Biosimilars 101: The Science, Approval Process & Implications for Your Practice

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Reviewing the Development of Biosimilars in the Marketplace

What Have You Heard About Biosimilars?

What Is a Biosimilar?

- A biological product that is demonstrated to be "highly similar" to an FDA-licensed biological product (reference product)
- May rely on certain existing scientific knowledge about the safety, purity, and potency of the reference product
- New licensure pathway permits a "biosimilar" biological product to be licensed based on less-than-full complement of product-specific, nonclinical and clinical data

What Is a Biosimilar?

- Technical definition from US Code of Federal Regulations
  - "Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man"
- Derived from living sources
  - Various cultures of bacteria or viruses
  - Human or animal sources
- Biologics do not always have therapeutic intent
- For now, think of biologics as "therapeutic proteins"

Benefits of Biotechnology

- Provides new approaches to discovery, design, and production of drugs
- Biotechnology makes possible:
  - Prevention, cure, and treatment of more diseases
  - Targeted, more effective, less toxic medicines
  - Proactive vs. reactive approach
  - Production of replacement human proteins
  - Production of "pure" drugs (no contamination by infectious pathogens from human or animal sources)

Current Biologics on the Market

Generic	Brand	Indication
Human insulin	Several	Diabetes mellitus
Interferons: α, β, γ	Several	Several
Epoetin alfa Darbepoetin alfa	Procrit , Epogen, Aranesp	Anemias
Filgrastim Pegfilgrastim Sargramostim	Neupogen Neulasta Leukine	Febrile neutropenia
Trastuzumab	Herceptin	Her2Neu cancers
Rituximab	Rituxan	Lymphomas, NHL
Cetuximab Bevacizumab	Erbitux Avastin	EGFR-expressing cancers

General Classes of Biologics

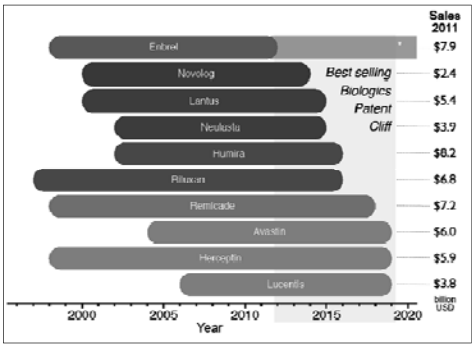
- Monoclonal antibodies
- Complex sugars
- Blood derivatives
- Vaccines
- Recombinant or purified proteins, such as:
  - Cytokines
  - Thrombolytic agents
  - Enzymes

Annual Sales of Biologic Agents

Brand	Generic	Manufacturer	Approval	Patent Exp	US 2012 Sales (in thousands)	CA 2012 Estimated Sales (in thousands)
Avastin	bevacizumab	Genentech	02/26/2004	06/18/2019	$2,642,842	$ 292,912.62
Epogen	eopetin alfa	Amgen	06/01/1989	05/26/2015	$3,954,945	$ 347,966.95
Herceptin	trastuzumab	Genentech	09/25/1998	08/27/2019	$ 1,837,693	$ 202,146.23
Humira	adalimumab	AbbVie	12/31/2002	12/31/2016	$4,565,380	$ 495,591.80
Intron A	Interferon alfa-2a	Merck	06/04/1986	08/26/2020	$ 94,009	$ 10,340.99
Neulasta	pegfilgrastim	Amgen	01/31/2002	10/20/2015	$3,472,988	$ 382,028.68
Neupogen	filgrastim	Amgen	02/20/1991	11/10/2013	$ 1,007,172	$ 110,788.92
PEG-Intron	Peginterferon alfa-2b	Merck	01/19/2001	08/26/2020	$ 121,828	$ 13,401.08
Procrit	eopetin alfa	Janssen Products	06/01/1989	05/26/2015	$ 1,127,024	$ 123,972.64
Remicade	infliximab	Janssen Biotech	08/24/1998	09/04/2018	$3,795,422	$ 417,606.42
Rituxan	rituximab	Genentech	11/26/1997	07/05/2015	$3,183,625	$ 350,198.75

Frazee SG, et al. Ten-Year Potential Savings from Biosimilars in California. Express Scripts; Research Report; September 26, 2013. Available at: http://patentdocs.typepad.com/files/ten-year-potential-savings-from-biosimilars-in-california.pdf.

