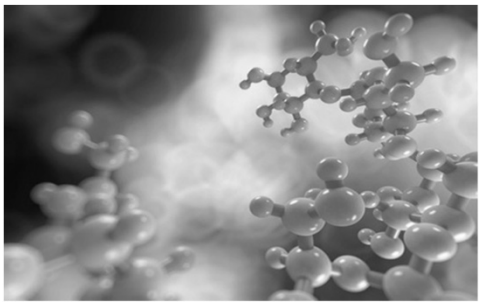
Biosimilar Drugs
An Update for 2018



Ross Day, R.Ph., Doctor of Pharmacy
NPPA Conference - August 23rd, 2018

Definition of Biologicals and Biosimilar Drugs

As stated in the BPCIA (Biologics Price Competition and Innovation Act of 2009- A Subsection of the Affordable Care Act)

- **Biological- "a virus, therapeutic serum, toxin, blood component or derivative, allergenic product….applicable to the prevention, treatment, or cure of a disease or condition of human beings"**
- **Biosimilar Drugs- "the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency of the product"**

Disclosures

I am a registered pharmacist → retired from active pharmacy practice

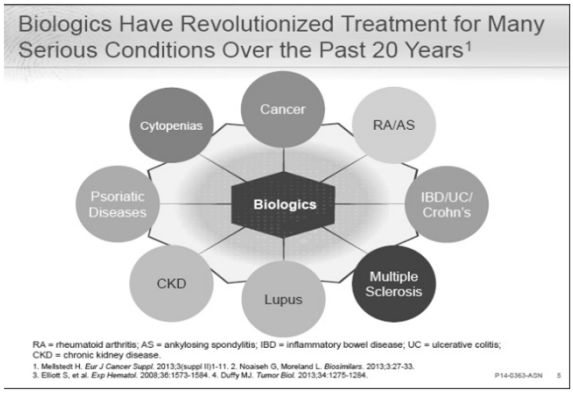
I am a former employee of Novation/Vizient → retired from that organization as of January 1st, 2017

I have provided consultation services to several pharmaceutical companies since my retirement from Novation/Vizient, but I am not currently on retainer with any pharmaceutical company for consultation services

I do not own any pharmaceutical company stock or financial assets related to the pharmaceutical industry

I do not intend to discuss any off-label or non-indicated uses for any pharmaceutical during my presentation

Uses For Biologicals → Biosimilar Drugs

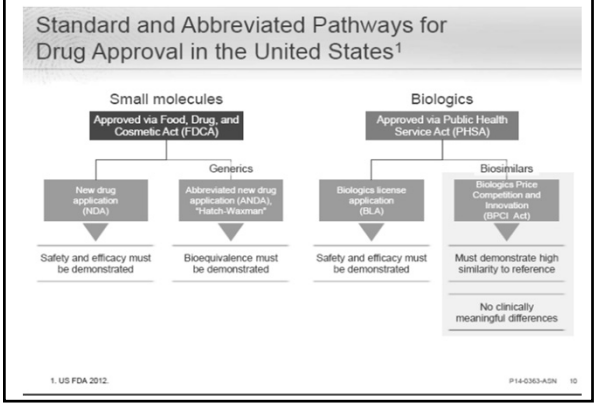


Learning Objectives

At the conclusion of this presentation, participants will be able to:

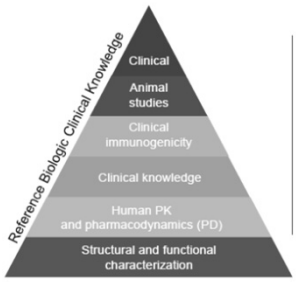
- List the biosimilar drugs currently with applications on file at the FDA
- Identify the biosimilar drugs currently approved by the FDA
- Discuss the biosimilar drugs currently launched in the USA
- Provide estimate dates for those approved but not yet launched
- Describe barriers that must be addressed educationally for optimal adoption in hospitals

Unique Approval Pathway for Biosimilar Drugs



The Pyramid- (Opposite Process from NDA's)

The FDA Will Evaluate Biosimilars Based on a "Totality of Evidence" Approach[1,2]



It is not scientifically beneficial to repeat the entire development program of the reference product[3,4]

A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing[1]

1. FDA Draft Guidance for Industry. Scientific Considerations. 2012. 2. Sherman RE. Biosimilar Guidance Webinar. February 15, 2012.
3. Kozlowski S, et al. *N Engl J Med.* 2011;365:385-388. 4. Noaiseh G, Moreland L. *Biosimilars.* 2013;3:27-33.

