Role of Biosimilars

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Biosimilars:
What you need to know

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66 year old former firefighter presents with severe back pain, found to have an L1 compression fracture associated with paraspinous mass and spinal cord compression. The mass was biopsied, found to be plasmacytoma, with t(4;14) found by FISH . Additional evaluation reveals monoclonal IgG kappa 7.3 g/dL, kappa free light chain 1740 mg/dL, lambda 1.3 mg/dL, Cre 3.4.

He undergoes radiation to the site of the paraspinous mass with resolution of back pain. He is treated with 4 cycles of bortezomib/cyclophosphamide/dexamethasone, with decline in M protein to 1.4 g/dL and decline in kappa free light chain to 221. He arrives for autologous transplant, and the decision is made to treat with a cycle of VRD-PACE.

Which growth factor should he receive after completion of the chemotherapy drugs?

1. Filgrastim
2. Tbo-filgrastim
3. Filgrastim-sndz
4. Any of the above

Audience Polling Results

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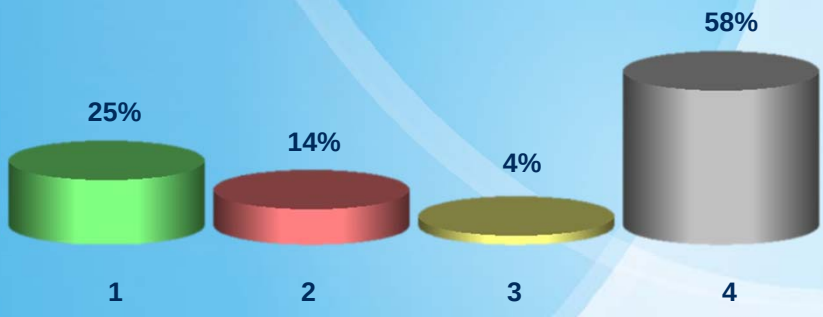
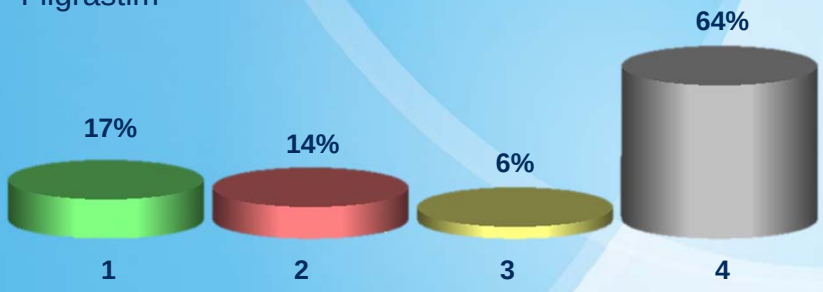


Audience Polling Results

If the regimen were being used for mobilization of peripheral blood stem cells and you were restricted to FDA approved indication, which could be used?

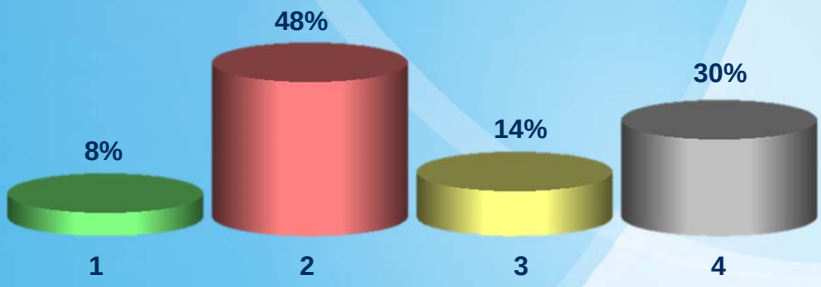
1. Filgrastim or Tbo-filgrastim
2. Filgrastim or Filgrastim-sndz
3. Tbo-filgrastim or Filgrastim-sndz
4. Filgrastim



Audience Polling Results

Tbo-filgrastim was FDA approved through the application process as:

1. A generic
2. A biosimilar
3. A biologic
4. An interchangeable biologic product

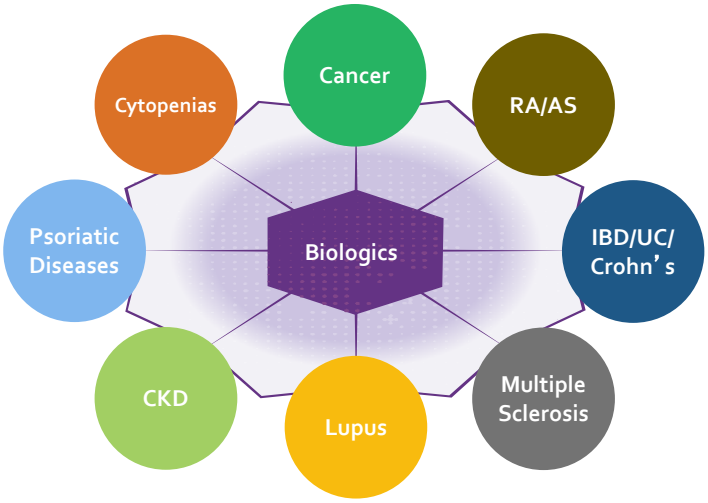


Outline

- Review the role impact of biologics in medicine generally and oncology in particular
- Define "biosimilar" based on the current FDA definition
- Describe potential differences between biosimilars and reference biologics, and between biosimilars and generics
  - Differentiate between biosimilar and generic pharmacotherapies
  - Review the manufacture of biologics and its implications for biosimilarity
  - Understand variation in reference products

Biologics and their role in Oncology

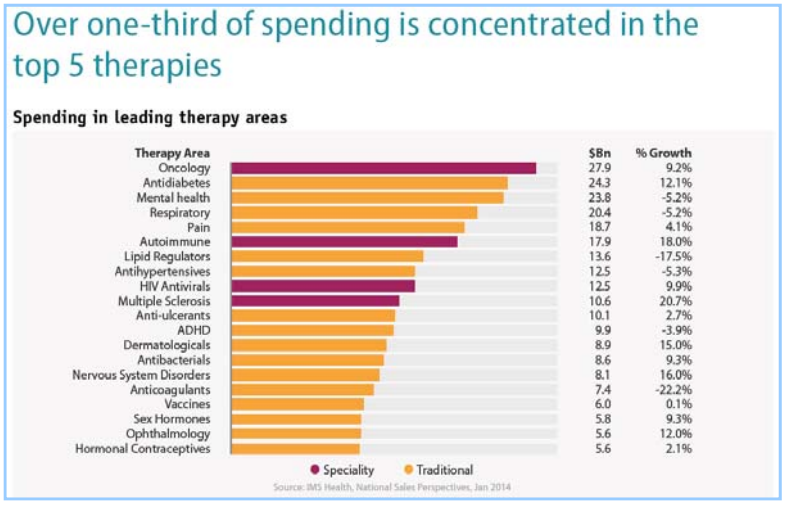
Biologics Have Revolutionized Treatment for Many Serious Conditions Over the Past 20 Years



RA = rheumatoid arthritis; AS = ankylosing spondylitis; IBD = inflammatory bowel disease; UC = ulcerative colitis; CKD = chronic kidney disease.

1. Mellstedt H. *Eur J Cancer Suppl.* 2013;3(suppl II)1-11. 2. Noaiseh G, Moreland L. *Biosimilars.* 2013;3:27-33. 3. Elliott S, et al. *Exp Hematol.* 2008;36:1573-1584. 4. Duffy MJ. *Tumor Biol.* 2013;34:1275-1284.

Spending on Medicines in Leading Therapy Areas: Driven by Biologics



http://www.imshealth.com/portal/site/imshealth. Accessed May 2014.

Top Ten Medicare Drugs 2012: Driven by Biologics and Cancer Drugs

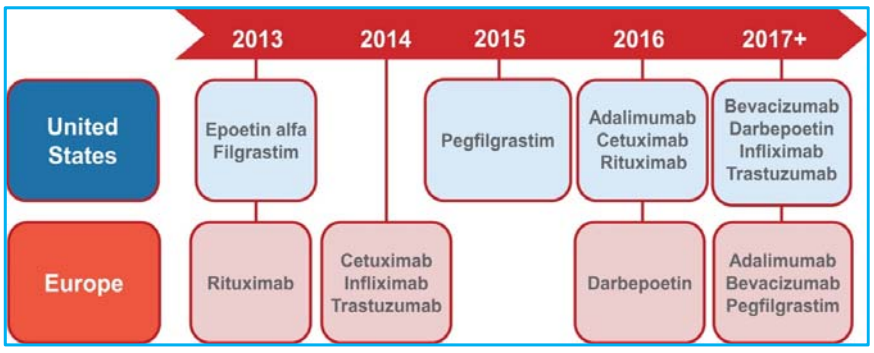
Durg	Oncology	In millions
Ranibizumab		$ 1,220
Rituximab	✓ (principle use)	$ 876
Infliximab injection		$ 704
Pegfilgrastim	✓	$ 642
Bevacizumab	✓	$ 624
Aflibercept	✓ (partial use)	$ 384
Denosumab	✓	$ 347
Oxaliplatin	✓	$ 309
Pemetrexed	✓	$ 292
Bortezomib	✓	$ 278

Biological
Small molecule

Includes carrier claims only (physician office and DME).
Outpatient Prospective Payment System (OPPS) claims are excluded.