Period of Exclusivity: Top 10 Biologics



* Enbrel was granted an extension in 2011 for a patent filed in 1995, which competitors can still challenge.

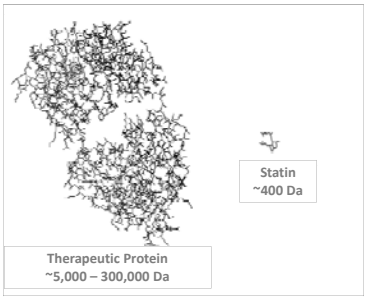
Calo-Fernandez B, Martınez-Hurtado JL. *Pharmaceuticals.* 2012;5:1393-1408.

Differentiating Biologics and Traditional Drugs

Biosimilars Production: More Complex Than for Traditional Drugs

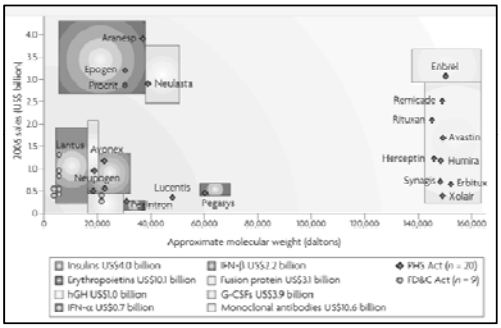
	Small Molecule Drug	Small Biologic	Large Biologic
Size	Aspirin 21 atoms	hGH ~ 3000 atoms	IgG Antibody ~ 25,000 atoms
Manufacture Complexity	Bike ~ 20 lb	Car ~ 3000 lb	F16 Jet ~ 25,000 lb (w/o fuel)

Difference in Size Between Biologics and Small-Molecule Drugs



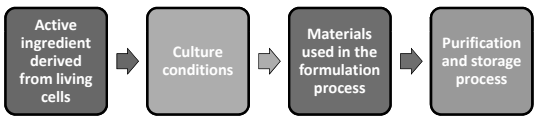
Behram RE. Follow-on Biologics: A Brief Overview. Presented at U.S. Federal Trade Commission workshop "Competition Issues Involving Follow-on Biologic Drugs." November 21, 2008.

Current Biologic Agents



Lanthier M, et al. *Nat Rev Drug Discov.* 2008;7:733-737.

Manufacturing Processes



Advantages and Disadvantages of Host Cell Systems

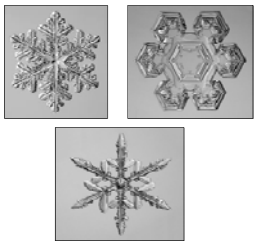
Host Cell	Advantages	Disadvantages
Bacteria	• Ease of growth • Well-studied genetics • High product yield • Large-scale fermentation capability • Low cost	• Synthesis of biologically inactive products • Inability to produce large complex proteins, such as glycoproteins • Proteins can be difficult to harvest and purify
Yeasts	• Ease of growth • Large-scale fermentation capability • Ease of purification • Low cost • Ability to produce some large complex proteins	• Proteolysis (breakdown of proteins) may result in low product yield • Inability to produce some sophisticated proteins • Additional steps may be required to ensure proper protein folding
Mammalian cells	• Ability to produce sophisticated proteins • Proteins produced may exhibit higher stability and lower antigenic properties • Large-scale fermentation capability	• Low product yield • High cost • Additional product testing required by regulatory agencies • Additional steps may be required to ensure purification

Biotech Batch Preparation

- Specific diluents (preservative free)
- Specific IV infusion solutions
- IV infusion containers may become an issue (polyvinyl chloride, glass, or plastic)
- Environmental safety issues related to IV preparation and disposal (hazardous materials?)
- Special “training” for drug preparation?
- Unique reconstitution techniques
- Storage

Differences in Biologic Products

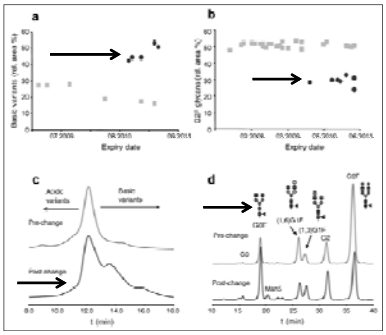
Differences Between Proteins



Post-translation Modifications

- Amino acid substitution
- N-and C-terminal mods
- Mismatched S-S bonds
- Post-translation modifications folding
  - Carboxylation
  - Formylation
  - O-linked glycosylation
  - N-linked glycosylation
  - Methylation
  - Phosphorylation
  - Sulphation
- PEGylation

Enbrel® Batch Variances



Schiestl M, et al. Nat Biotechnol. 2011;29:310-312.