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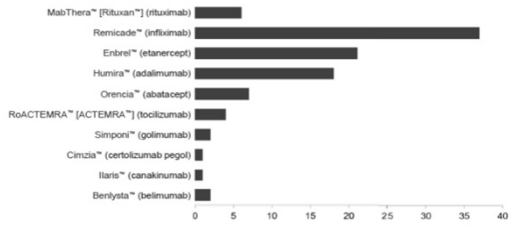
Manufacturing Changes for Reference Biologicals

Many Biologics Have Undergone Multiple Manufacturing Changes During Their Life Cycle[1]

Number of manufacturing changes for biologics used in rheumatologic indications, from time of first approval in Europe



1. Schneider CK. *Ann Rheum Dis.* 2013;72:315-318.

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FDA's Unique Regulatory and Approval Process

The FDA Has Adopted Robust Biosimilar Regulation

The FDA regulatory approach to biosimilars has developed from pre-existing knowledge and experience

1. FDA — Assessments of reference products undergoing manufacturing changes[1]
2. FDA — Abbreviated approval pathway for biologics citing previously approved reference products[2,3]
3. EMA — Biosimilars regulation and postapproval experience[4]

FDA Draft Guidances → Interchangeability guidance due EOY 2018 (B.I. doing trial)

EMA = European Medicines Agency

1. FDA Draft Guidance for Industry. Comparability Protocols – Protein Drug Products and Biological Products. 2003.
2. Woodcock J, et al. *Nat Rev Drug Discov.* 2007;6:437-442. 3. FDA. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products. 1996. 4. Kozlowski S, et al. *N Engl J Med.* 2011;365:385-388.

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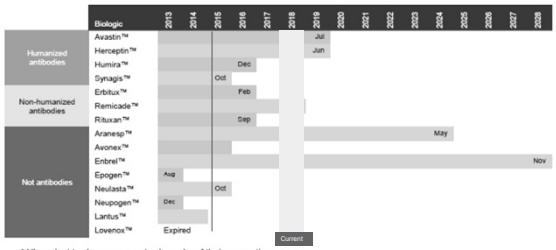
The Patent Landscape for Biosimilar Drugs

Many Biologics Have Upcoming Patent Expirations in the United States[1]

Biosimilars May Provide Multiple Benefits to the US Healthcare System*



*All product trade names are trademarks of their respective owners.
1. Generics and Biosimilars Initiative web site. http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020. Accessed October 2, 2014.

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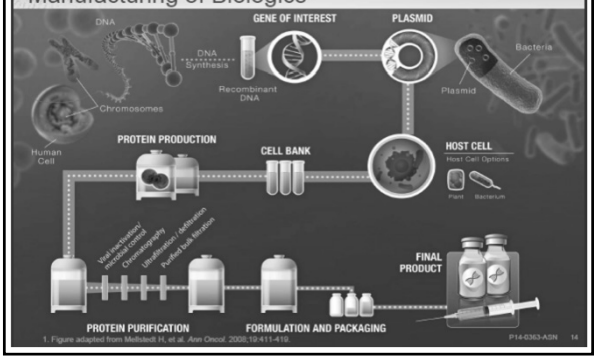
Variability in the Manufacturing of Biologicals

There Is Inherent Variability in the Manufacturing of Biologics[1]



