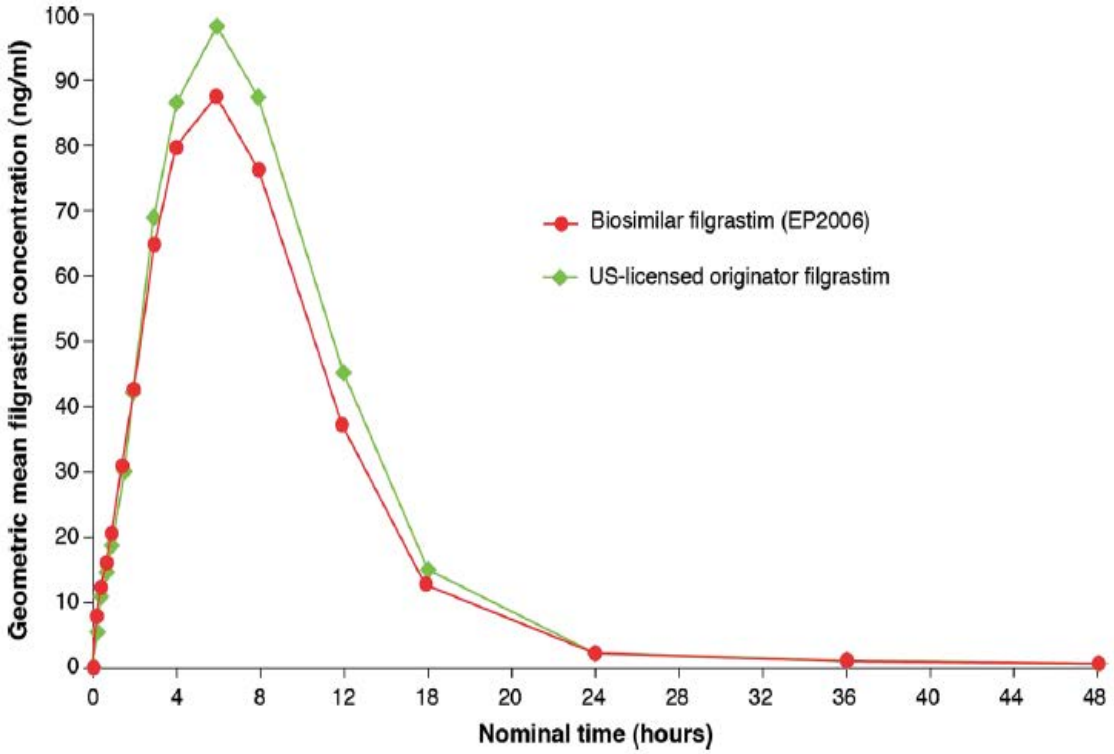
# Biosimilar Filgrastim

- Data to support the demonstration of biosimilarity
  - Analytical data
  - Animal studies
  - Clinical studies
    - Immunogenicity
    - PK/PD
    - Clinical efficacy and safety

"BLA 125553 EP2006, a Proposed Biosimilar to Neupogen® (filgrastim) Sandoz Inc., a Novartis Company." (n.d.): n. pag. Jan. 2015. Web. 11 Oct. 2016.
"FDA Oncologic Drugs Advisory Committee Meeting: Zarxio (filgrastim)." (2015): n. pag. 27 Jan. 2015. Web. 11 Oct. 2016.

# Comparability of Biosimilar Filgrastim with Reference Filgrastim

**Pharmacokinetic Analysis**




Sorgel F, et al. *BioDrugs*. 2015;29:123-131.

# Controversies about Biosimilars

- The WMDA recommends"… that biosimilars not be used for mobilization in normal donors unless the donor is follow on study."