Generic Equivalents as Defined in the "Orange Book"

- FDA stipulates that "pharmaceutically equivalent" drug products must be formulated to:
  - Contain the same amount of active ingredient in the same dosage form
  - Meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity)
- Products are therapeutic equivalents only if:
  - They are pharmaceutical equivalents
  - They can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

Food and Drug Administration. Center for Drug Evaluation and Research. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.

Equivalence of Biotech Drugs

- New products, chemically similar to the originator, could infringe on one or more of the originator's patents
- New products may not be therapeutically equivalent to the originator (per FDA)
- The "real world" considers drugs in similar therapeutic category, with equivalent outcomes, to be "therapeutically equivalent"
  - Supported or required by many payers
  - Antibiotic classes
  - Leuprolide acetate – goserelin acetate
  - Interferon alfa-2a and alfa-2b
  - Colony-stimulating factors (granulocyte vs. granulocyte macrophage; epoetin alfa vs. darbepoetin alfa)
  - "Taxanes"

Antibody Formation: "Immunogenicity"

- Potential increases with changes in amino acid sequence
- Some antibodies produce neutralizing effect against rDNA product (interferon alfa)
- Human antibody formation seen with some Mabs, especially human anti-mouse antigen (HAMA)
  - HAMA: neutralizing effect or hypersensitivity reactions
- Macromolecules (proteins) such as biologic drugs can trigger immune responses with varying consequences, e.g.:
  - Antibodies may neutralize the molecule, making it therapeutically ineffective
  - There may be no clinical effect
  - Rare but serious autoimmune responses can be life-threatening
- Immunogenicity of biologic drugs is unpredictable, unforeseeable

Kessler M, et al. Nephrol Dial Transplant. 2006;21(suppl 5):v9-v12.

Immunogenicity

- Up to 60% of enrolled patients developed antibodies to Omnitrope in first European phase III study
- Problem was high concentration of protein in host cells, which are known to enhance antibody reaction against growth hormone
- Additional purification steps were introduced
- New phase III studies were conducted
- Antibody levels were significantly reduced to within authorized ranges

Omnitrope: EPAR Scientific Discussion. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500043692.pdf.

Small-Molecule Drugs vs. Biologics

Key Attributes	Generics	Biosimilars
Approval	No clinical trials required	Must conduct at least one trial
Indications	Same as originator	May not include all indications
Same generic name	Yes	Likely will have different name
Interchangeable	Yes, upon approval	Possible; not granted immediately
Cost to develop	$1 to $4 million	$100 to $250 million
Price discounts	50% to 90%	15% to 30%
Role of the originator	Limited	Prominent
Member review prior to formulary addition	No	Yes

What Lessons Have We Learned from Europe?

Biosimilar Medicinal Products Working Party of the EMA

"A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients"

EMA = European Medicines Agency.
Weise M, et al. *Blood.* 2012;120:5111-5117.

Biosimilars Approved in Europe

Drug Name	First Approved	Suppliers
Somatropin	April 2006	Sandoz Gmb, Biopartners GmbH
Epoetin alfa	August 2007	Hexal AG, MEDICE Pharma GmbH & Co. KG
Epoetin zeta	December 2007	STADA Arzneimittel AG, Hospira
Filgrastim	September 2008	Ratiopharm GmbH, CT Arzneimittel, Teva, Sandoz, Hexal AG, Hospira

- Inflectra (infliximab; Hospira): first biosimilar monoclonal antibody approved in Europe; September 10, 2013

Hirsch BR, Lyman GH. JNCCN. 2011;9:934-943.

The US biosimilars market: the challenges for pharmaceutical and generic drug companies. Special report from IN VIVO: The Business and Medicine Report. October 2010.