1. Figure adapted from Meltzedt H, et al. *Ann Oncol.* 2008;19:411-419.

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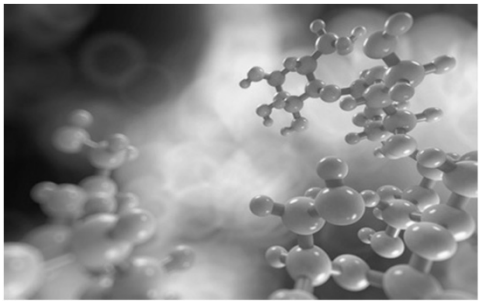
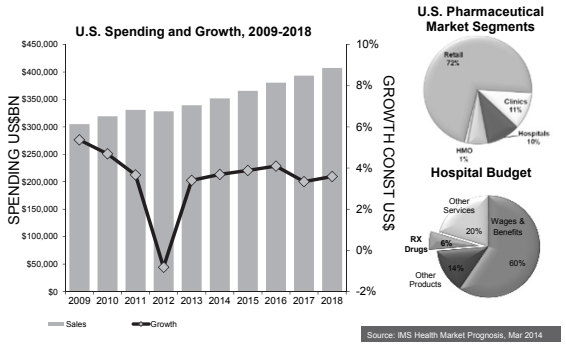
Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs



Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs



Source: IMS Health Market Prognosis, Mar 2014

Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs

The Utility of Biologics Continues to Pressure Healthcare Budgets

- $ 2013 US medical spending on biologics — $92 BILLION[1] → 9.6% growth from 2012
- 1/3 of pharmaceutical products now in development are biologics[2] → 20% forecasted annual increase
- Projected ↑ of 67% in US specialty drug spending by the end of 2015
- By 2025, 71% of new drug approvals may be for biologics[3]

1. IMS Institute for Healthcare Informatics. April 2014. 2. Simoens S. *Clinicoecon Outcomes Res.* 2011;3:29-36.
3. Express Scripts web site. http://lab.express-scripts.com/insights/specialty-medications/specialty-drug-spending-to-jump-67-percent-by-2015. Accessed October 2, 2014.

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Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs

Innovator	Company	Indication	Forecast Sales 2020	Biosimilar Players
Humira (adalimumab)	AbbVie	RA, CD, US, PsO, PsA, AS	$26.2B	~10
Enbrel (etanercept)	**Amgen**	**RA, PsO, PsA, AS**	**$7.4B**	**~10**
Remicade (infliximab)	Janssen	RA, CD, UC, PsO, PsA, AS	$5.9B	~5
Lantus (insulin glargine)	**Sanofi**	**Type 2 Diabetes**	**$3.7B**	**<5**
Rituxan (rituximab)	Genentech/Biogen	NHL, CLL, RA, GPA, MPA	$5.0B	~15
Avastin (bevacizumab)	**Genentech**	**mCRC, NSCLC, mRCC, rGBM**	**$6.4B**	**~10**
Herceptin (trastuzumab)	Genentech	Breast Cancer, Metastatic Gastric/ GEJ Cancer	$5.7B	~10
Neulasta (pegfilgrastim)	**Amgen**	**Neutropenia related to cancer chemotherapy**	**$3.4B**	**~5**
Lucentis (ranibizumab)	Genentech	wAMD, macular edema following RVO, DME	$3.0B	<5
Acetemra (tocilizumab)	**Genentech**	**RA**	**$1.8B**	**<5**

Sources: EvaluatePharma based on data pulled January 2015, company websites

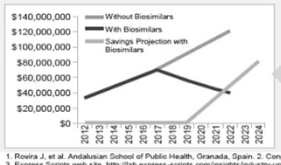
Non- Confidential

Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs

Cost Savings From Biosimilars to the US Healthcare System May Be Significant

- Typical price reductions for biosimilars are 10%-35%[1]
- Competition from biosimilars could reduce federal drug spending in the US by roughly $25 billion over 10 years[2]
- Potential savings with biosimilars could reach $250 billion by 2024[3]

Projected US Spend on 11 Specific Biologics (in 000s)



Estimate based on the 11 existing biologic drugs that are *the most likely candidates* for biosimilars in the next 10 years

1. Rovira J. et al. Andalusian School of Public Health, Granada, Spain. 2. Congressional Budget Office. S. 1695. 2008.
3. Express Scripts web site. http://lab.express-scripts.com/insights/industry-updates/the-$250-billion-potential-of-biosimilars. Accessed October 1, 2014.

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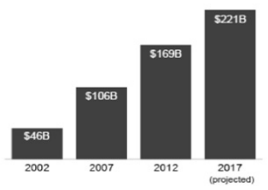
Importance to U.S. Hospitals for Successful Adoption of Biosimilar Drugs

Global Spending on Biologics Continues to Increase and May Impact Access to Treatments

Global Biologics Sales, 2002-2017[1]



- Biologics continue to outpace overall spending growth and are expected to represent 19%-20% of global market value by 2017[1]
- Patient access to biologic therapies is a concern[2]

1. IMS Institute for Healthcare Informatics. The global use of medicines: outlook through 2017. November 2013.
2. Baer WH, et al. *Pharmaceuticals.* 2014;7:530-544.