1. Is there data to support the use of biosimilar growth factor in transplant

2. What data exists for biosimilar growth in engraftment

Shaw BE et al. Haematologica 2011;96:942-947
Bonig H et al. Transfusion 2015;55:430-9

# Biosimilars in Mobilization

- Ratiograstim granted EU approval as a biosimilar in 2008
- There were few publications evaluating the use of a biosimilar in stem cell mobilization
- Retrospective analysis was evaluated in 131 patients who underwent autologous stem cell mobilization

# Biosimilars in Mobilization

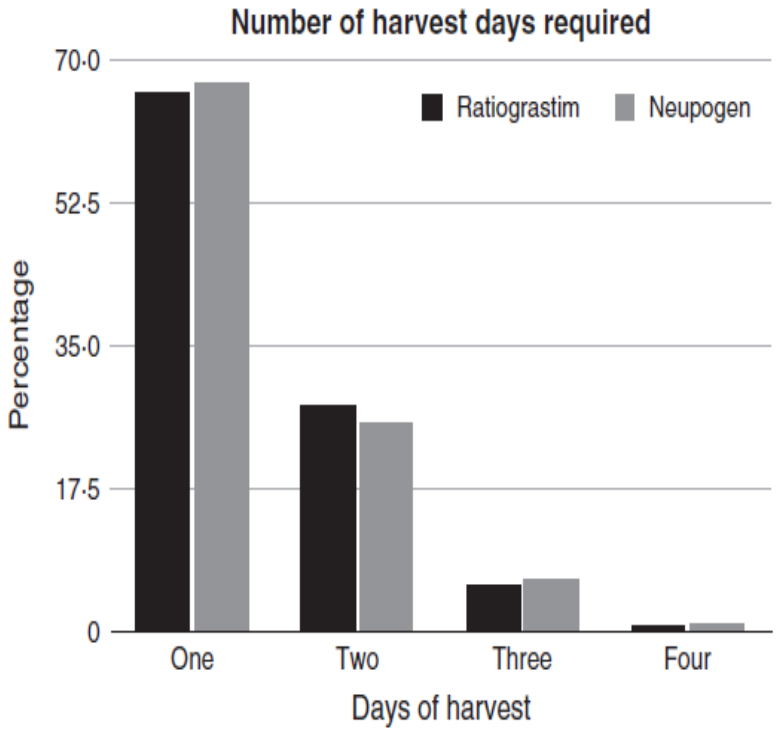



Table III. Time to neutrophil and platelet engraftment.

| | Originator | Biosimilar | *P*-value |
|---|---|---|---|
| Patients | 131 | 154 | |
| Proceeded to SCT | 84 (64%) | 111 (72%) | |
| Median days to neutrophils >0·5 × $10^9$/l (range) | 13 (9–23) | 13 (9–22) | 0·13 |
| Median days to platelets >20 × $10^9$/l (range) | 12 (8–24) | 12 (7–35) | 0·64 |

Publicover A, et al. British Journal of Haematology 2013;162:107-11

# Biosimilar G-CSF - Mode and dose for autologous hematopoietic stem cell mobilization

| References | Type of Transplant | Biosimilar | Dose (µg/kg/ day) | MM | NHL | HL | AML / ALL | GCT |
|---|---|---|---|---|---|---|---|---|
| Publicover A. et al. (2013) | Auto | Ratiograstim®/ Ref. G-CSF + Chemo | NA | 76 | 65 | 13 | - | - |
| Kirchner H. (2011) | Auto | Ratiograstim® + Chemo | NA | 7 | 11 | 1 | - | 1 |
| Sammassimo S. et al. (2011) | Auto | Tevagrastim® + Chemo | 300µg/ day | 6 | 8 | 1 | - | - |
| Sever M. et al. (2012) | Auto | Tevagrastim® | 10 | - | - | - | - | - |
| Andreola G. et al. (2012) | Auto | Tevagrastim® + Pleri + Chemo | 10 | 8 | 4 | 2 | - | - |
| Lanza F. et al. (2012) | Auto | Tevagrastim® + Pleri + Chemo | NA | 81 | 105 | 25 | - | - |
| Lazlo D. et al. (2012) | Auto | Ref. G-CSF / Tevagrastim® + Pleri + Chemo | 10 | 10 | 10 | 1 | - | - |
| Morabito L. et al. (2012) | Auto | Ref. G-CSF / Tevagrastim® + Pleri | 10 | 3 | 1 | - | - | - |
| Total | | | | **191** | **204** | **43** | **-** | **1** |