Forbes. June 28, 2013. Available at: http://www.forbes.com/sites/edsilverman/2013/06/28/a-landmark-for-biosimilars-eu-endorses-copies-of-a-jj-drug/

Hospira press release, September 10, 2013. Available at: http://www.hospirainvestor.com/phoenix.zhtml?c=175550&p=irol-newsArticleIR&ID=1853480&highlight=

First- and Second-Generation Market Share: Epoetin and Filgrastim

	Market Share, by Revenue (Q4 2011)				
	Germany	**UK**	**France**	**Sweden**	**Italy**
Epoetin					
Aranesp	60.8%	70.7%	68.6%	67.6%	41.2%
Eprex	12.9%	26.0%	26.8%	10.7%	52.0%
Biosimilars	26.3%	3.2%	4.6%	21.7%	6.8%
Filgrastim					
Neulasta	73.5%	57.1%	77.0%	58.6%	59.4%
Neupogen	14.6%	5.1%	11.2%	13.7%	24.9%
Biosimilars	11.9%	37.8%	11.8%	27.7%	15.7%

Grabowski H, et al. *Nat Rev Drug Discov.* 2014;13:99-100.

Clinical and Formulary Considerations for Biosimilars

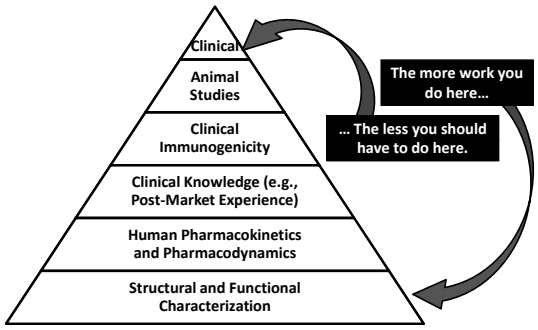
Approval Pathways (Small Molecules)

Product Type	Application Type	Application Pathway	Clinical Studies	Application Requirements
Drug (Food Drug and Cosmetic Act)	New Drug Application (NDA)	505(b)1	Yes	Full evaluation of safety and efficacy
		505(b)2	Yes	Studies do not have to be done by the application sponsor
	Abbreviated New Drug Application (ANDA)	505(j)	No	Approval based upon bioequivalence determination

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)

Totality of the Evidence



Adapted from Sherman RE. *Biosimilar Biological Products.* FDA Center for Drug Evaluation and Research. Biosimilar guidance webinar. February 15, 2012.

FDA Draft Guidance Documents

- First set of 3 documents; published in February 2012
  - Quality considerations in demonstrating biosimilarity
  - Scientific considerations in demonstrating biosimilarity
  - Question-and-answer document
- Formal meetings between FDA and biosimilar sponsors or applicants; published in March 2013
- 5 documents planned for 2014
  - **Clinical pharmacology data to support demonstration of biosimilarity; published in May 2014**
  - **Reference product exclusivity for 351(a)-filed biological products; published in August 2014**
  - Additional questions and answers
  - Considerations in demonstrating interchangeability with a reference product
  - Labeling for biosimilar biological products

Am J Health-Syst Pharm. 2013;70:2004-2017; *The Pink Sheet*, February 10, 2014.

Challenge of Biosimilar Pathway

- Within 20 days of FDA accepting a biosimilar application, that information must be shared with the originator company
- Key Question
  - Will biosimilar applicants use the 351(k) pathway or file a full BLA? (Teva tbo-filgrastim example)

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

State Legislation Restricting Substitution of Biosimilars

Nat Biotech. 2013;31:947. doi:10.1038/nbt1113-947. Published online November 8, 2013.

The Battle Over Biosimilar Naming

Support Unique Name for Biosimilars	Support Same Name for Biosimilars
Biotechnology Industry Organization (BIO)	Generic Pharmaceutical Association
Amgen	Hospira
Janssen Pharmaceuticals	Novartis
Pfizer	Mylan

The Pink Sheet, February 10, 2014.
www.gabionline.net, January 10, 2014.
Mylan press release, September 23, 2013.
www.fdalawblog.net, October, 31, 2013.

