TPIreg
Navigating Regulatory Affairs

Biosimilars in Europe, the US, and Canada

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- **WHO Held Meeting For Compromise Proposal To Name Biosimilars in Mid June 2015.**
  - A compromise approach towards naming biosimilars.
  - According to the proposal, regulatory agencies should add a four-letter suffix to the end of each biosimilar's name, which is otherwise the same.
  - The FDA used a similar approach when it approved a biosimilar by Sandoz in March 2015 (filgrastim-sndz) and by Celltrion in April 2016 (infliximab-dyyb).
    - FDA issued a guidance in March 2016 regarding nomenclature of biosimilars.

- **US Labelling**

  - INFLECTRA (infliximab-dyyb) is biosimilar to REMICADE (infliximab) for the indications listed.
  - Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

BIOSIMILARS IN EUROPE

- Guidelines
  - Overarching biosimilar guidance
    - Nov 2014
      - Revised General Guideline on Biosimilars published
        - » Allowed for use of non-European reference.
  - Non-clinical and clinical aspects for the development of biosimilars – adopted July 2015
  - Quality issues – adopted Dec 2014

- Product-class Specific Guidelines
  - epoetins;
  - filgrastims;
  - insulins;
  - growth hormones;
  - alfa interferons;
  - monoclonal antibodies;
  - beta interferons;
  - follitropins;
  - low-molecular-weight heparins (LMWH).

Comparison of Canadian, European and US Biosimilar Approvals

Compound	No. of Applications			EU First One Approved
	Europe	Canada	US	
Somatropin	2	1	2	April 12, 2006
Epoetin alfa	3	0	0	Aug 28, 2007
Epoetin zeta	2	0	0	Dec 18, 2007
Filgrastim	8	0	1	Sept 15, 2008
Infliximab	2	2	0	Sept 10, 2013
Follitropin alfa	2	0	0	Sept 27, 2013
Insulin Glargine	1	0	0	Aug 2014

BIOSIMILARS IN THE US

Biosimilars in the US

- April 2015, the FDA issued three guidance documents on biosimilar product development:
  1) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product;
  2) Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and
  3) Biosimilars: Questions and Answers Regarding Implementation of the *Biologics Price Competition and Innovation Act* of 2009.
- Also available is a draft Guidance for Industry entitled *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*, which has not been published in the Federal Register. The FDA has not yet issued any final rules on this topic.
- Naming guideline could issued in March 2016

351(k) Applications

- Subsection (k) Application Information – Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant
  - shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application.

Biosimilars in the US

- FDA has been authorized to assess and collect fees for biosimilar biological products from October 2012 through September 2017 under the *Biosimilar User Fee Act* ("BsUFA").
- According to the November 15, 2013, statement by Dr. Woodcock before Congress, the BsUFA program "includes fees for products in the development phase to generate fee revenue in the near-term and to enable sponsors to have meetings with FDA early in the development of biosimilar biological product candidates."

Biosimilars in the US

- Purple Book
  - List all Brand Products and any biosimilars with which they are interchangeable.
  - Separate lists for biologics regulated by CDER and biologics regulated by CBER

Precedents in the US

- **Insulin Glargine Injection:** On August 18, 2014, there was a tentative approval from the FDA for Basaglar (insulin glargine injection), pending resolution of patent issues.
- Final approval granted December 17, 2015
  - The approval was for an NDA under 21 CFR 314.105.
  - This has been referred to in the press as an approval of a biosimilar, although it was not filed through the biosimilar process in the US.

Precedents in the US

- **Filgrastim (Zarxio):**
  - On July 24, 2014, FDA accepts first biosimilar application.
  - March 6, 2015 – FDA approves first US biosimilar, Zarxio
    - Generic name is filgrastim-sndz.
    - Labelling closely replicates the package insert for the reference biologic
    - Labelling does not identify the drug as a biosimilar
  - March 19, 2015 – US district court dismisses Amgen's petition to block launch of Zarxio.
  - March 25, 2015 – Amgen appealed decision .
  - May 12, 2015 – temporary injunction issued to prevent Sandoz from marketing pending patent infringement litigation
  - June 2015 Federal appeals court considers whether to lift the temporary injunction
  - Sept 2, 2015 – sales can start – final court decision.
  - Sept 4, 2015 – Zarxio launched at 15% discount to Neupogen.

Precedents in the US

- **Infliximab:**
  - Filed August 13, 2014.
  - The originator (Remicade) is scheduled to lose patent protection in the US in 2018.
  - Bioequivalence of US Reference to EU Reference required.
  - This is the first 351(k) biosimilar mAb application to be filed in the US and the second application for a biosimilar to be filed through the US BPCIA.
  - It has been announced that Celltrion and Hospira are seeking interchangeability in the US.
  - Advisory Committee in February/15 requested more data.
  - Advisory Committee in February/16 strongly backed Celltrion's product.
  - Approved by the FDA on April 5, 2016. All indications approved.
  - Second biosimilar approved.
  - To be marketed by Hospira (now Pfizer).