Auto - Autologous mobilization; Auto*****- Autologous transplantation; Pleri - Plerixafor; Ref. G-CSF - Reference G-CSF (Neupogen®, Amgen); Chemo- Chemotherapy; MM - Multiple Myeloma; NHL - Non Hodgkin Lymphoma; HL - Hodgkin's Lymphoma; AML / ALL - Acute Myeloid Leukemia / Acute Lymphoblastic Leukemia; ****** - Acute Lymphoblastic Leukemia ; GCT- Relapsed Germ cell tumors

Schmidt M et al. Theranostics. 2014; 4: 280–289

# Biosimilar G-CSF - Mode and dose for autologous hematopoietic stem cell mobilization

| References | Type of Transplant | Biosimilar | Dose (µg/kg/ day) | MM | NHL | HL | AML / ALL | GCT |
|---|---|---|---|---|---|---|---|---|
| Czerw T. et al. (2012) | Auto * | Filgrastim-sndz/Ref. G-CSF | 5 | 55 | - | - | - | - |
| Dmoszynska A. et al. (2012) | Auto | Filgrastim-sndz/Ref. G-CSF + Chemo | 10 | 23 | 14 | 13 | 4 | - |
| Yafour N. et al. (2013) | Auto | Filgrastim-sndz/ Ref. G-CSF | NA | 4 | - | 6 | - | - |
| Kotwica K. et al. (2012) | Auto * | Filgrastim-sndz + Chemo | NA | 12 | 4 | 6 | 1 | - |
| Gopcsa L. et al. (2013) | Auto | Filgrastim-sndz + Chemo | NA | 11 | 8 | 2 | - | - |
| Ostuni A. et al. (2013) | Auto | Filgrastim-sndz + Chemo | 10 | 11 | 22 | 9 | 2 (1+1**) | - |
| De Giorgi U. et al. (2012) | Auto | Filgrastim-sndz + Chemo | NA | - | - | - | - | 22 |
| Lefrere F. et.al. (2011) | Auto | Filgrastim-sndz + Chemo | 5 -10 | 19 | 21 | - | - | - |
| **Total** | | | | **135** | **69** | **36** | **7** | **22** |

Auto - Autologous mobilization; Auto*****- Autologous transplantation; Pleri - Plerixafor; Ref. G-CSF - Reference G-CSF (Neupogen®, Amgen); Chemo- Chemotherapy; MM - Multiple Myeloma; NHL - Non Hodgkin Lymphoma; HL - Hodgkin's Lymphoma; AML / ALL - Acute Myeloid Leukemia / Acute Lymphoblastic Leukemia; ****** - Acute Lymphoblastic Leukemia ; GCT- Relapsed Germ cell tumors