Biosimilar Review and Adoption Requirements

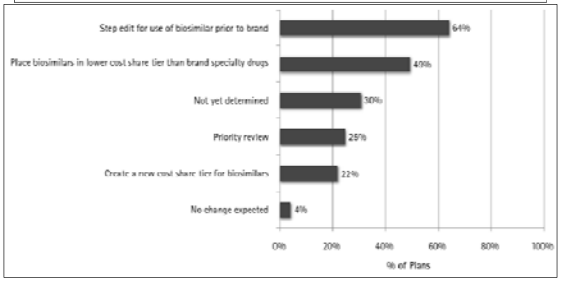
- Unlike generics, initial adoption of biosimilars to health-system formularies will be more complex
  - Pharmacy & Therapeutics Committee involvement
  - Detailed evaluation of safety and efficacy
  - Mechanisms for prescribing, administration, and documentation
- Requires substantial education of all clinicians and patients

Biosimilar Formulary Evaluation and Adoption

- Not a new process: health systems have existing therapeutic standardization/formulary management expertise
- Application of previous experiences with other molecules/drug categories
  - Generic tacrolimus
  - Topical thrombins
  - Erythropoietin-stimulating agents
  - Recombinant human growth hormone
  - Tumor necrosis factor alpha inhibitors
  - Immune globulin (intravenous)

Biosimilars: Anticipated Payer Management Strategies

Survey question: In anticipation of FDA approval of biosimilars/follow-on biologics, what benefit design strategies will your organization use to manage these products?



EMD Serono Specialty Digest 8th edition. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15229.

Formulary Evaluation

The "Tbo" Example

The Tbo-filgrastim Example

- Granix (Teva)
  - Approved in the US via a biologics license application (BLA) or 351(a)
    - Not the 351(k) biosimilars pathway
  - However, approved as a biosimilar in EU (TevaGrastim)
- Approved for only one of the indications for which Neupogen (filgrastim; Amgen) is licensed

Comparative Properties

Indications	Neupogen	Granix
Cancer patients receiving myelosuppressive chemotherapy	Yes	Yes
Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy	Yes	No
Cancer patients receiving bone marrow transplant	Yes	No
Patients undergoing peripheral blood progenitor cell collection and therapy	Yes	No
Patients with severe chronic neutropenia	Yes	No
Pregnancy category	C	C
Data for use in pediatrics	Yes	No

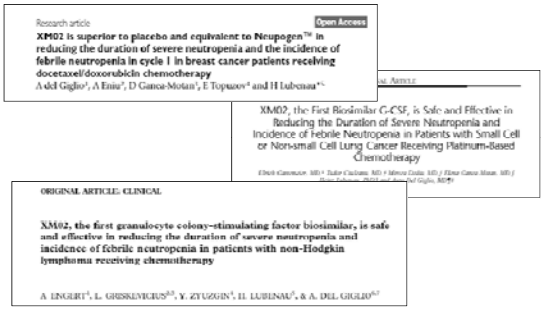
Neupogen (filgrastim) package insert. Thousand Oaks, CA: Amgen; 2012 May; Tbo-filgrastim package insert. North Wales, PA: Teva Pharmaceuticals USA; 2013 May.

Comparative Properties

	Amgen G-CSF	Teva G-CSF
Brand name	Neupogen	Granix
Generic name	Filgrastim	Tbo-filgrastim
Application type	BLA	BLA
Ingredient	r-metHuG-CSF	r-metHuG-CSF
Molecular Weight	18,800 daltons	18,800 daltons
Protein length	175 amino acids	175 amino acids
Expression system	*E. coli*	*E. coli*
Dosages	300 mcg, 480 mcg	300 mcg, 480 mcg
Dosage forms	Vial and syringe (both PF)	Syringe (PF)
Storage conditions	2° to 8°C	2° to 8°C

Neupogen (filgrastim) package insert. Thousand Oaks, CA: Amgen; 2012 May; Tbo-filgrastim package insert. North Wales, PA: Teva Pharmaceuticals USA; 2013 May.