Source: Moran Company Analysis of Medicare Physician/Supplier Procedure Summary File

Biologic Product Patents Expiring Before 2020



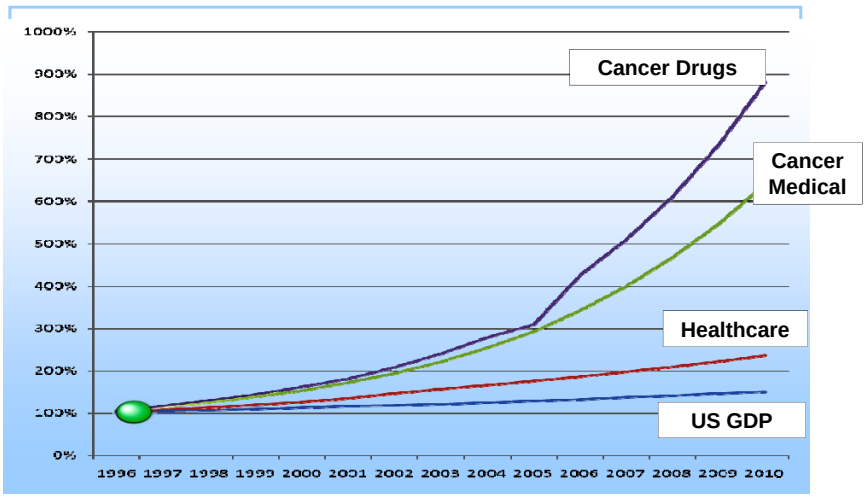
http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020

Biologics in Oncology

- Biologics represent approximately 50% of the pharmaceutical market in oncology
- Biologics play a critical role in clinical care:
  - Supportive care
    - Myeloid growth factors
    - Erythropoietin stimulating agents
  - Active therapy
    - Monoclonal antibodies
    - Antibody drug conjugates
    - Interferons

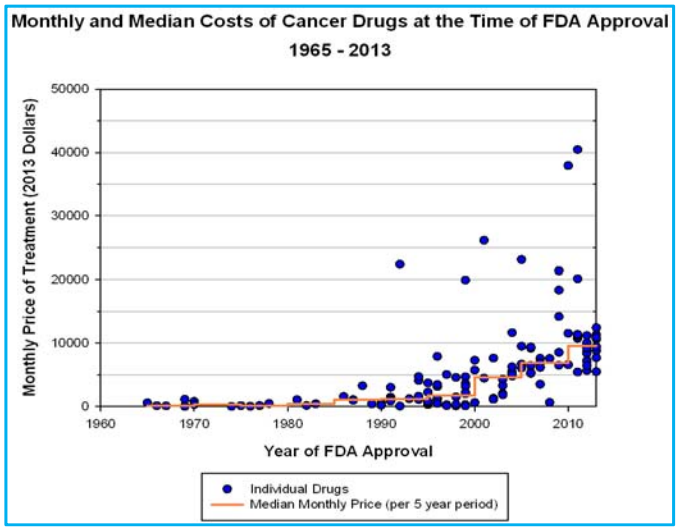
Nowicki M. *Kidney Blood Press Res* 2007;30:267-272

Cancer Care Costs Rising Faster Than Overall Healthcare Costs



Source: Blue Cross Blue Shield Association

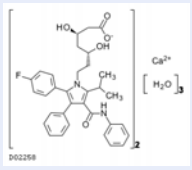
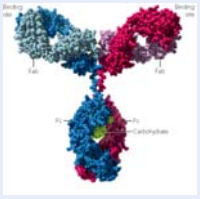
Rising Cost of Cancer Drugs at the Time of FDA Approval



Source: Memorial Sloan-Kettering Cancer Center. Center for Health Policy and Outcomes. http://www.mskcc.org/research/health-policy-outcomes/cost-drugs. Accessed May 2014.

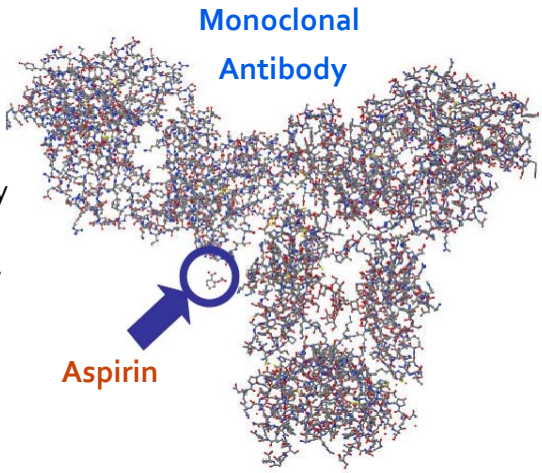
Biologics and Small Molecules

Pharmaceuticals vs. Biologics

	Pharmaceuticals	Biologics
Size (MW)	Small (MW < 1000)	Large (MW > 10,000)
Source	Chemical synthesis	Culture of living cells
Form	Generally oral solids	Often injected or infused
Dispensed from	Retail pharmacies	Hospital or physician offices
Example	Atorvastatin (lipid lowering agent)  MW = 558.64	Trastuzumab (breast cancer)  MW = 185,000

Small Molecule vs. Biologic Drugs

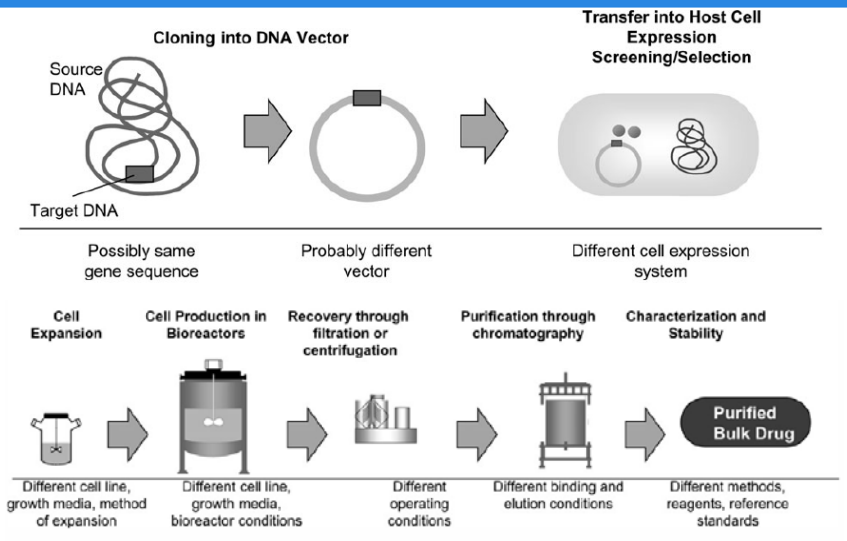
- Biological products are generally produced using a living system or organism.
- Biological products may be manufactured through biotechnology, derived from natural sources, or produced synthetically.



Biosimilar Guidance Webinar February 15, 2012

Biologics: Manufacturing and Drift

Manufacturing biosimilars



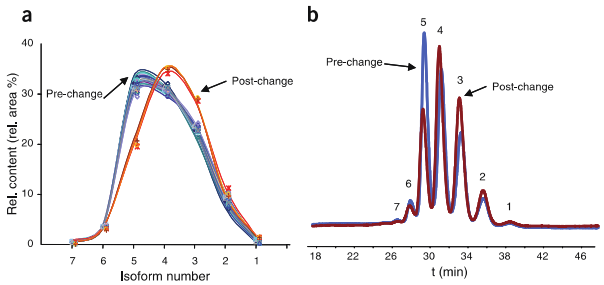
Mellstedt H, et al. *Ann Oncol* 2008;19:411-419.

ICH Q5E: Regulatory Guidance for Changes in Manufacturing of Biologics

- Over the life of a biopharmaceutical changes are invariable introduced into manufacturing
  - Improve yield
  - Changes in sourcing of components
  - Changes in production scale
- Manufacturing changes are governed by ICH Q5E regulation recognized by both the FDA and EMA.
  - Guidance aims to minimize the drift inherent in a reference product
  - The regulations provide guidance to conduct a comprehensive assessment on the impact to the product
- Key requirements include:
  - Analytics should be selected and optimized to maximize the likelihood of detecting potential differences
  - Apply more than one analytical procedure to evaluate the same quality to maximize the detection of potential differences
  - Evaluate critical control points in the manufacturing process that affect product characteristics

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128076.pdf

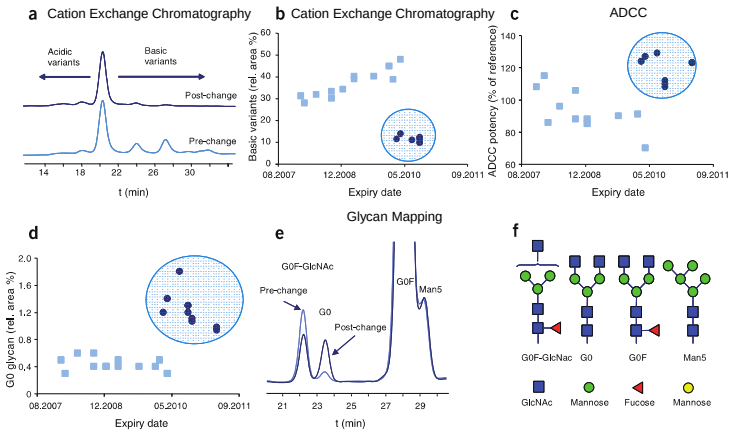
What is acceptable variation? Lot to lot variation of innovator products: darbepoietin



- Comparison of lots of darbepoietin by capillary zone electrophoresis pre- and post- EMA approved process change base on an extensive comparability exercise
  a. Relative isoform content
  b. Representative electropherograms

Schiestl et al. Nature Biotechnology 2011:29 310-12

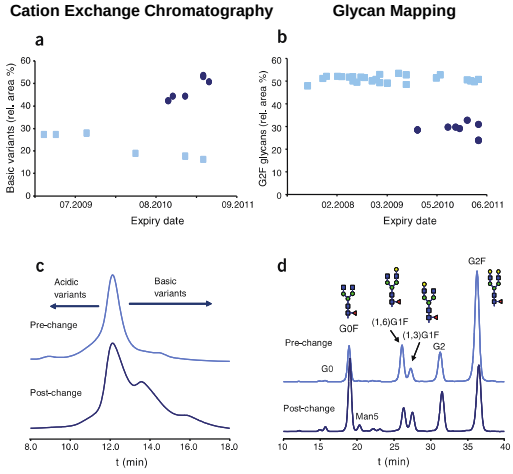
What is acceptable variation? Lot to lot variation of innovator products: rituximab



- Significant change in ADCC likely related to the altered glycan map for unfucosylated Go glycans

Schiestl et al. Nature Biotechnology 2011:29 310-12

What is acceptable variation? Lot to lot variation of innovator products: etanercept



- Significant change in glycans and basic variants seen in batches over time

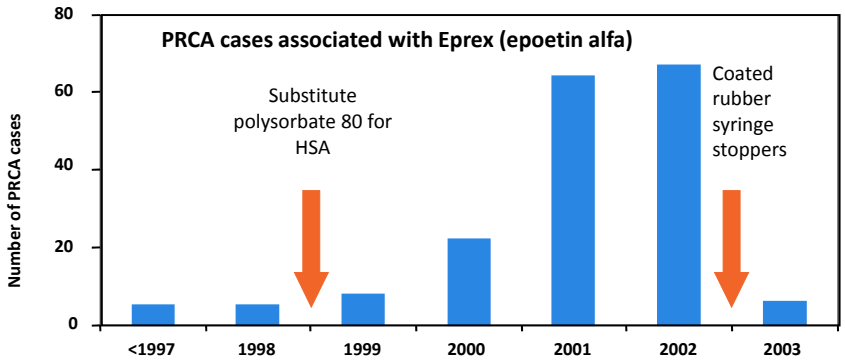
Schiestl et al. Nature Biotechnology 2011:29 310-12