Schmidt M et al. Theranostics. 2014; 4: 280–289

# Clinical Practice Guidelines for Biosimilars

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# Biosimilar Market

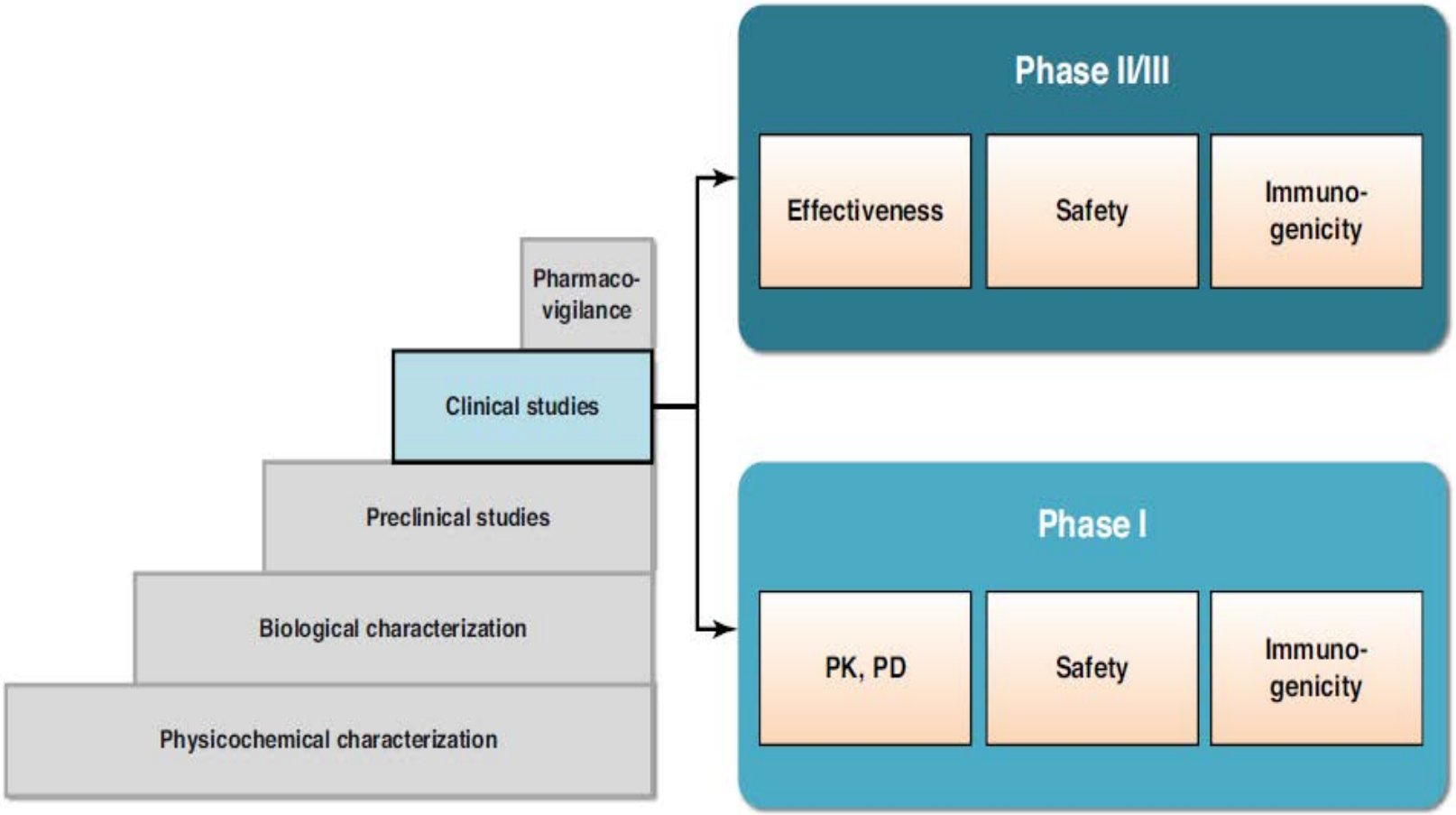
## Approved Biosimilars

- Adalimumab-atto (Amjevita)
  - Approved September 23,2016
- Infliximab-dyyb (Inflectra)
  - Approved April 7, 2016
- Filgrastim-sndz (Zarxio)
  - Approved March 6, 2015