Tbo-filgrastim (XM02): Clinical Trial Data



Research article — Open Access

XM02 is superior to placebo and equivalent to Neupogen™ in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy

A del Giglio[1], A Enio[2], D Ganea-Motan[3], E Topuzov[4] and H Lubenau*[5]

XM02, the First Biosimilar G-CSF, is Safe and Effective in Reducing the Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Patients with Small Cell or Non-small Cell Lung Cancer Receiving Platinum-Based Chemotherapy

ORIGINAL ARTICLE: CLINICAL

XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy

A. ENGERT[1], L. GRISKEVICIUS[2,3], Y. ZYUZGIN[4], H. LUBENAU[5], & A. DEL GIGLIO[6,7]

Del Giglio A, et al. BMC Cancer. 2008;8:332. doi: 10.1186/1471-2407-8-332.
Gatzemeier U, et al. J Thorac Oncol. 2009;4:736-740.
Engert A, et al. Leuk Lymphoma. 2009;50:374-379.

XM02-02 Study Design

Design	Treatment

Double-blind, randomized, single dose, placebo	• Breast cancer patients receiving docetaxel/doxorubicin chemotherapy
	• 5 mcg/kg daily for at least 5 days and a maximum of 14 days in each cycle
	• 348 patients randomized to:
	  • XM02 (n=140)
	  • Non-US Neupogen (n=136)
	  • Placebo (n=72)

*FDA approval based on XM02 and placebo patients only (n = 212).

Del Giglio A, et al. BMC Cancer. 2008;8:332. doi: 10.1186/1471-2407-8-332.

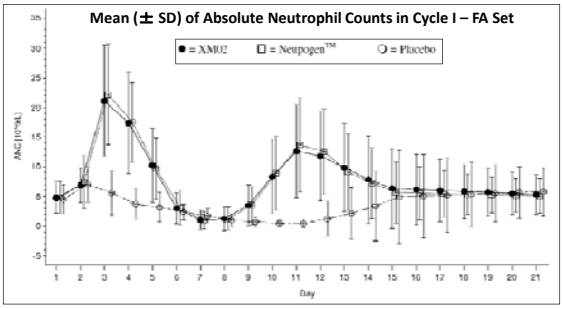
XM02-02: Safety

	XM02	Non-US Neupogen	Placebo
Duration of severe neutropenia, days	1.1	1.1	3.9
Incidence of febrile neutropenia, %	12.1	12.5	36.1

- Similar safety profile between XM02 and non-US Neupogen
- One exception: Incidence of drug-related adverse events across all cycles
  - Non-US Neupogen group: 39.7%
  - XM02 group: 25.7% (P=0.0149)

Del Giglio A, et al. BMC Cancer. 2008;8:332. doi: 10.1186/1471-2407-8-332.

XM02-02: Efficacy



Del Giglio A, et al. BMC Cancer. 2008;8:332. doi: 10.1186/1471-2407-8-332.

Safety and Efficacy Studies: XM02-03 and XM02-04

- Treatment of lung cancer (XM02-03) and non-Hodgkin's lymphoma patients (XM02-04)
- Comparison of XM02 vs. non-US Neupogen; no placebo control
- No statistically significant difference in:
  - Duration of severe neutropenia
  - Incidence of febrile neutropenia
  - Adverse events

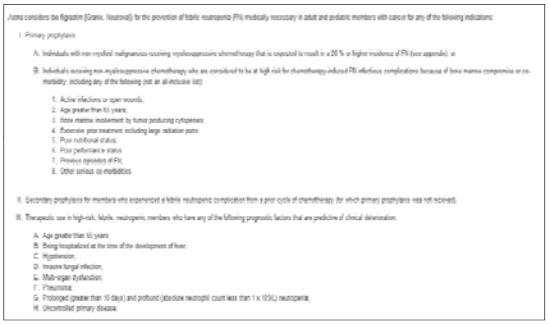
Gatzemeier U, et al. J Thorac Oncol. 2009;4:736-740.
Engert A, et al. Leuk Lymphoma. 2009;50:374-379.

Safety Perspective Regarding Biosimilar G-CSFs

- Review of EMA dossiers for all the European biosimilar G-CSFs (including XM02), FDA dossier for XM02, and journal publications
- Conclusions:
  - All 3 biosimilar agents have similar safety profiles
  - None was statistically higher on safety parameters than what is known about originator filgrastim
  - What is known about filgrastim, in general, regarding safety can be extended to biosimilar filgrastim

Abraham I, et al. Expert Opin Drug Saf. 2013;12:235-246.