Immunogenicity Concerns

- All biologics confer a risk of immunogenicity
  - Related to patient, disease, and product factors
  - Consequences include neutralizing antibodies or cytokine release
  - Scientific tools for detecting immunogenicity exist, but they are not precise
- Changes to the structure of the protein increase variation in immunogenicity
  - Lot-to-lot and between manufacturers
  - Variations in manufacturing must be minimized
- Clinical consequences:
  - Loss or diminished efficacy or safety
  - Case reports of rare but serious adverse reactions have been reported

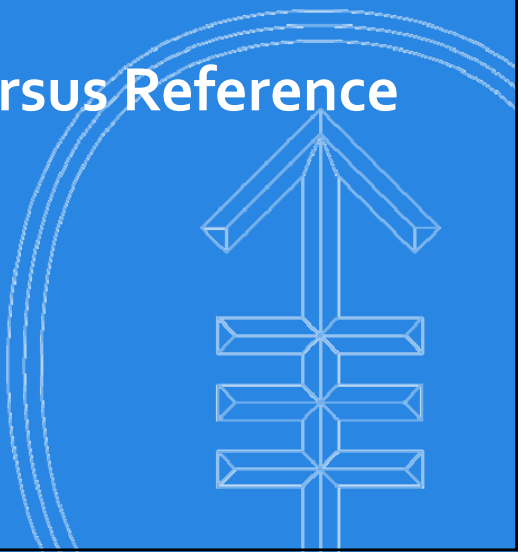
U.S. FDA. Immunogenicity Assessment for Therapeutic Protein Products. August 2014. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

One Change in the Formulation of an Established Biopharmaceutical Led to Unpredicted Immunogenicity



Boven K, et al. *Nephrol Dial Transplant*. 2005;20 Suppl 3:iii33-40.
Locatelli F, et al. *Perit Dial Int*. 2007;27(S2):S303-S307.

Biosimilar versus Reference Product



Regulatory Definitions of a Biosimilar

- US Food and Drug Administration (FDA)
  - A biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in inactive components, and for which there are no clinically meaningful differences in safety, purity, or potency of the product.
- European Medicines Agency (EMA)
  - …structurally highly similar versions of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise.

FDA Draft Guidance. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
Weise M, et al. *Nat Biotechnol*. 2011; 29:690-3.

Copying the Reference Product: Small Molecule Drugs versus Biologics

Small molecules (generics)

- Have a precisely defined structure (or structures, e.g. racemic mixtures)
- Generally produced by chemical synthesis
- Structure can be interrogated with high precision
- Thus, generic forms demonstrating chemical identity can be validated with pre-clinical analytic methods

Biologics (biosimilars)

- Have inherent variability based on a complex manufacturing process
- Biosimilar drugs ***will not be identical*** to the reference product
- Therefore, preclinical ***and*** clinical (i.e., safety/efficacy) studies are essential to demonstrate comparability

Copying the Reference: Different Paths

	Reference	Biosimilar	Interchangeable Biosimilar	Full BLA Copy
Description	First-to market biologic molecule	"Highly similar" to reference product; approved via Biosimilars pathway	A biosimilar deemed that can be substituted for the reference without permission from prescriber*	It is like a biosimilar but it is approved via a full BLA data package
Depth of data submitted to the FDA	"Standard" data package	Abbreviated data package	Abbreviated data package, more information on sequencing and safety	"Standard" data package; efficacy and safety on its own merit
Compared to reference?	N/A	Yes	Yes	Not necessarily
Current examples in USA	N/A	Filgrastim-sndz	None	Tbo-filgrastim

*Subject to pharmacy practice regulations which vary state to state

Biosimilars in Oncology: Competing Interests

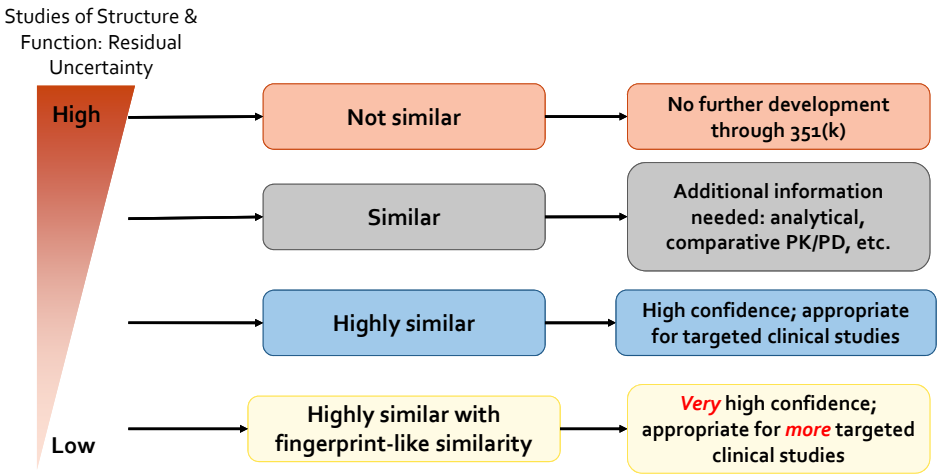
CONS

- Preservation of innovation
- Well established safety and efficacy
- Availability of data in a wide variety of indications

PROS

- Access to medications
- Affordability
- Extrapolate clinical utility from "key" efficacy data

Preclinical Assessment: 4 Levels of Analytical Characterization



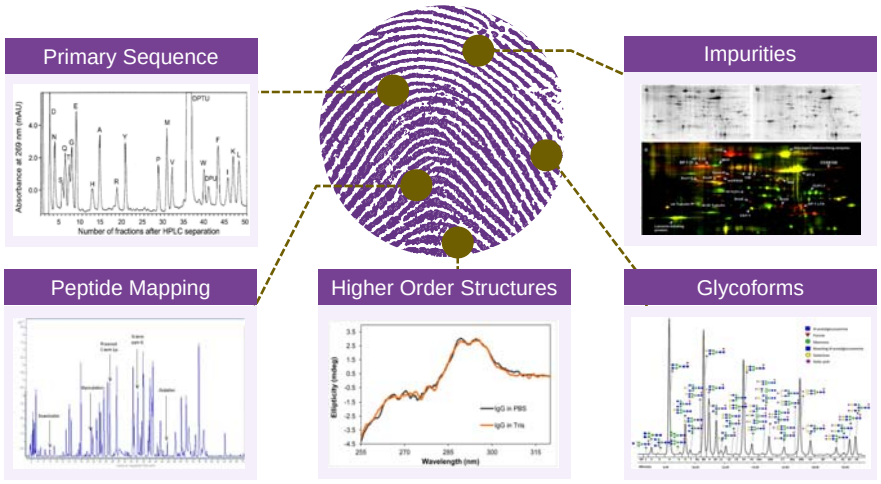
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf. Accessed July 2014.

Preclinical Assessment: Structure and Function

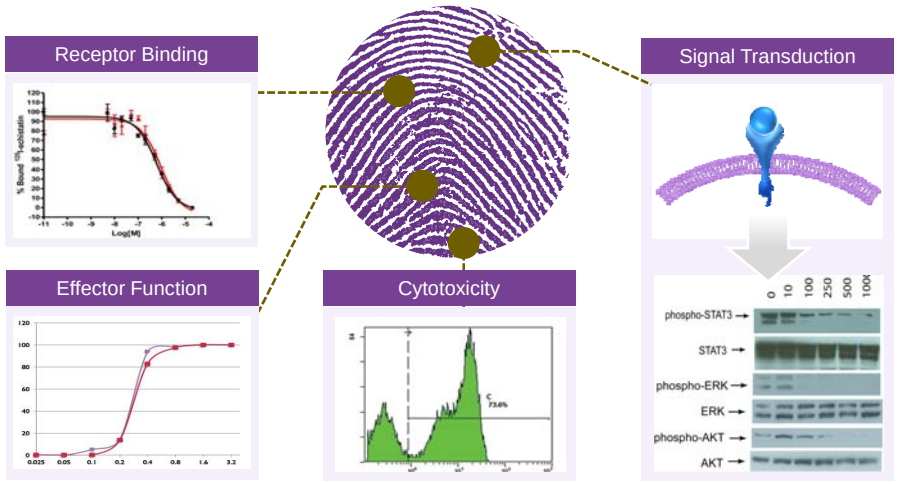
- Serve as the "foundation" of biosimilar development
- Useful in determining what future studies are necessary
- Structure
  - Amino acid sequence, higher-order structures, glycosylation, pegylation, etc.
  - Analyze lot-to-lot variability
- Function
  - Evaluate pharmacologic activity via *in vitro* and/or *in vivo* experiments
  - Functional evaluation that compares candidate to reference

FDA Draft Guidance. Available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Establishing Fingerprint-Like Similarity: Physiochemical Properties



Establishing Fingerprint-Like Similarity: Functional Assay



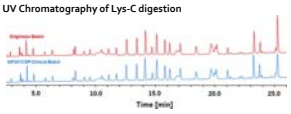
Analytics for characterization of biosimilar GP2013

Category	Quality attribute	Methods
Physicochemical characterization		
Primary structure	Amino acid sequence	Red. RP-HPLC–ESI–MS peptide mapping, intact mass of whole mAB, HC and LC by RP-HPLC–ESI–MS, Red. RP-HPLC-UV peptide mapping
Higher order structure	Disulfide bridging	Non-red. RP-HPLC–ESI–MS peptide mapping
	Free thiols	Ellman's assay
	Secondary and tertiary structure	CD, FTIR, HDX-MS, X-ray
	Thermodynamic stability	DSC
General charge heterogeneity and amino acid modifications	oK variant, acidic variants, basic variant, Gln-variant, Lys-variant, amidated proline	CEX digested/undigested
	Glycation	Boronate affinity
	Oxidation/deamidation/C-terminal variants	RP-HPLC-UV/MS peptide mapping
Glycosylation	Galactosylation, sialylation, mannosylation, afucosylation, bisecting GlcNAc, NGNA, α-galactose, qualitative glycosylation pattern	NP-HPLC-FL
Size heterogeneity	Monomer, low-molecular weight (LMW) and high molecular weight (HMW) variants (aggregates)	SEC, AF4
	Heavy chain (HC), light chain (LC), aglycosylated HC, clipped variants	Red. CE-SDS
	Monomer, LMW (e.g., half antibodies (HL) and HHL variant) and HMW variants	Non-red. CE-SDS
	Subvisible particles	Light obscuration (PhEur, ≥10 µm and >25 µm)
	Visible particles	Visual inspection (PhEur)
Functional characterization		
Target and receptor binding	FcRn binding	SPR
	FcγR binding (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa(F158), FcγRIIIa(V158), FcγRIIIb)	SPR
Bioactivity	CD20 target binding	Cell-based binding assay
	CDC potency	Cell-based CDC assay
	ADCC potency	Cell-based ADDC assay
	Apoptosis	Cell-based apoptosis assay