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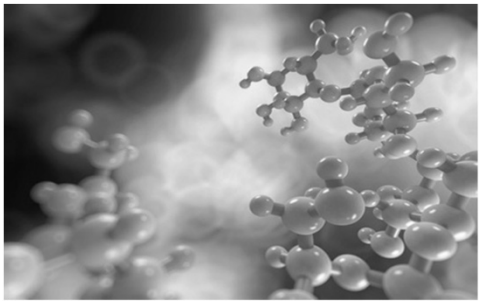
Approval of Biosimilar Drugs in Europe Has Been Successful



Approval of Biosimilar Drugs in Europe Has Been Successful

Over 500 million patient days of experience, with negligible safety issues

- **Nine biosimilar versions of Humira have or will be filed with EMA**
  - Three versions have been approved (Amgen, Bioepsis and B.I.)
  - Three versions likely to be approved before year end (Sdz, Mylan, & FK)
  - Three versions end trials before year end (Pfe, Coherus & Momenta)
  - Market will materialize in Oct 2018, with six simultaneous launches
  - AbbVie projects 20% decline in sales 1st year, smaller declines thereafter
- **AbbVie's market retention strategies**
  - Arguing BS versions are from old Humira formulations, not current ones
  - Convincing pt. advocacy groups to lobby for newer less painful version
  - Contracting strategies (give up price but not volume)
  - Not a hospital drug, so reinforce brand loyalty to patient groups

Approval of Biosimilar Drugs in Europe Has Been Successful

Biosimilar Oncology Drugs in Europe

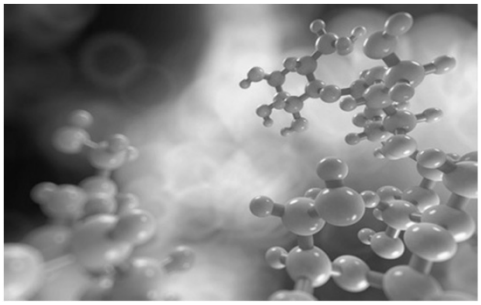
- **Biosimilar versions (2) of Herceptin now launched in Europe**
  - Ontruzant (Merck/Bioepsis) approved Nov '17 → launched in UK Mar '18
  - Herzuma (Celltrion) launched in UK and Germany May '18
  - Market share at 1% after first data release of sales (July)
  - US market expected to materialize mid 2019 (several entries)
- **Biosimilar versions (2) of Rituxan now launched in Europe**
  - Truxima (Celltrion) launched Apr '17
    - First to launch and has gained most of market share
  - Rixathon (Sdz) launched July '17
  - Market share at 36%, in 1 year (most successful BS launch in EU)
  - Market share gained at expense of infusion, none from SQ
  - US market expected to materialize in 2019

Approval of Biosimilar Drugs in Europe Has Been Successful

Launched → Epogen , Enbrel, Neupogen, Remicade, Rituxan, & Herceptin Biosimilars

- **Biosimilar versions (4) of Neupogen now at 93% of total EU market**
  - Late entrants gaining share just as fast as original biosimilar versions
- **Biosimilar versions (2) of Epogen now at 74% of total EU market**
- **Biosimilar versions (3) of Remicade now at 60% of total EU market**
  - Remicade BS share increasing 1-2% per month (Inflectra & Remsima)
  - Late entrants not gaining share as fast (Biogen's version very slow)
- **Biosimilar versions of Enbrel (2) now at 37% of total EU market (July)**
  - Second launched version (Sdz) much slower than first (Biogen)
  - Enbrel BS share increasing 1-2% per month (price now ↓ 31%)
- **Biosimilar versions of Rituxan now at 36% of total EU market (July)**
  - Adoption rate for BS Rituxan more robust than other biosimilar drugs
  - Familiarity with other agents, lack of safety issues with others
- **Biosimilar version of Herceptin launched→ no data to report as of May**

Approval of Biosimilar Drugs in U.S. Has Been "A Work in Progress"