## Biosimilars in Development

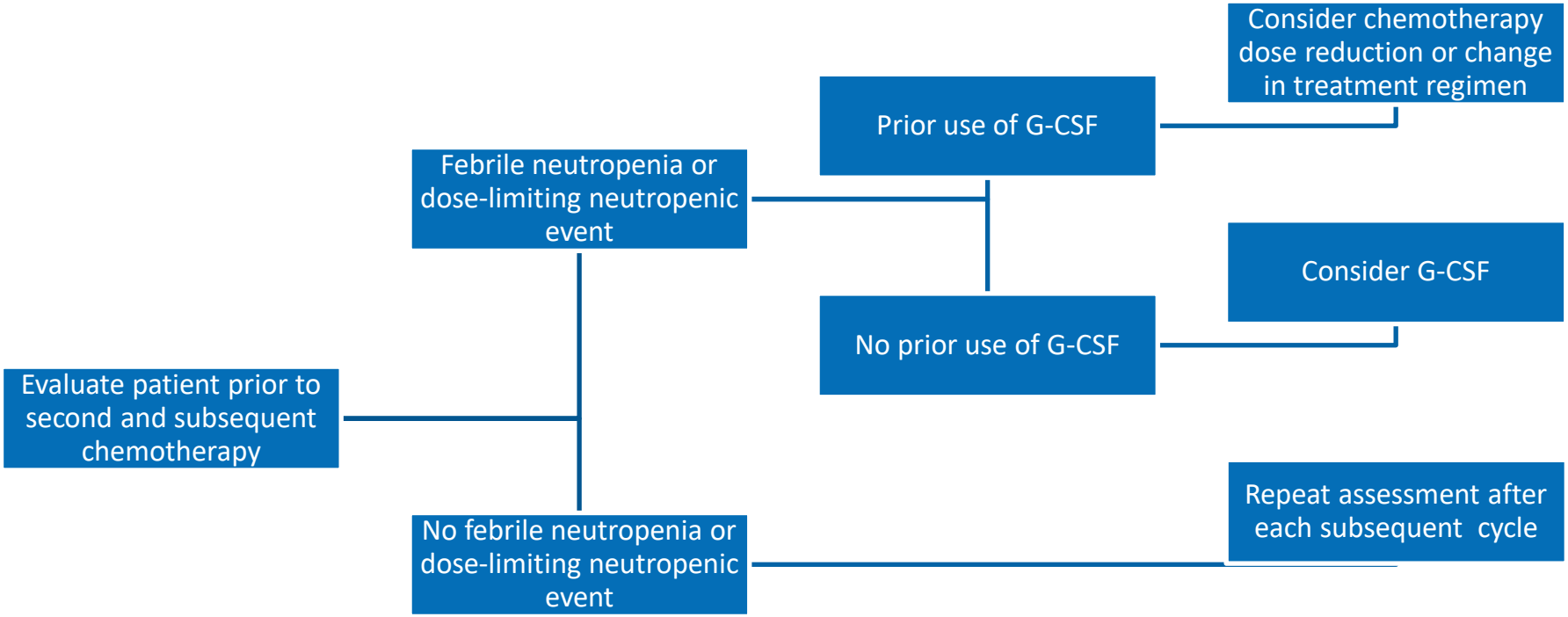
- Filgrastim – Apotex
- Pegfilgrastim – Apotex
- Filgrastim- Spectrum
- Rituximab
- Pegfilgrastim - Sandoz
- Bevacizumab
- Trazstuzumab - Samsung
- Epoetin alfa

# Clinical Studies




Li EC, et al. *Drug Discov Today*. 2015;20(S2):1-9.
"Biosimilars." *Biosimilars*. Food and Drug Administration, 17 Nov. 2015. Web. 11 Oct. 2016. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>.

# Guideline Recommendations




- Febrile neutropenia is defined as a single temperature ≥ 38.3 degrees Celsius or ≥ 38 degrees Celsius for over 1 hour
- Neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 hours
- G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim
- Dose-limiting neutropenic event could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy

National Comprehensive Cancer Network (NCCN).
Myeloid growth factors version 2.2016. 2016 Feb 2; National Comprehensive Cancer Network.

# Clinical Guideline Incorporating Biosimilars

| Indication | Recommendation |
|---|---|
| G-CSF for prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery | Filgrastim (Category 1); tbo-filgrastim (Category 1); filgrastim-sndz (Category 1); pegfilgrastim (Category 1) |
| Myeloid growth factors for therapeutic use and maintenance of scheduled dose delivery | Filgrastim; filgrastim-sndz; sargramostim |
| Mobilization of hematopoietic progenitor cells in autologous setting | 1. Single agent growth factor<br>• Filgrastim; filgrastim-sndz; tbo-filgrastim<br>2. Combination chemotherapy followed by MGF<br>• Filgrastim; filgrastim-sndz; tbo-filgrastim<br>3. Concurrent MGF<br>• Filgrastim/filgrastim-sndz + sargramostim<br>4. MGF + plerixafor<br>• Filgrastim; filgrastim-sndz; tbo-filgrastim |

Adapted from: Version 2.2016 National Comprehensive Cancer Network Guidelines Myeloid Growth Factors.

# THE NEED FOR U.S. BIOSIMILARS

EXPRESS SCRIPTS®

Generic drugs were introduced 30 years ago, saving billions of dollars, improving patient access and changing healthcare forever. Biosimilars now hold the same potential.