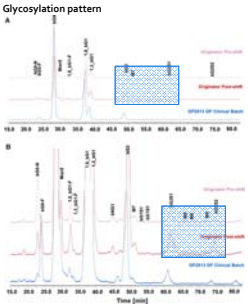
Visser et al. BioDrugs 2013, 27:495

Characterization of Biosimilar Rituximab GP2013 and Originator Rituximab

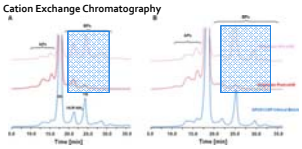
UV Chromatography of Lys-C digestion



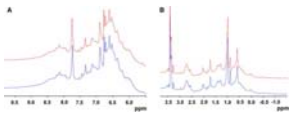
Glycosylation pattern



Cation Exchange Chromatography

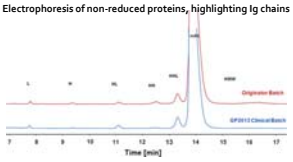


1D ^{1}H NMR

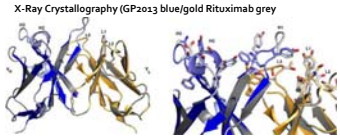


Originator drift complicates biosimilar development

Electrophoresis of non-reduced proteins, highlighting Ig chains



X-Ray Crystallography (GP2013 blue/gold Rituximab grey



Functional Assays

	Target binding	ADCC	CDC	Apoptosis
GP2013 (%)	97–108	86–105	99–111	88–97
Reference range (%)	96–110	70–132	95–127	88–102
p (TOST)	<0.0001	<0.0001	<0.0001	<0.0001

Visser et al. BioDrugs 2013, 27:495

Demonstrating Biosimilarity: General Principles

- The clinical efficacy and safety of the biologic molecule has already been demonstrated (ie, by the innovator)
- The biosimilar sponsor only requires evidence that the candidate biosimilar is not significantly different from the reference product
  - Goal is not to replicate unnecessary clinical trials
  - Smaller-scale direct comparisons and extrapolation
- When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy

FDA Draft Guidance. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291128.pdf. Accessed May 2014.

Biosimilarity: Preclinical v Clinical

- Biosimilarity is evaluated in two steps:
  - Highly similar pre-clinically
  - No clinically meaningful differences
- Highly similar molecules in pre-clinical evaluation:
  - Have a 'highly similar' protein structure and post-translational modifications
  - Biosimilarity supported by comprehensive package of functional assays and other pharmacology
  - Comparative toxicology assessment indicates no difference or unexpected toxicity

Identical amino acid sequence is a prerequisite for a mAb; differences in conformation and post-translational modifications may affect functional assays, clinical efficacy and immunogenicity

Animal Toxicity Studies

- Useful when there are unresolved questions about the safety of the candidate biosimilar based on studies of structure/function
- Utilize comparative animal toxicology
- "The scope and extent of any animal toxicity studies will depend on the body of information available on the reference product, the proposed product, and the extent of known similarities or differences between the two."

FDA Draft Guidance. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291128.pdf. Accessed May 2014.

Moving a biosimilar into the clinic: Equivalent pharmacokinetics is the first critical hurdle

- Molecules that have been demonstrated to be 'highly similar' in preclinical evaluation need to be evaluated in the clinic
- Showing of biosimilar PK, within pre-defined equivalence margins, should be the first clinical 'go/no go' step for biosimilars
- The biosimilar concept implies the same dose, strength and route of administration
- PK is a critical measure in assessing bioavailability of 'highly similar' structure

Product class-specific PK equivalence margins will be important to extrapolation decisions that occur later in the development program

Human Pharmacokinetics and Pharmacodynamics

- "Fundamental" for demonstrating biosimilarity
- Both PK and PD will be necessary
  - PK: patient population considerations
  - PD should study measures that:
    - are relevant to clinical outcomes
    - can be quickly assessed with precision
    - have the sensitivity to detect clinically meaningful difference
- Ideally correlate exposure to clinical outcomes
- Utilize crossover and parallel designs

FDA Draft Guidance. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291128.pdf. Accessed May 2014.

Clinical Studies: FDA

- Clinical Immunogenicity
  - Goal is to evaluate potential differences in incidence and severity of immune responses using endpoints such as antibody formation (binding, neutralizing), cytokine levels, etc.
  - FDA recommends a comparative parallel study
- Efficacy & Safety: specific clinical trial design will depend on what residual questions remain
  - Clinical studies should be designed to demonstrate neither decreased nor increased activity
  - Use clinically relevant and sensitive endpoints in the right population
  - The extent of trials will differ between 'highly similar' and 'fingerprint similarity

Schellekens H. *NDT Plus*. 2009; 2(Suppl 1):i27-i36.

Unlike innovator development programs, biosimilar programs do not prove outcomes

- Biosimilars are not an exercise in demonstrating clinically meaningful benefit; that has been shown by the reference product
- However the biosimilar product must be significantly similar to the reference product to 'permit some degree of reliance on the findings of safety and effectiveness for the approved product'[1]

1. Testimony by Janet Woodcock, M.D., before the Subcommittee on Health of the Committee on Energy and Commerce, House of Representatives (Serial No 110-40), 28 (May 2, 2007)

Conclusions

- Biologic drugs have become the centerpiece of clinical care in oncology
- Biologics are complex drugs that cannot be made "generic"
- Biosimilars are inherently different drugs but may not be clinically meaningfully different
- Biosimilarity is measured on an extensive pre-clinical analytical exercise
  - The more 'finger-print' like identity, the fewer clinical studies will be necessary
- Clinical evaluation
  - Includes PK and PD at a minimum
  - The design of comparability trials is base on non-inferiority
  - The extent of the clinical trials is based on the residual uncertainty about biosimilarity

Clinician Perspective

- Physicians skeptical of unfamiliar therapies, concerns include
  - Efficacy
  - Safety
  - Impact on reimbursement
- Strong clinical data will be important for acceptance
- Physicians concerned that use will be forced upon them
- Perception will be that cost is the main issue
- Education will accelerate uptake after approval
  - Unbiased experts, focused on clinical data
  - National meetings and online education

Industry Perspective

- Biosimilar development is complex and costly
  - Biosimilar takes 8-10 years and $100-200 million
- Unlike generics, biosimilars will likely be priced at a 20% to 40% discount compared to the reference biologics
  - Given the costs of biologics, this may represent a substantial saving
- Several biosimilars are under FDA review, we should understand the landscape in anticipation
  - Filgrastim-sndz was recently approved

Federal Trade Commission 2009. Emerging Health Care Issues: Follow-on Biologic Drug Competition. Federal Trade Commission Report June 2009 http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf. Accessed May 2014.

Implications for NCCN Panels

- Biosimilars represent a functional and equivalent molecule to the originator product
  - When a biosimilar is available it should be added an alternative to the originator
  - For example in the NHL Guidelines
    - R-CHOP is approved for DLBCL
    - Biosimilar-Rituximab + CHOP would be appropriate to add as an alternative
    - It would NOT be appropriate to change the anti-CD20 monoclonal + CHOP because ofatumumab and obinutuzumab (approved anti-CD20 antibodies) are NOT biosimilar to rituximab

NCCN Guidelines Meet the Biosimilar Myeloid Growth Factors

Pamela S. Becker, MD, PhD

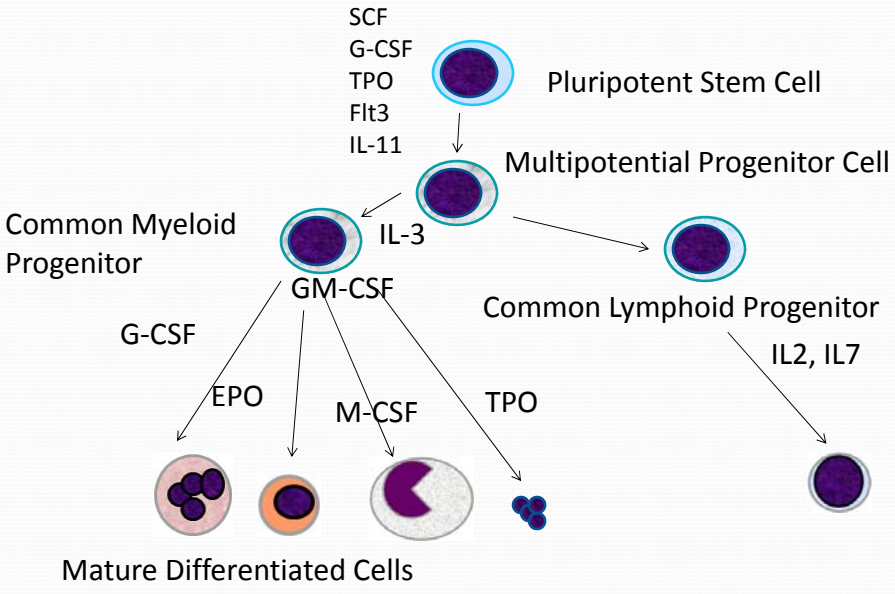
Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center

Disclosure Information

Pamela Becker, MD, PhD

- I **WILL** include discussion of investigational or off-label use of a product in my presentation.

Hematopoietic Stem Cells



FDA Approved Recombinant Growth Factors and Growth Factor Mimetics

Erythropoietin (3 N-linked oligosaccharide chains)
Darbepoetin (5 N-linked oligosaccharide chains)
Filgrastim (G-CSF)
Pegfilgrastim
Sargramostim (GM-CSF)
Oprelvekin (Interleukin 11)
Romiplostim
Eltrombopag

NEW: Similar and Biosimilar Growth Factors

What are Biosimilars?