Approval of Biosimilar Drugs in Europe Has Been Successful

Biosimilar versions of Neupogen and Epogen in EU for a decade

- **Biosimilar versions of Neupogen now at 93% of total EU market**
  - Innovator (Amgen) and 4 biosimilar competitors (most crowded market)
  - Late entrants (Aptx) gaining share just as fast as originals- now 18%
    - May reflect commodity effect, and likely will translate to US
- Significant price declines due to competition (75% - 80%)
- **Biosimilar versions of Epogen now at 73% of total EU market**
  - Innovator (Amgen) and 2 biosimilar competitors
  - Market share is growing about 5% per year
    - Sandoz biosimilar version is the leader with over 50% of total mkt
  - Apotex version is completing clinical trials
  - US market expected to materialize mid-2018 (Pfe Retacrit just approved)

Approval of Biosimilar Drugs in U.S. Has Been "A Work in Progress"

Only Four Biosimilars Launched in the U.S. Market

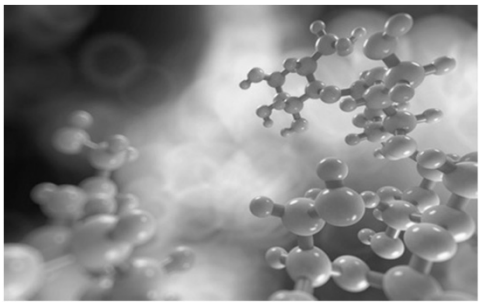
- **Biosimilar versions of Neupogen (Amgen) → One launched**
  - One biosimilar (Zarxio-Sndz) and one brand competitor (Granix-Teva)
  - Market share for Zarxio and Granix now at 58%
    - Granix in market for 4.5 yrs and Zarxio in market for 2.5 yrs.
  - Two additional filgrastim versions on file → expect approvals in 2018
  - Amgen's strategy → Move pts to Neulasta with Onpro® device
- **Biosimilar versions of Neulasta (Amgen) → One launched**
  - Spoiler alert……Mylan's approved June '18, three more on file
  - Mylan/Biocon's version (Fulphila®, pegfil.jmdb) launched 7-30-18
    - Mylan may have waited for favorable ASP establishment
  - Coherus, Sndz, and Aptx versions also received subsequent CRL's
  - Neulasta U.S. market likely not to form till late 2018

Approval of Biosimilar Drugs in U.S. Has Been "A Work in Progress"

Only Four Biosimilars Launched in the U.S. Market

- **Biosimilar versions of Remicade (J&J) → Two launched**
  - Pfizer version of Remicade (Inflectra/Celltrion) launched Nov '16
  - Merck/Bioepsis version of Remicade (Renflexis) launched Sept '17
  - Total infliximab biosimilars market share only 4%, as of May '18
  - J&J market preservation strategies:
    - Bundling of Remicade prices to other J&J hospital supplies
    - Aggressive contracting with plans (Pfizer is litigating)
    - Heavy discounts in 340B arena
  - J&J plans for 20% reduction in price for 2018
    - ASP's are trending down for all infliximab agents

Educational Requirements to Improve Biosimilars Adoption in U.S. Hospitals



Approval of Biosimilar Drugs in U.S. Has Been "A Work in Progress"

Seven Biosimilars approved in the U.S. and not launched

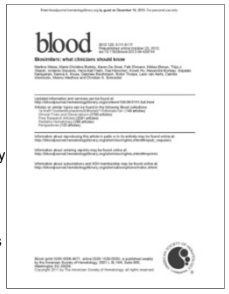
- Etanercept (Enbrel) → 1 biosimilar version approved
- Bevacizumab (Avastin) → 1 biosimilar version approved
- Traztusamab (Herceptin) → 1 biosimilar version approved
- Adalimumab (Humira) → 2 biosimilar versions approved
- Epoetin (Epogen) → 1 biosimilar version approved
- Filgrastim (Neupogen) → 1 biosimilar version approved

Nine Biosimilars filed with FDA and not yet approved

- Peg-filgrastim (Neulasta) → 3 versions filed with FDA
  - Coherus, Sndz and Aptx (all CRL's)
  - US mkt formed July 2018 (Mylan)

EOvercoming Barriers for the Clinical Adoption of Biosimilars
Educate Providers (and do some myth busting)

- Refute the myths that foment a fear of "low quality" or "substandard" biosimilar drugs
- Broaden the understanding of "similar but not identical" (not a bad paradigm)
- Educate practitioners that the biosimilars safety database is sufficient, especially related to immunogenicity
- Use of biosimilars in extrapolated indications is supported by data that is viewed favorably by regulating agencies (e.g. EMA, FDA)
- Biosimilar interchangeability will be addressed with guidance, but not of significance in HCO's.