Aetna Approval Criteria



Aetna considers the filgrastim (Granix, Neutrexal) for the prevention of febrile neutropenia (FN) medically necessary in adult and pediatric members with cancer for any of the following indications:

I. Primary prophylaxis

A. Individuals with non-myeloid malignancies receiving myelosuppressive chemotherapy that is expected to result in a 20 % or higher incidence of FN (see appendix); or

B. Individuals receiving non-myelosuppressive chemotherapy who are considered to be at high risk for chemotherapy-induced FN/ infectious complications because of bone marrow compromise or co-morbidity; including any of the following (not an all-inclusive list):

1. Active infections or open wounds;
2. Age greater than 65 years;
3. Bone marrow involvement by tumor producing cytopenias;
4. Extensive prior treatment, including large radiation ports;
5. Poor nutritional status;
6. Poor performance status;
7. Previous episodes of FN;
8. Other serious co-morbidities.

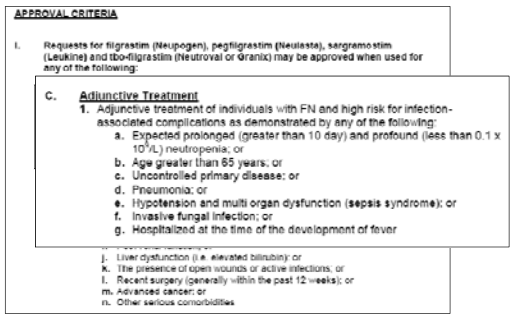
II. Secondary prophylaxis for members who experienced a febrile neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received).

III. Therapeutic use in high-risk, febrile, neutropenic members who have any of the following prognostic factors that are predictive of clinical deterioration:

A. Age greater than 65 years;
B. Being hospitalized at the time of the development of fever;
C. Hypotension;
D. Invasive fungal infection;
E. Multi-organ dysfunction;
F. Pneumonia;
G. Prolonged (greater than 10 days) and profound (absolute neutrophil count less than 1 x 10^9/L) neutropenia;
H. Uncontrolled primary disease.

Aetna Clinical Policy Bulletin: Hematopoietic Colony-Stimulating Factors (CSFs)

Anthem Approval Criteria



APPROVAL CRITERIA

I. **Requests for filgrastim (Neupogen), pegfilgrastim (Neulasta), sargramostim (Leukine) and tbo-filgrastim (Neutroval or Granix) may be approved when used for any of the following:**

C. Adjunctive Treatment
1. Adjunctive treatment of individuals with FN and high risk for infection-associated complications as demonstrated by any of the following:
- **a.** Expected prolonged (greater than 10 day) and profound (less than 0.1 x 10^9/L) neutropenia; or
- **b.** Age greater than 65 years; or
- **c.** Uncontrolled primary disease; or
- **d.** Pneumonia; or
- **e.** Hypotension and multi organ dysfunction (sepsis syndrome); or
- **f.** Invasive fungal infection; or
- **g.** Hospitalized at the time of the development of fever
- **j.** Liver dysfunction (i.e. elevated bilirubin); or
- **k.** The presence of open wounds or active infections; or
- **l.** Recent surgery (generally within the past 12 weeks); or
- **m.** Advanced cancer; or
- **n.** Other serious comorbidities

Available at: https://www.anthem.com/provider/noapplication/f0/s0/t0/pw_b157349.pdf?na=pharminfo.

Caremark Tbo-filgrastim Coverage

- 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

Granix clinical rationale. Available at : http://www.caremark.com/portal/asset/FEP_Rationale_Granix.pdf.

BCBS: Coverage Across Various States

- Illinois
  - GRANIX: Tier 4
  - Neupogen: Tier 5 (prior authorization)
- Michigan
  - GRANIX (preferred brand)
- Montana
  - Neupogen (preferred brand)

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, AMCP dossier, expert organization guidelines
- 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 (Cont'd)

- What modifications need to be made to existing order sets and protocols to include biosimilar products?
- What education will need to be provided to physicians, nurses, and other clinicians to prepare for biosimilar adoption?
- What patient education materials will be needed to support biosimilar use?
- What is the financial value associated with use of a biosimilar?
  - Comparative cost and reimbursement

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

Biosimilars Resources

- **www.fda.gov**
  - Content for consumers, healthcare professionals, and industry
- **National Comprehensive Cancer Network white paper**
  - Zelenetz AD, et al. *J Natl Compr Canc Netw.* 2011;9:S-1-S-22
- **www.biosimcentral.org**
  - ASHP Advantage/Amgen
- **AMCP dossiers**
- **Recent AJHP article**
  - Lucio SD, Stevenson JG, Hoffman JM. *Am J Health-Syst Pharm.* 2013;70:2004-2017

What's Next for Biosimilar Development?