"Biosimilar biologics: Never identical but close enough"

- Abi-Raad and Smith. TRANSFUSION 2015;55:229–231

Legal Pathway to Development of Biosimilars

- Biologics Price Competition and Innovation (BPCI) Act of 2009
- Patient Protection and Affordable Care Act of 2010

FDA Approval Process

1. *Biologics*-Biologics License Application
   – Demonstrate safety and efficacy

OR

2. *Biosimilars*-Biosimilar Biologics License Application
   – Must demonstrate that it is highly similar
   – For interchangeable biosimilar, need more data

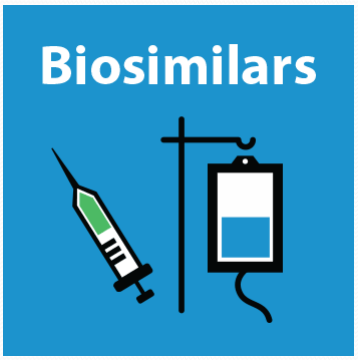
What are biosimilars and interchangeable biological products?

- *Biosimilars* are a type of biological product that are licensed (approved) by FDA because they are highly similar to an already FDA-approved biological product, known as the biological reference product (reference product), and have been shown to have no clinically meaningful differences from the reference product.

- An *interchangeable biological product*, in addition to meeting the biosimilarity standard, is expected to produce the same clinical result as the reference product in any given patient

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm

From FDA website



http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm

Filgrastim

- Cloned in 1986
- Recombinant in E. coli (bacteria)
- Non-glycosylated (Natural G-CSF is O-glycosylated at the Thr-133 position)
- N-terminal methionine
- Identical biological activity as natural G-CSF[1]
- FDA Approved in 1991
- Patent expired in Europe in 2006, in US in 2013

[1] Souza LM et al. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. Science 1986;232:61-5.

G-CSF: Indications

- **Filgrastim**
  - ***Patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia***
  - ***Patients with cancer undergoing bone marrow transplantation (nonmyeloid malignancies undergoing myeloablative chemotherapy)***
  - ***Patients undergoing peripheral blood progenitor cell collection and therapy***
  - ***Patients with severe chronic neutropenia***
  - ***Patients with AML receiving induction or consolidation chemotherapy***
  - ***Patients with HIV infection***
- **Pegfilgrastim**
  - ***Patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia***
  - ***Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).***

From the Prescribing Information for filgrastim and pegfilgrastim

Filgrastim and Pegfilgrastim: Side Effects

- Bone pain
- Allergic reactions
- Acute respiratory distress syndrome (ARDS)
- Alveolar hemorrhage/hemoptysis
- Splenic rupture

- Fatal sickle cell crises
- Sweet's syndrome
- Cutaneous vasculitis
- Incidence of MDS/AML (Lyman et al JCO 2010) RR death 0.897 (3.4% absolute) but HR 1.92 for MDS/AML (0.4% absolute)

From the Prescribing Information for filgrastim and pegfilgrastim

G-CSF Products

- Filgrastim (reference product) – E. Coli, non-glycosylated
- Tbo-filgrastim – E Coli, non-glycosylated, approved in Europe as a biosimilar in 2008, approved in US as tbo-filgrastim (not a biosimilar) in 2012
- Filgrastim-sndz – E coli, non-glycosylated identical to filgrastim except glutamate buffer instead of acetate, approved as a biosimilar in Europe (2008) then in US as filgrastim-sndz
- Lenograstim – glycosylated, produced in Chinese hamster ovary (CHO) cells, approved overseas
- Europe Medicines Agency has also approved in 2008 and 2010 two additional biosimilar filgrastim

The Name: Tbo-filgrastim

- Prefix "tbo-" stands for toluidine blue O[1]
- Nonglycosylated recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF)
- FDA Approved Aug 2012 not as a biosimilar but as a biologic, so narrower indication

[1]FDA notes that "tbo" stands for the medical abbreviation, "toluidine blue O.2" However, it is not thought that this abbreviation would cause confusion in this context or conflict with the proper name, "tbo-filgrastim" and therefore FDA has no objection to its possible selection. The proposed prefix "tbo-" is acceptable based on the criteria outlined in the July 17, 2012 communication…
From CENTER FOR DRUG EVALUATION AND RESEARCH PROPRIETARY NAME REVIEW DHHS Memorandum August 2, 2012
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf

Product Composition: Tbo-filgrastim vs. Filgrastim

Tbo-filgrastim

- Glacial acetic acid 0.3 mg
- Sorbitol 25 mg
- Polysorbate 80 0.0275
- Sodium hydroxide qs to pH 4.2
- Water for injection

Filgrastim

- Sodium acetate buffer pH 4.0
- 5% Sorbitol
- 0.004% Polysorbate 80

Studies supporting Tbo-filgrastim

- 2 PK and PD studies in healthy controls[1]
- Pooled clinical data from 3 studies with a placebo or filgrastim [2]
  - Breast cancer - 348 patients
    - Placebo 1st cycle then randomized 2:2:1 Tbo to filgrastim to placebo
    - Reduction in days of severe neutropenia: 3.8 to 1.1, p<0.0001
    - No difference in efficacy
  - Lung cancer - 237 patients
    - Tbo-filgrastim 1st cycle then randomized Tbo- vs. filgrastim
    - No difference in efficacy
  - Non-Hodgkin's lymphoma-92 patients
    - Randomized 2:1 Tbo-filgrastim vs. filgrastim
    - No difference in efficacy
  - The most common drug-related AEs were bone pain (7.1%), myalgia (4.0%), and asthenia (4.4%)

1. ODAC Advisory Committee Briefing Documents 2013 2. Pettengell R. et al Supportive Care Cancer Jan 2016 [Epub ahead of print]

Tbo-filgrastim: Indications and Dosing

INDICATIONS AND USAGE----------

- Tbo-filgrastim is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

DOSAGE AND ADMINISTRATION----------

- Recommended dose: 5 mcg/kg/day subcutaneous injection.
- Administer the 1st dose ≥24 hours following myelosuppressive chemotherapy. Do not administer within 24 hours prior to chemotherapy.

Prescribing information. http://tinyurl.com/http-tbo-info-com

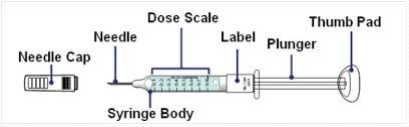
EMA Approval of Tbo-filgrastim as Biosimilar

The biosimilar G-CSF XM02 (Tbo-filgrastim in US) was fully approved in 2008 by the European Medicines Agency (EMA) for all indications of the reference filgrastim:

- Chemotherapy-induced neutropenia
- Mobilization of stem cells in the autologous and allogeneic settings
- Agranulocytosis
- Neutropenia due to infection with HIV

FDA Approves Tbo-filgrastim Injection for Self-Administration

- December 23, 2014



Prescribing information. http://tinyurl.com/http-tbo-info-com

Presenting the First US Biosimilar Filgrastim-sndz 5 years from BPCI Act…

The New York Times

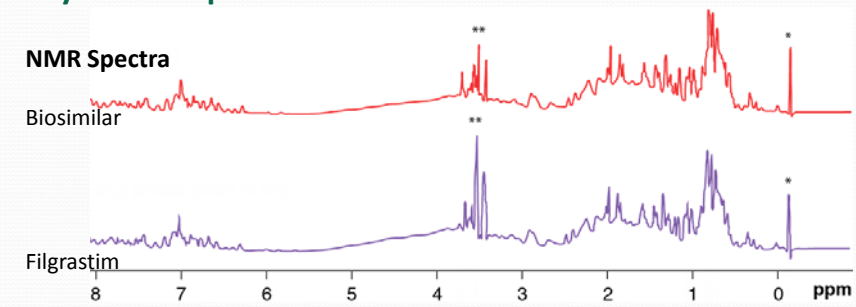
HEALTH

F.D.A. Approves ?#@&%!, Its First Biosimilar Drug*

By SABRINA TAVERNISE and ANDREW POLLACK MARCH 6, 2015

- Approved as a biosimilar
- Interchangeable for all indications with filgrastim

FDA Approval of Biosimilar Filgrastim
Physical comparison



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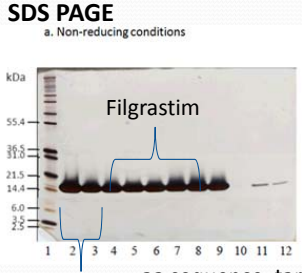
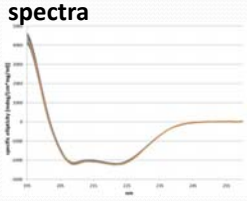
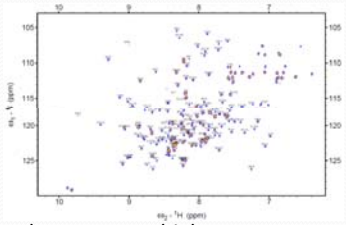


Circular dichroism spectra

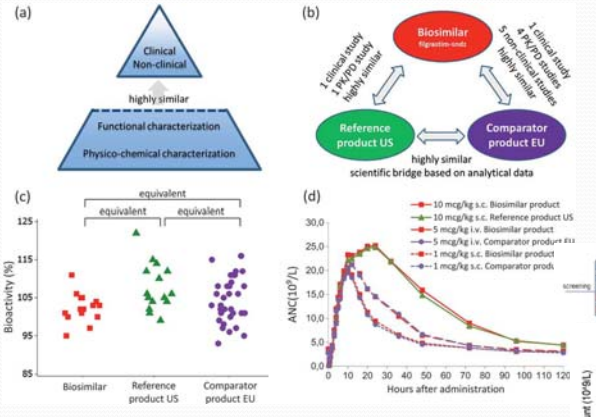


2D NMR



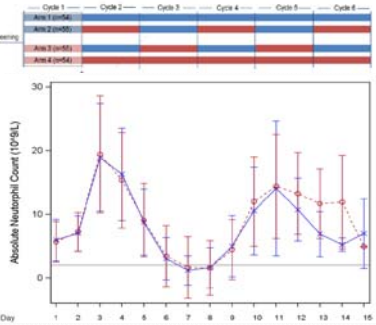
aa sequence, target binding, potency, higher order structure, high MW aggregate
-from FDA ODAC Meeting materials 1/7/2015