Weise M, Bielsky MC, De Smet K, et al. *Blood.* 2012;120:5111-5117.

Approval of Biosimilar Drugs in U.S. Has Been "A Work in Progress"

Nine Biosimilars filed with FDA and not yet approved (continued)..

- Rituximab (Rituxan) → 2 biosimilar versions filed with FDA
  - Teva/Celltrion → Feb 2018
  - Sndz → May 2018
- Traztusamab (Herceptin) → 3 biosimilar versions filed with FDA
  - Amgen/Allergan → July 2017 → subsequent CRL
  - Teva/Celltrion → May 2018 → subsequent CRL
  - Pfizer → May 2018 → subsequent CRL
- Filgrastim (Neupogen) → 1 biosimilar version filed with FDA
  - Adello → May 2018
- Note: Some oncology biosimilars may launch in the U.S. in 2019

Educate Providers (Myth Busting, continued)

- Physicians don't believe U.S. made biosimilars offer any advantage to others…it's quality
- Only 50% of U.S. physicians know what extrapolation means for biosimilar approval
- Less than 50% of U.S. physicians believe biosimilars are safe for naïve patients
- Will adoption success readily evident with GCSF's translate to chronic therapies? EU evidence indicates yes…
- Eventually, payors will be more relevant with adoption decisions, particularly with Medicare Part B to Part D switching (2019… PBM involvement)

Weise M, Bielsky MC, De Smet K, et al. *Blood.* 2012;120:5111-5117.

Overcoming the "Similar But Not Identical" Paradigm
"Fingerprint Like"

	Amgen G-CSF	Teva G-CSF	Sandoz G-CSF
Brand name	Neupogen®	Granix®	Zarxio®
Generic name	Filgrastim	Tbo-filgrastim	Filgrastim-sndz
Application type	BLA – 351(a)	BLA – 351(a)	BLA – 351(k)
Ingredient	r-metHuG-CSF	r-metHuG-CSF	r-metHuG-CSF
Molecular Weight	18,800 daltons	18,800 daltons	18,800 daltons
Protein length	175 amino acids	175 amino acids	175 amino acids
Expression system	E. Coli	E. Coli	E. Coli
Dosages	300 mcg, 480 mcg	300 mcg, 480 mcg	300 mcg, 480 mcg
Dosage forms	Vial and Syringe (both PF)	Syringe (PF)	Syringe (PF)
Storage conditions	2° to 8°C	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.; FDA Briefing Document, BLA 125553, Oncologic Drug Advisory Committee Meeting, January 7, 2015.

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Share FDA's Willingness to Encourage Biosimilar Adoption (Extrapolated Indications and BAP)

Indications	Remicade® - 351a	Inflectra® - 351k
Rheumatoid arthritis	Yes	Yes
Ankylosing spondylitis	Yes	Yes
Crohn's disease	Yes	Yes
Pediatric Crohn's disease	Yes	Yes
Plaque psoriasis	Yes	Yes
Psoriatic arthritis	Yes	Yes
Ulcerative colitis	Yes	Yes
Pediatric ulcerative colitis	Yes	No*

*The pediatric ulcerative colitis indication for Remicade is protected by Orphan Drug Exclusivity

Expiration of pediatric exclusivity for that indication is Sept. 23, 2018

Remicade (infliximab) package insert–– FDA Briefing Document, April 5, 2016.