First Official Biosimilar Filing! (Possible March 2015 Approval)

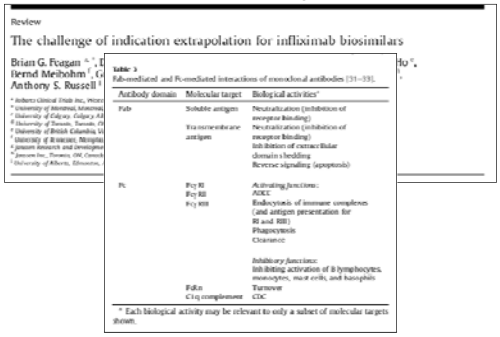
http://www.novartis.com/newsroom/media-releases/en/2014/1835571.shtml.

Celltrion Files Complaint for Declaratory Judgment and Files for Approval

- According to Celltrion:
  - Filed for FDA approval of Remsima (infliximab) on August 8, 2014
  - Expects FDA approval in early 2015
  - Seeks judgment that multiple Remicade patents are invalid and unenforceable

Celltrion files for US FDA approval of Remsima. Celltrion press release, August 11, 2014. Available at: http://www.celltrion.com/en/COMPANY/notice_view.asp?idx=456&code=ennews&intNowPage=1&menu_num=&align_year=all
Celltrion's Complaint for Declaratory Judgment. Available at: http://www.hpm.com/pdf/blog/REMICADE%20-%20Celltrion%20DJ%20Complaint.pdf

Increasing Focus on Indication Extrapolation



Feagan BG, et al. Biologicals. 2014;42:177-183.

Conclusions

- The biosimilar approval mechanism will offer a process for the introduction of clinically similar, less-expensive biologics
- However, biosimilar adoption will be more complex and will require substantial education of pharmacists, physicians, patients, and many other stakeholders
- Healthcare organizations will need to invest greater resources to evaluate and use biosimilars

Questions?

CE Activity Evaluation and Credit Instructions

Biosimilars 101: The Science, Approval Process & Implications for Your Practice

September 11, 2014 - Oakbrook Terrace, Illinois

1. To receive CE credit for this activity, you must complete the post-test and activity evaluation online **no later than Friday, October 10, 2014**.
2. Read the **CPE Monitor** information below.
3. Visit **www.ProCE.com/evaluation**.
4. Click on the **Evaluation** button which is listed with the **Biosimilars 101 - September 11, 2014** CE activity.
5. Enter the **Event Code** for this CE activity: _____ (note: the event code will be announced at the conclusion of the CE activity).
6. Follow the online instructions to complete the post-test and activity evaluation, and to receive CE credit.
7. If you need assistance or have questions, please contact ProCE at 630.540.2848 or via email at **info@proce.com**.

CPE Monitor – for Pharmacists and Pharmacy Technicians

CPE Monitor is a collaborative program between the National Association of Boards of Pharmacy (NABP) and the Accreditation Council for Pharmacy Education (ACPE). This national e-system is designed to store and authenticate data for completed CPE units for both pharmacists and pharmacy technicians. To create a new user account at the ProCE LMS (Learning Management System), you will need to enter your **NABP e-Profile ID** and the month and day of your birthday (in **MMDD** format). For more information, click the hyperlink near the top of the ProCE evaluation web page (i.e., where you see **Pharmacists and Pharmacy Techs: NEW CE POLICY EFFECTIVE MAY 1, 2014**).

Note: It is ProCE policy that CE requirements (i.e. post-test, if applicable for the specific CE activity, and evaluation) be completed within 30 days of the live activity date to ensure an on-time submission to your CPE Monitor account. ProCE uploads completed CE activities to NABP/CPE Monitor twice per month, during the first and third week of each month.

PDF version of the handout is located at: www.ProCE.com/res/pdf/BIO101_ICHP.pdf

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