FDA Approval of Biosimilar Filgrastim
Clinical comparison



Clinical Study Comparing Biosimilar Filgrastim to Filgrastim

Biosimilar
Filgrastim



Published in: J. Holzmann; S. Balser; J. Windisch; *Expert Opinion on Biological Therapy* **2016,** 16, 137-142.
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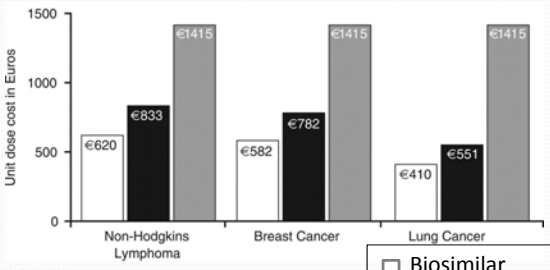
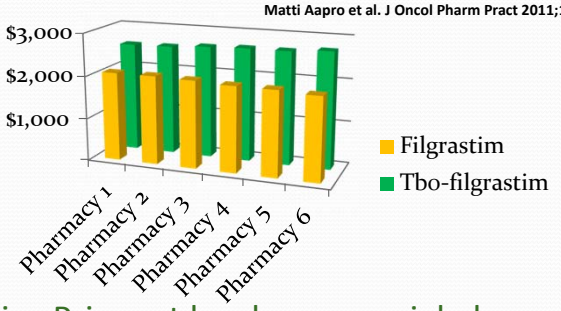
from FDA ODAC Meeting materials 1/7/2015

Relative Cost of Treatment with Different Growth Factors for 3 Cancers

JOURNAL OF ONCOLOGY PHARMACY PRACTICE



Matti Aapro et al. J Oncol Pharm Pract 2011;18:171-179



Relative Prices at local commercial pharmacies

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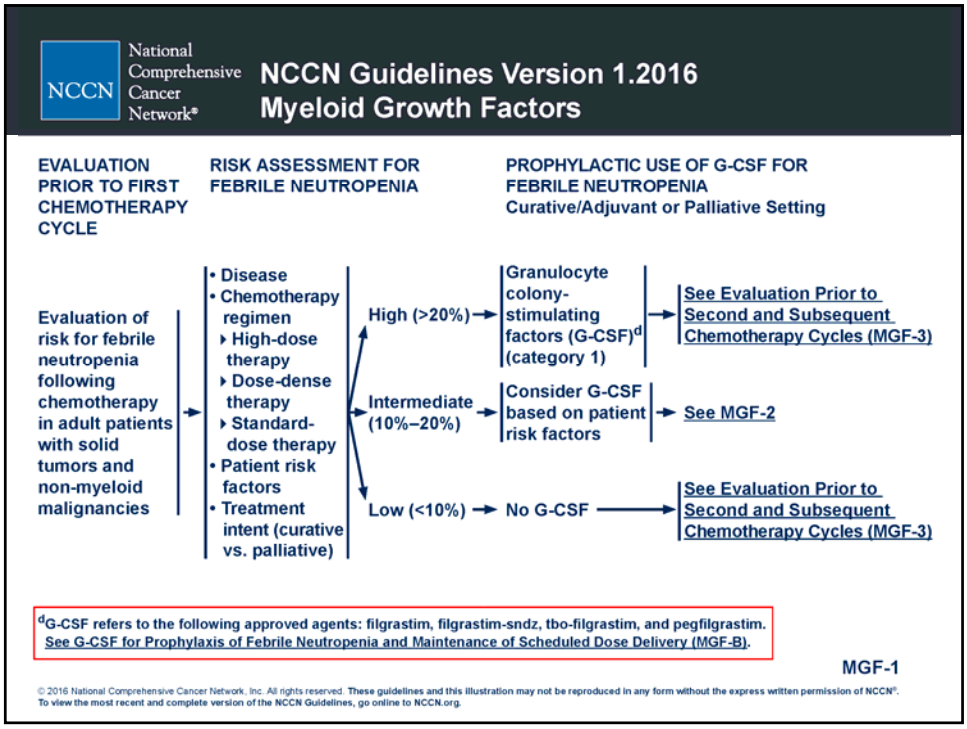
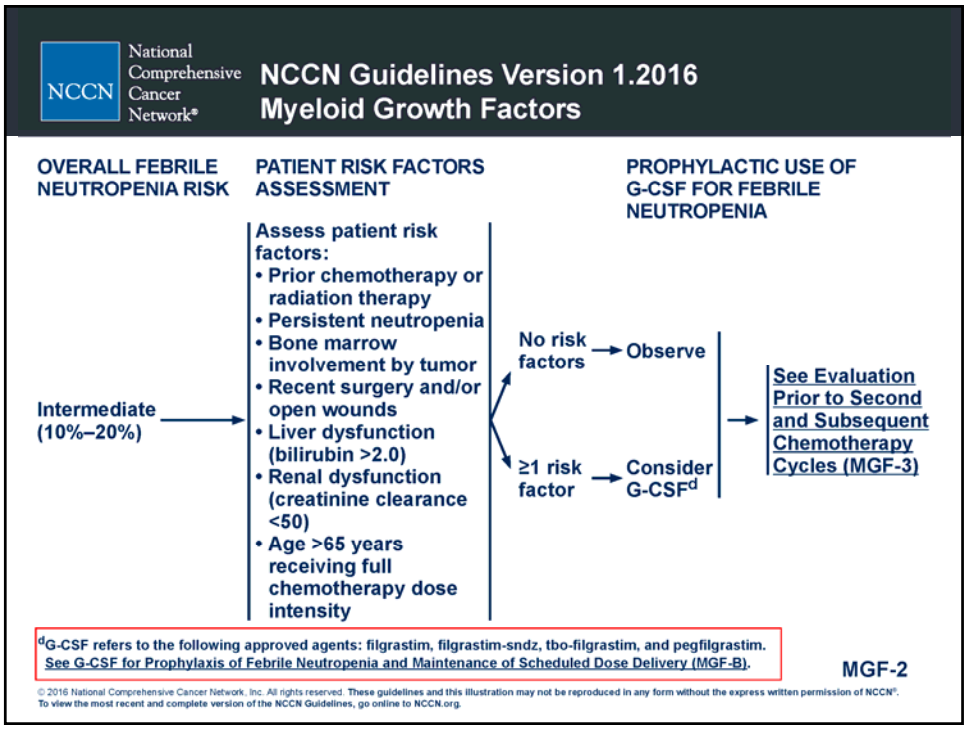
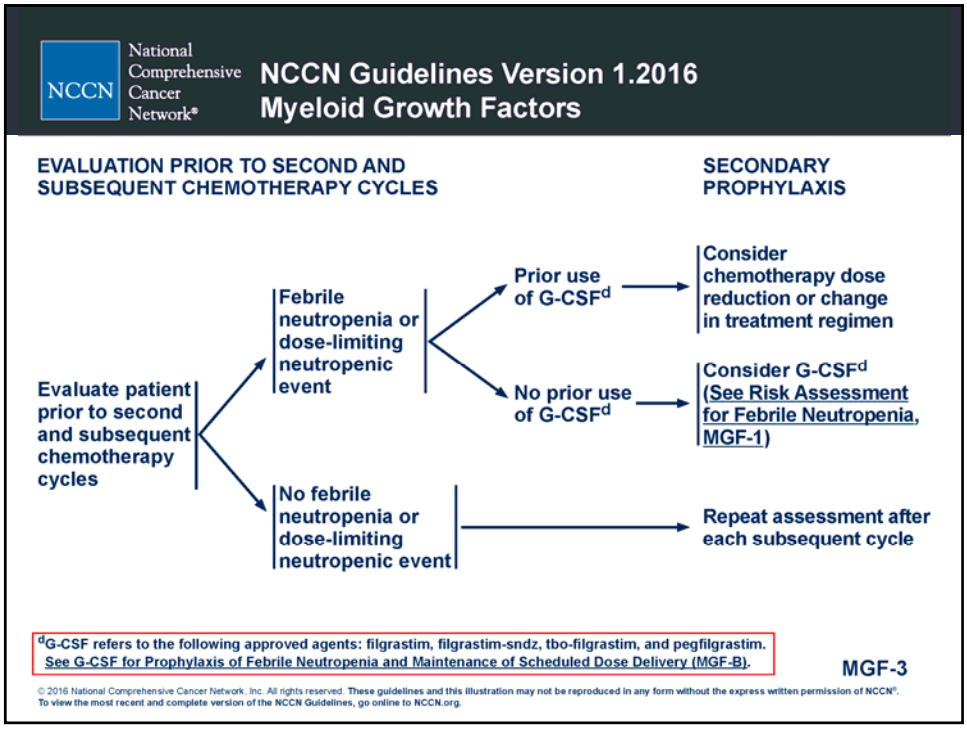
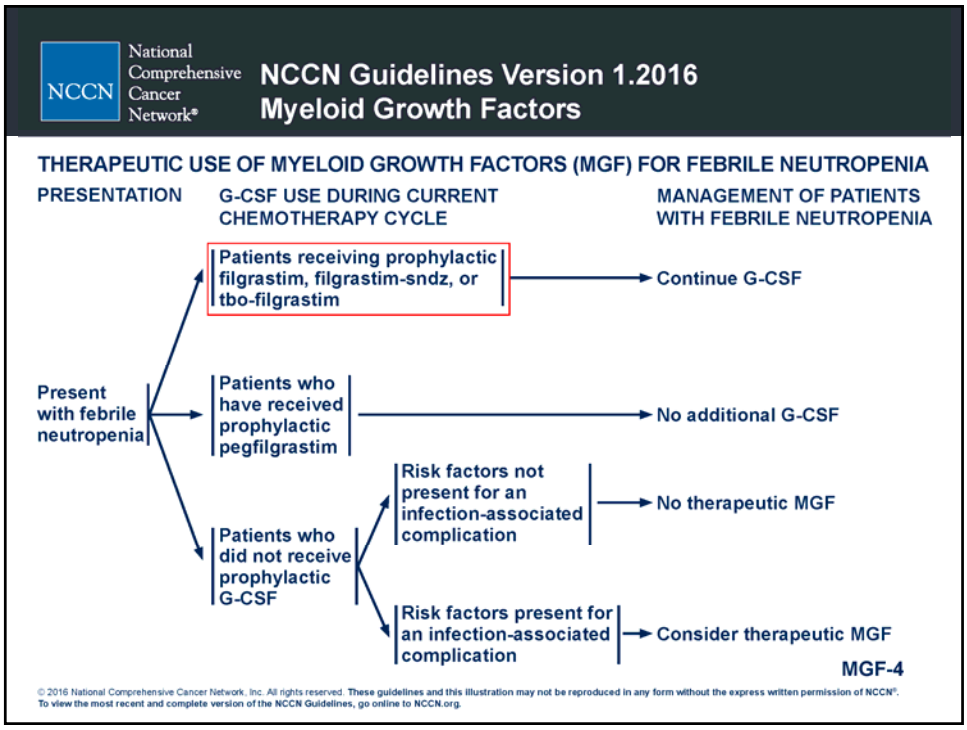
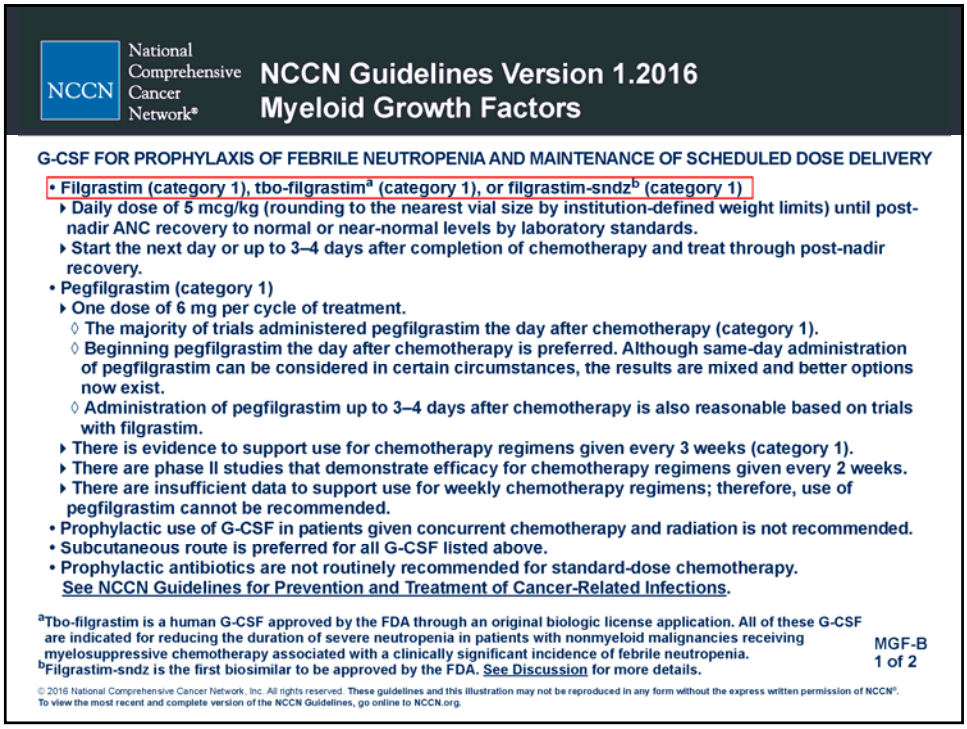