**U.S. SPECIALTY Rx SPEND**

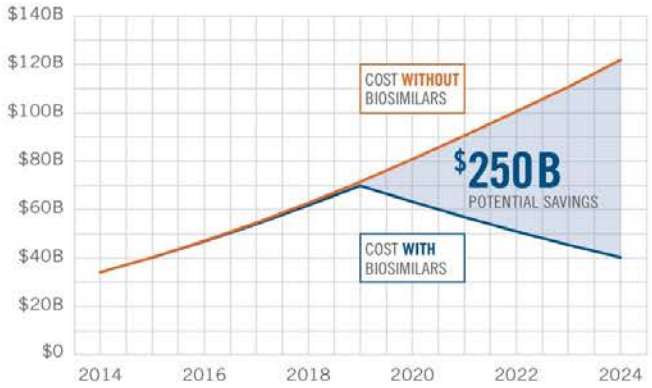
**4X SINCE 2006**


**BY 2018, SPECIALTY DRUGS WILL ACCOUNT FOR:**


OF ALL U.S. PRESCRIPTIONS

OF ALL Rx COST

## $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)*



*Awaiting FDA approval.

## WE KNOW
### BIOSIMILARS CAN DRIVE COST DOWN SAFELY


Biosimilars have been lowering healthcare costs around the globe **since 2006 with no related safety issues.**

## WE NEED
### A CLEAR PATH FORWARD IN THE U.S.

FDA APPROVAL


NO UNNECESSARY HURDLES IN STATE SUBSTITUTION LAWS


EASY-TO-USE NAMING STRUCTURE

For the latest Express Scripts research, visit: http://Lab.Express-Scripts.com.



"Biosimilars Market in the US - 2015 - HealthCare Recruiters International."*Biosimilars Market in the US – 2015*. HealthCare Recruiters International, 30 Sept. 2015. Web. 11 Oct. 2016. <http://www.hcrnetwork.com/biosimilars-market-in-the-us-2015/>.

# PBM Formulary Impact

| Category | Medication Name | Change |
|---|---|---|
| Neutropenia | Filgrastim | Excluded |
| | Filgrastim-sndz | Replace filgrastim |
| Cancer | Dasatinib (Sprycel®) | Excluded |
| | Imatinib (Gleevec®) | Excluded |
| | Imatinib | Replace Gleevec® |
| | Nilotinib (Tasigna®) | Step therapy;<br>step 1 medication: imatinib |

"UnitedHealth's 2017 Formulary to Support Generic and Biosimilar Drugs." *AJMC*. AMJC, 23 Sept. 2016. Web. 11 Oct. 2016. <http://www.ajmc.com/newsroom/unitedhealths-2017-formulary-to-support-generic-and-biosimilar-drugs>.

# Therapeutic Outcomes for Biosimilars

# Oncologic Indications

- Therapeutic intent
  - Outcomes based on overall survival and increased efficacy
- Outcomes based on numerous studies with different treatment regimens
  - Timing and type of regimen play a role in treatment
- Numerous chemotherapy regimens in combination may vary outcomes based on disease state at initial diagnosis
- Large quantities of studies may be used in the off-label indications

# The Next Big Decision!

# Extrapolation in Rituximab

- From “Biosimilars: what clinicians should know”
  - “Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.”
- With a rituximab biosimilar can we extrapolate:
  - From non-malignant use (e.g. RA) to lymphoma?
  - From use in lymphoma to autoimmune disease?
  - From single agent to combination?
  - From combination to single agent?

Weise M et al. *Blood.* 2012;120:5111-5117.

Zelenetz A. Presentation to New York Academy of Sciences (NYAS); March

# Rituximab

- Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells
- Rituximab destroys B cells and is therefore used to treat diseases that are characterized by excessive number of B cells, overactive B cells, or dysfunctional B cells
- This includes many lymphomas, leukemias, transplant rejections, and autoimmune disorders
- The originator product, Roche's MabThera/Rituxan (rituximab), was approved by the US Food and Drug Administration (FDA) in November 1997 and by the European Medicines Agency (EMA) in June 1998

"US$67 Billion worth of Biosimilar Patents Expiring before 2020 - GaBI Journal." *GaBI Journal US67 Billion worth of Biosimilar Patents Expiring before 2020 Comments*. GaBi Online, 24 Sept. 2012. Web. 11 Oct. 2016.