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Overcoming the Fear of Lack of Sufficient Safety Data
>500 million patient days of experience in Europe
the fear of lack of safety databases

International Non-Proprietary Name (INN)	Trade Name	Company	Approval Date
Somatropin	Omnitrope	Sandoz Gmb	April 2006
	Valtropin	Biopartners GmbH	April 2006
Epoetin alfa	Epoetin alfa Hexal	Hexal AG	August 2007
	Abseamed	MEDICE Pharma GmbH & Co. KG	August 2007
Epoetin zeta	Silapo	STADA Arzneimittel AG	December 2007
	Retacrit	Hospira, Inc.	December 2007
Filgrastim	Ratiograstim	Ratiopharm GmbH	September 2008
	Biograstim	CT Arzneimittel	September 2008
	Tevagrastim	Teva Pharmaceutical Industries Ltd.	September 2008
	Zarzio	Sandoz International GmbH	February 2009
	Filgrastim Hexal	Hexal AG	February 2009
	Nivestim	Hospira, Inc.	June 2010
Epoetin theta	Biopoin	CT Arzneimittel GmbH	October 2009
	Eporatio	Ratiopharm GmbH	October 2009

Transparency—Honesty with the Provider Community → Sharing Issues with Stakeholders

Drug Product	Potential Issues
Filgrastim	• Tbo-filgrastim – no bone marrow transplant indications; only syringe formulations (peds problem) • Filgrastim-sndz – also absence of vial formulations • Both products helped by availability of European data and patient experiences
Pegfilgrastim	• One injection per course of therapy; will there be same degree of comfort as with daily dosed product? • Not approved in EU (no history yet) • Onpro® infusion device from innovator will not be immediately available in biosimilar versions • Carved out indication (neutropenia following radiation) for the biosimilar just approved

Neupogen and Neulasta are both used for supportive care; oncologists accustomed to prescribing potentially toxic drugs

Share FDA's Willingness To Approve extrapolated indications

Indications	Neupogen® - 351a	Granix® - 351a	Zarxio® - 351k
Cancer patients receiving myelosuppressive chemotherapy	Yes	Yes	Yes
Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy	Yes	No	Yes
Cancer patients receiving bone marrow transplant	Yes	No	Yes
Patients undergoing peripheral blood progenitor cell collection and therapy	Yes	No	Yes
Patients with severe chronic neutropenia	Yes	No	Yes
Pregnancy category	C	C	C
Data for use in pediatrics	Yes	No	No

Neupogen (filgrastim) package insert. Thousand Oaks, CA: Amgen; 2012 May; Tbo-filgrastim package insert. North Wales, PA: Teva Pharmaceuticals USA; 2013 May.; FDA Briefing Document, BLA 125553, Oncologic Drug Advisory Committee Meeting, January 7, 2015.

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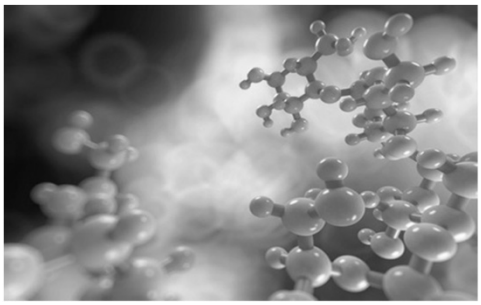
Transparency → Sharing Issues with Stakeholders

Drug Product	Potential Issues
Epoetin	• Eprex hangover? Can that be refuted with studies?
Infliximab	• Indication variation for two distinct patient populations; two distinct prescribing audiences • Higher potential for toxicity as consequence of therapy • A "buy and bill" drug administered in clinics or physician practices → subject to additional variances associated with reimbursement • Initial biosimilar versions not aggressively priced by Pfizer and Merck, but aggressively defended by J&J → lackluster adoption (gaining modestly now ~ 4-5%)
Rituximab	• Even more indication variances and variety of prescribers • To what extent will extrapolation of indications be possible?
Oncology mAbs	• Variation of indications and prescribers • How much outcome data required to substantiate comparable efficacy?

Questions? My Two Questions First!



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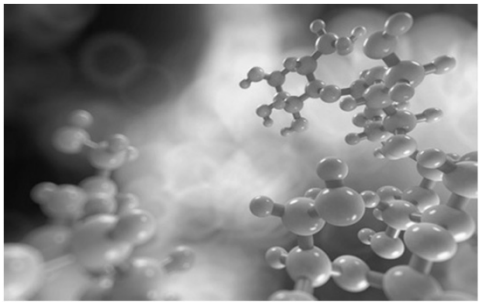
Questions? Now Yours…



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