Use of Tbo-filgrastim in Autologous Transplant (ASCT): Mobilization and Engraftment

Elayan et al 2015 -185 patients-86 filgrastim, 99 tbo-filgrastim
- No difference in the primary outcome of median total $CD34^+$ cells collected
- No difference in engraftment
- Tbo-filgrastim use was associated with decreased costs ($1406 per patient)

Trifilio et al 2015-182 patients-91 filgrastim then formulary change then 91 tbo-filgrastim
- No difference in CD34+ cell dose
- No difference in time to neutrophil recovery

- Elayan MM, Horowitz JG, Magraner JM, et al. Tbo-filgrastim versus filgrastim during mobilization and neutrophil engraftment for autologous stem cell transplantation. Biol Blood Marrow Transplant 2015;21:1921-1925.
- Trifilio S, Zhou Z, Galvin J, et al. Filgrastim versus tbo-filgrastim to reduce the duration of neutropenia after autologous hematopoietic stem cell transplantation: **TBO, or not TBO, that is the question**. Clin Transplant 2015;29:1128-1132.

NCCN Category of Evidence and Consensus for Tbo-filgrastim in various settings:

Recommendations from the NCCN MGF Panel

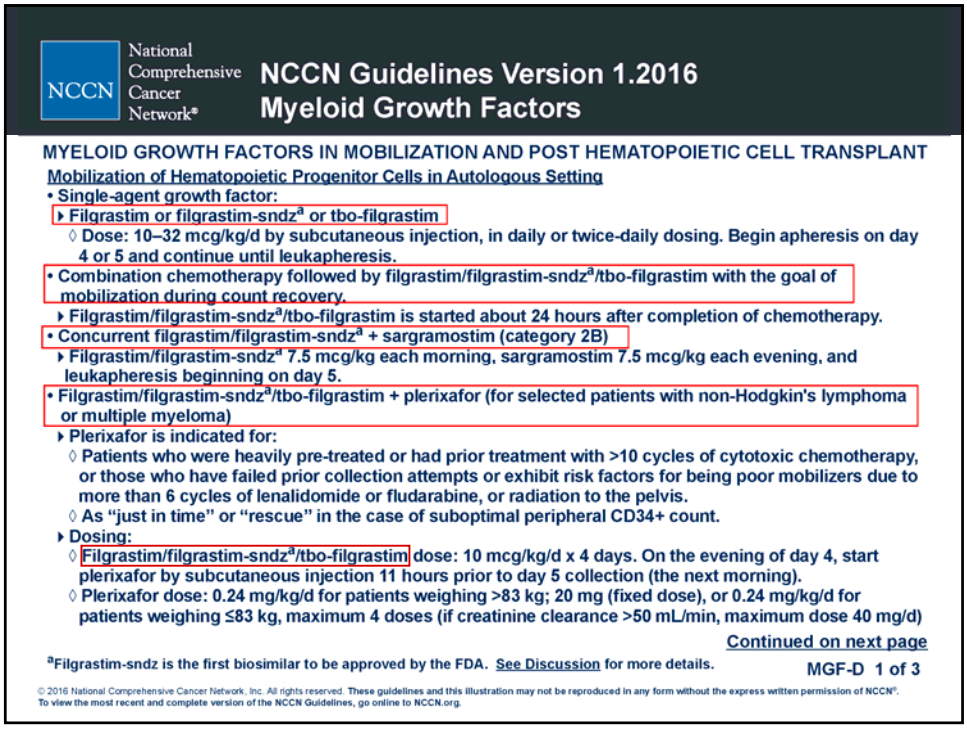
Addition of tbo-filgrastim as an acceptable option for the following:	
• Mobilization of hematopoietic progenitor cells in the autologous setting	2A
• Following combination chemotherapy pre-autologous transplant with the goal of mobilization during count recovery	2A
• In combination with plerixafor for mobilization of hematopoietic progenitor cells in the autologous setting	2A
• Mobilization of allogeneic donors	2B
• For granulocyte transfusion in the allogeneic setting	2B

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

Cost effectiveness in Autologous Transplant (ASCT): Filgrastim vs. Biosimilar Filgrastim (Europe)

- No difference in
  - Number of G-CSF injections (7 in all groups)
  - Duration of hospitalization
  - Days with white blood cell count WBC <1X10^9/L
  - Days with Hgb <90 g/L or platelet count <50X10^9/L
  - Number of units of RBC or platelet transfusions
  - Days of TPN
- Cost comparison
  - 131.2 v. 617 p=0.000016 (lymphoma); 138 v. 564 (myeloma) p=0.000065 [Euros]
  - Transplant 42.5K vs. 39K p=0.25; 30.8K vs. 28K p=0.24 [Euros]

Ianotto J-C et al. Biosimilars of filgrastim in autologous stem cell transplant: reduction in granulocyte-colony stimulating factor costs, but similar effects on bone marrow recovery. Leukemia & Lymphoma 2014; 55(1): 74–77.



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Myeloid Growth Factors

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- Single-agent growth factor:
  - Filgrastim or filgrastim-sndz[a] or tbo-filgrastim
    - Dose: 10–32 mcg/kg/d by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.
- Combination chemotherapy followed by filgrastim/filgrastim-sndz[a]/tbo-filgrastim with the goal of mobilization during count recovery.
  - Filgrastim/filgrastim-sndz[a]/tbo-filgrastim is started about 24 hours after completion of chemotherapy.
- Concurrent filgrastim/filgrastim-sndz[a] + sargramostim (category 2B)
  - Filgrastim/filgrastim-sndz[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.
- Filgrastim/filgrastim-sndz[a]/tbo-filgrastim + plerixafor (for selected patients with non-Hodgkin's lymphoma or multiple myeloma)
  - Plerixafor is indicated for:
    - Patients who were heavily pre-treated or had prior treatment with >10 cycles of cytotoxic chemotherapy, or those who have failed prior collection attempts or exhibit risk factors for being poor mobilizers due to more than 6 cycles of lenalidomide or fludarabine, or radiation to the pelvis.
    - As "just in time" or "rescue" in the case of suboptimal peripheral CD34+ count.
  - Dosing:
    - Filgrastim/filgrastim-sndz[a]/tbo-filgrastim dose: 10 mcg/kg/d x 4 days. On the evening of day 4, start plerixafor by subcutaneous injection 11 hours prior to day 5 collection (the next morning).
    - Plerixafor dose: 0.24 mg/kg/d for patients weighing >83 kg; 20 mg (fixed dose), or 0.24 mg/kg/d for patients weighing ≤83 kg, maximum 4 doses (if creatinine clearance >50 mL/min, maximum dose 40 mg/d)

Continued on next page

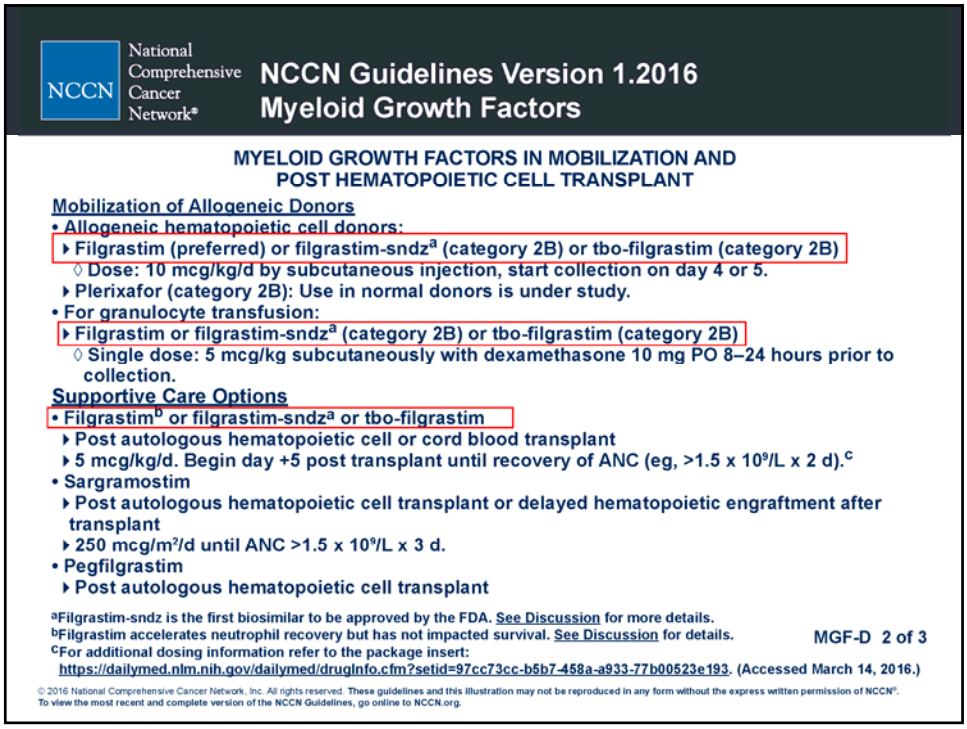
[a]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.