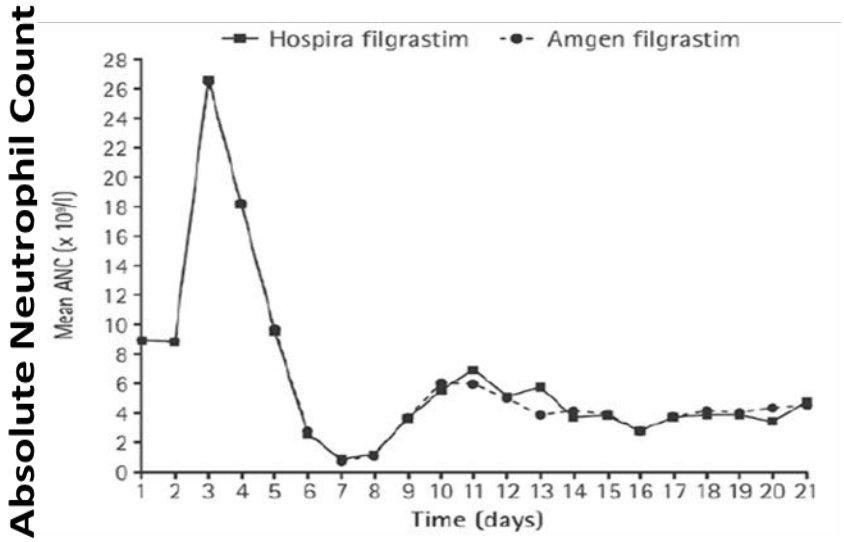
# Rituximab Biosimilar Clinical Trials

| Company Name, Country | Product Name | Stage of Development |
|---|---|---|
| Amgen, USA | ABP 798 | Biosimilar in active development, according to Amgen's Form 10-K for 2013. One of four biosimilars for oncology indications that Amgen is developing in collaboration with Actavis |
| Biocad, Russia* | AcellBia | Non-originator biological approved in Russia in April 2014 |
| BioXpress Therapeutics, Switzerland | - | Biosimilar in pipeline |
| Boehringer Ingelheim, Germany | BI 695500 | Phase I and III trials expected to be completed in June and August 2015, respectively, but halted in October 2015 |
| Celltrion/Hospira, South Korea/USA | CT-P10 | Phase I trial completed. Phase III trials for RA and lymphoma expected to be completed in January 2017 and February 2017/March 2018, respectively |
| Dr Reddy's Laboratories, India* | Reditux | Reditux marketed in Bolivia, Chile, India and Peru |
| Hetero Group, India* | Maball | 'Similar biologic' approved in India in August 2015 |
| iBio, USA | - | Rituximab produced in non-transgenic green plants. Alliance made with GE Healthcare in 2012. |
| Intas Biopharmaceuticals, India* | MabTas | 'Similar biologic' approved in India in February 2013 |
| Laboratorio Elea, Argentina | Novex | *Medicamento biológico similar* approved in Argentina in October 2013 |
| Mabion, Poland | MabionCD20 | Phase III trial in lymphoma expected to be completed in June 2016 |

"Biosimilars of Rituximab." *Home*. GaBi Online, 9 Sept. 2016. Web. 11 Oct. 2016. <http://gabionline.net/Biosimilars/General/Biosimilars-of-rituximab>.

# Why May Rituximab be Different?

- Therapeutic vs supportive medication
  - May have significant impact on clinician and patient comfort with biosimilars
  - Think generics
- Lack of visible efficacy




Waller CF et al. Onkologie. 2010;33(10):504-511.