MGF-D 1 of 3

Use of Tbo- or biosimilar filgrastim for mobilization in normal allogeneic donors

- 22 donors, half Tbo-filgrastim, half filgrastim, no significant differences in $CD34^+$ cell count after mobilization, number of leukapheresis procedures, number of $CD3^+$ T lymphocytes, regeneration of blood counts after transplant. (Schmitt et al 2013)
- 36 donors, randomized study biosimilar filgrastim vs. filgrastim, safe, slight difference in CD34+ cell number, all collections over minimal target. (Antelo et al 2016)
- 24 sibling donors, Tbo-filgrastim, compared to historical controls, no difference CD34+ cell counts, time to engraftment, side effects. (Danylesko et al 2016)

- Schmitt M et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. Bone Marrow Transplant. 2013;48:922-5.
- Antelo ML et al. Mobilization of Hematopoietic Progenitor Cells from Allogeneic Healthy Donors Using a New Biosimilar G-CSF J. Clin. Apheresis 31:48–52, 2016.
- Danylesko I et al Biosimilar Filgrastim for Allogenic Hematopoietic Stem Cell Mobilization and Transplantation in Patients with Acute Myelogeneous Leukemia/Myelodysplastic Syndromes. Biol Blood Marrow Transplant 2016;22:277-83.
- Liumbruno GM, Petrini C. Ethical issues and concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilisation of stem cells in normal donors. Blood Transfus 2012;10:550-2.
- Shaw B et al. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of theWorld Marrow Donor Association. Haematologica 2011; 96:942-7.



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Myeloid Growth Factors

MYELOID GROWTH FACTORS IN MOBILIZATION AND POST HEMATOPOIETIC CELL TRANSPLANT

Mobilization of Allogeneic Donors

- Allogeneic hematopoietic cell donors:
  - Filgrastim (preferred) or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)
    - Dose: 10 mcg/kg/d by subcutaneous injection, start collection on day 4 or 5.
  - Plerixafor (category 2B): Use in normal donors is under study.
- For granulocyte transfusion:
  - Filgrastim or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)
    - Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.

Supportive Care Options

- Filgrastim[b] or filgrastim-sndz[a] or tbo-filgrastim
  - Post autologous hematopoietic cell or cord blood transplant
  - 5 mcg/kg/d. Begin day +5 post transplant until recovery of ANC (eg, >1.5 x 10^9/L x 2 d).[c]
- Sargramostim
  - Post autologous hematopoietic cell transplant or delayed hematopoietic engraftment after transplant
  - 250 mcg/m^2/d until ANC >1.5 x 10^9/L x 3 d.
- Pegfilgrastim
  - Post autologous hematopoietic cell transplant

[a]Filgrastim-sndz is the first biosimilar to be approved by the FDA. See Discussion for more details.
[b]Filgrastim accelerates neutrophil recovery but has not impacted survival. See Discussion for details.
[c]For additional dosing information refer to the package insert: https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=97cc73cc-b5b7-458a-a933-77b00523e193. (Accessed March 14, 2016.)

MGF-D 2 of 3

Summary

1. Tbo-filgrastim was FDA approved by Biologics License Application to reduce duration of severe neutropenia with myelosuppressive chemotherapy
2. Filgrastim-sndz was approved as a biosimilar for all the same indications as filgrastim.
3. Practical issue: Hospital formularies interchanging G-CSF and insurer mandates are giving preference

66 year old former firefighter presents with severe back pain, found to have an L1 compression fracture associated with paraspinous mass and spinal cord compression. The mass was biopsied, found to be plasmacytoma, with t(4;14) found by FISH . Additional evaluation reveals monoclonal IgG kappa 7.3 g/dL, kappa free light chain 1740 mg/dL, lambda 1.3 mg/dL, Cre 3.4.

He undergoes radiation to the site of the paraspinous mass with resolution of back pain. He is treated with 4 cycles of bortezomib/cyclophosphamide/dexamethasone, with decline in M protein to 1.4 g/dL and decline in kappa free light chain to 221. He arrives for autologous transplant, and the decision is made to treat with a cycle of VRD-PACE.

Which growth factor should he receive after completion of the chemotherapy drugs?

1. Filgrastim
2. Tbo-filgrastim
3. Filgrastim-sndz
4. Any of the above

Audience Polling Results

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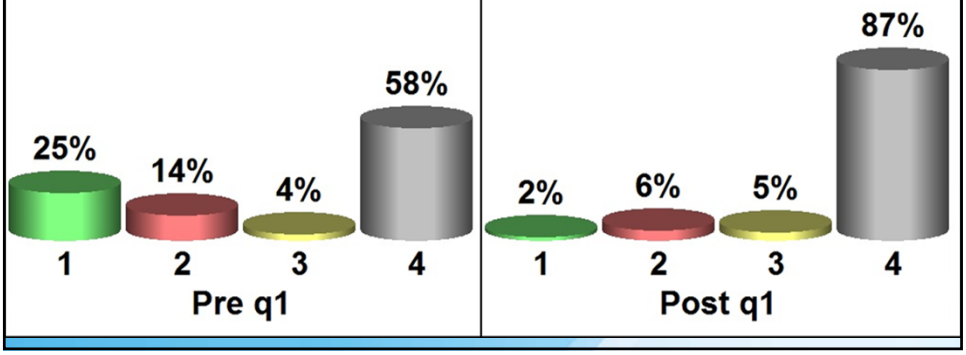

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If the regimen were being used for mobilization of peripheral blood stem cells and you were restricted to FDA approved indication, which could be used?

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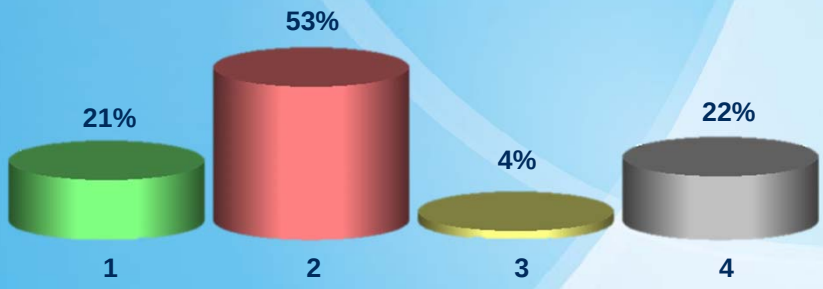

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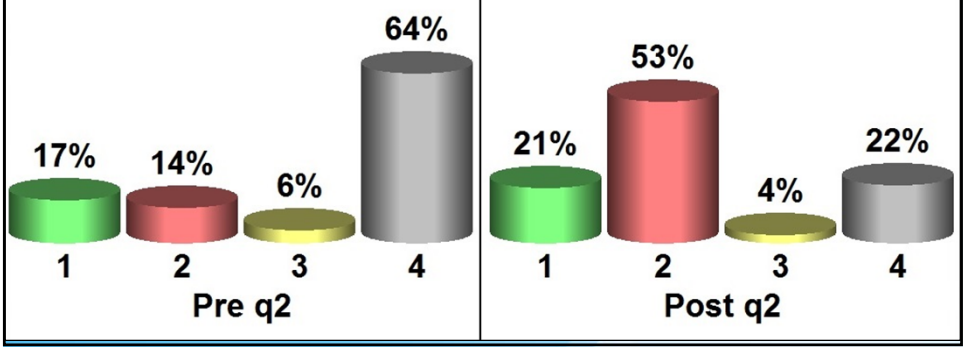

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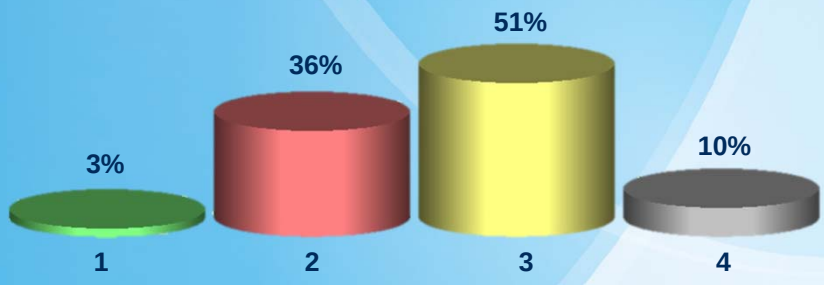
Tbo-filgrastim was FDA approved through the application process as:

1. A generic
2. A biosimilar
3. A biologic
4. An interchangeable biologic product



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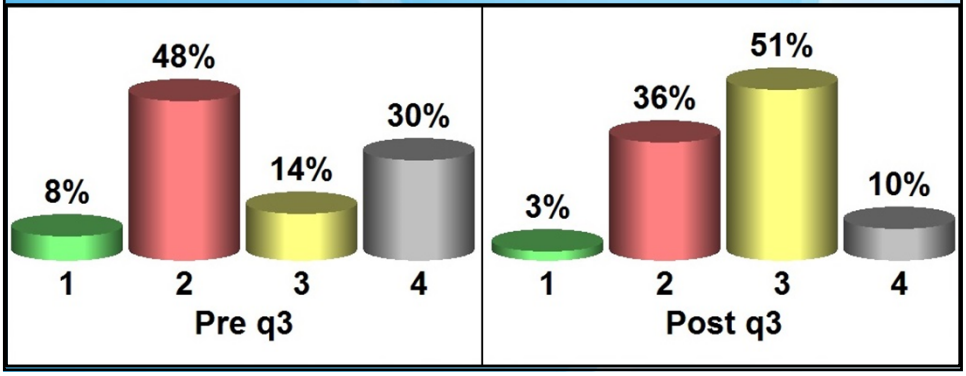

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