# US-Based Rituximab Biosimilar Trials

| Clinical Trial | Sponsor | Initiation | Schema | Primary Endpoint |
|---|---|---|---|---|
| NCT01419665[1] | Sandoz | December 2011 | A Randomized, Controlled, Double-Blind Phase III Trial to Compare the Efficacy, Safety and Pharmacokinetics of GP2013 vs. MabThera® in Patients With Previously Untreated, Advanced Stage Follicular Lymphoma | Overall Response Rate |
| NCT02213263[2] | Pfizer | September 2014 | PF-05280586 (Rituximab-Pfizer) Or MabThera® (Rituximab-EU) For The First-Line Treatment Of Patients With CD20-Positive, Low Tumor Burden, Follicular Lymphoma | Objective Response Rate |
| NCT02747043[3] | Amgen | May 2016 | Randomized, Double-Blind Study Evaluating the Efficacy, Safety and Immunogenicity of ABP 798 Compared With Rituximab in Subjects With CD20 Positive B-Cell Non-Hodgkin Lymphoma | Objective Response Rate |

1. GP2013 in the treatment of patients with previously untreated, advanced stage follicular lymphoma (ASSIST_FL). In: Clinicaltrials.gov (internet). Bethesda, MD: National Library of Medicine (US). 2011. Accessed Oct 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT01419665
2. A Study Of PF-05280586 (Rituximab-Pfizer) Or MabThera® (Rituximab-EU) For The First-Line Treatment Of Patients With CD20-Positive, Low Tumor Burden, Follicular Lymphoma (REFLECTIONS B328-06). In: Clinicaltrials.gov (internet). Bethesda, MD: National Library of Medicine (US). 2014. Accessed Oct 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02213263
3. Study to Access if ABP798 is Safe & Effective in Treating Non Hodgkin Lymphoma Compared to Rituximab (JASMINE) In: Clinicaltrials.gov (internet). Bethesda, MD: National Library of Medicine (US). 2016. Accessed Oct 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02747043

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# Bevacizumab

- Bevacizumab is a humanized monoclonal antibody; it inhibits angiogenesis (the formation of new blood vessels) by blocking the action of vascular endothelial growth factor A (VEGF-A)

- The originator product, Roche's bevacizumab, was approved by the US Food and Drug Administration (FDA) in February 2004 and by the European Medicines Agency (EMA) in January 2005

- The patents on brand-name bevacizumab are set to expire in Europe in January 2022 and in the US in July 2019; there are estimated to be around 15 biosimilars of bevacizumab in development

# Biosimilars and Non-originator Biologicals of Bevacizumab in Development

| Company name | Product name | Stage of development |
|---|---|---|
| Amgen/Allergan, USA | ABP 215 | Phase III trial completed in September 2015 |
| AstraZeneca/Fujifilm Kyowa Kirin Biologics, USA/Japan | | 50:50 joint venture established August 2015. Phase I trial started in November 2014 |
| Biocad, Russia* | BCD-021 | Phase III trials in lung cancer and wet AMD expected to be completed in November 2015 and February 2017, respectively |
| BioXpress Therapeutics, Switzerland | - | Biosimilar in pipeline |
| Boehringer Ingelheim, Germany | BI 695502 | Phase III trial in lung cancer expected to be completed in March 2019 |
| Oncobiologics/Viropro, USA | - | Biosimilar collaboration agreement signed in February 2013 for 6 biosimilars |
| Pfizer, USA | PF-06439535 | Phase III trial in lung cancer started in February 2019 |

"Biosimilars of Bevacizumab." GaBi Online. 16 Feb. 2014. Web. 11 Oct. 2016. <http://www.gabionline.net/Biosimilars/General/Biosimilars-of-bevacizumab>.

# Considerations for P&T Committee Members Evaluating Biosimilars for Formulary Inclusion

## Clinical Considerations

- Indications
- Evaluation of efficacy and safety using available data
- Immunogenicity

## Product Considerations

- Nomenclature
- Manufacturing and supply chain considerations
- Packaging, labeling, and storage

## Institutional Considerations

- Substitutions and interchangeability
- Therapeutic interchange
- Transition of care
- Pharmacovigilance
- Cost
- Reimbursement
- Provider and patient education
- Information technology

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Ventola CL. P&T 2015:40;680-9.

# Summary

- Biosimilars are forecasted to have a major impact in the management of hematologic malignancies
- Biosimilars used in supportive care and those used in the treatment of hematologic malignancies bring unique challenges to those evaluating their role in therapy
- It is imperative that health-system pharmacists are knowledgeable about the intricacies of the biosimilar pathway in order to make the best decisions

# Questions