SUBSEQUENT ENTRY BIOLOGICS IN CANADA

SEBs in Canada

- *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).*
  - *New draft issued in December 2015 (dated Aug 2015)*
    - *Simplified requirements for use of a foreign reference*
    - *Moving away from requiring comparative nonclinical. One repeat-dose tox should be sufficient.*
    - *Extrapolation of clinical data from tested indication to others is being clarified*
- SEBs are filed as NDSs and are reviewed by the Biologics and Genetic Therapies Directorate (BGTD).
- Canada has only very general guidelines for biosimilars.

SEB Filings in Canada

- As of April 2016, there had been
  - 9 NDSs for SEBs
  - 15 Pre-NDS Meetings
  - 30+ CTAs
- SEBs Approved
  - (Sandoz's somatropin (Omnitrope) was approved in 2009.)
  - Hospira's Infliximab (Inflectra) and Celltrion's Remsima were approved January 15, 2014.
  - Eli Lilly's Insulin Glargine (Basaglar) approved September 1, 2015
  - Apotex filgrastim (Gastofil) approved December 7, 2015
- The Canadian courts have, to date (2012), dealt with very few biologics patents and no SEB patent cases.
- As of now (2016) three (four) products has been approved as SEBs

CASE STUDY

Inflectra

- Reference product: Remicade
- Indications requested:
  - Rheumatoid Arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's Disease, ulcerative colitis
- Indications NOT approved for Inflectra:
  - Crohn's Disease, ulcerative colitis
- Animal Studies:
  - Rats: 12-week comparative repeat-dose rat toxicity

Inflectra

- Clinical Studies:
  - 1 pilot initial PK, safety & efficacy; 9 patients with RA
  - 1 pivotal clinical safety & efficacy;
    - 606 adults with RA;
    - 54 wks
  - 1 pivotal PK,
    - 250 patients with ankylosing spondylosis;
    - 54 wks
  - Note: no studies on psoriatic arthritis, plaque psoriasis, Crohn's Disease, ulcerative colitis
  - Extrapolated data accepted for psoriatic arthritis, plaque psoriasis
  - Extrapolated data NOT accepted for Crohn's Disease, ulcerative colitis

Submission Milestones: Inflectra (and Remsima)

Submission Milestone	Date
Pre-submission meeting	2011/10/14
Submission filed	2012/11/14
Screening	
Screening Deficiency Notice issued	2013/01/14
Response filed	2013/02/04
Screening Acceptance Letter issued	2013/03/21
Review	
On-Site Evaluations	2013/11/25 to 2013/11/29 2013/12/02 to 2013/12/06 2013/12/09 to 2013/12/10
Quality Evaluation complete	2014/01/15
Clinical Evaluation complete	2014/01/15
Labelling Review complete	2014/01/15
Notice of Compliance issued	2014/01/15

INTERCHANGEABILITY

PROSIT-BIO

- Observational study
  - Conducted in 49 centres in Italy
  - 397 patients with UC and CD's
    - 165 Inflectra
    - 231 Remsima
  - 93 patients switched to biosimilar
  - Comparable efficacy and safety after 12 months compared to
    - Naïve patients
    - Those remaining on their biologic treatment

Newly Presented Data From The Largest Real World Study To Date Demonstrate Effectiveness Of Biosimilar Infliximab In Patients With Inflammatory Bowel Diseases Who Have Been Switched From Reference Infliximab, Jan 2016. http://www.biosimilardevelopment.com/doc/newly-presented-largest-real-world-effectiveness-reference-0001.

Interchangeability and Norway - Infliximab

- Remsima (Celltrion product; Orion distributor) is biosimilar
- Nor-Switch Study
  - The purpose of this study is to assess the safety and efficacy of switching from Remicade to the biosimilar treatment Remsima in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis
  - DB, randomized study in 500 patients
  - Results to be released in 2016
- June 2014 - price differential 39% discount vs Remicade – 20% market share
  - February 2015 – price cut of 72% discount – led to 66% market share by April

Interchangeability and Finland

- 39 consecutive patients [mean age 53] with various rheumatic diseases were switched after a mean of 4.1 years on Remicade.
- 31 patients were on concomitant methotrexate.
- At a median of 11 months following the first administration of biosimilar, AUCs for disease activity and PROs were similar.
- They were better compared to those prior to INX.
    - Expert Opin Biol Ther. 2015;15(12):1677-83. Epub 2015 Nov 7.

Interchangeability and Finland

- 45% discount off the European price of branded drug.
- Position of Finland – biosimilars are interchangeable under the supervision of a healthcare professional

Reimbursement in US

- California
  - Feb 27 – Bill to require pharmacists switching a brand for a biosimilar to make note of the swap in electronic medical records.
  - If no electronic medical record, involve the MD
- Illinois
  - Pharmacies must notify prescribers of a swap within 3 business days.
  - Patients may reject swap.
- Washington, Utah, Tennessee, Georgia and Colorado passed laws to allow biosimilars to be substituted for more costly biologics if the FDA approved the biosimilar as interchangeable.
- Centers for Medicare & Medicaid Services has announced that it plans to begin paying for biosimilars through its Part B, Part D and state coverage policies by summer 2015

Canada - Common Drug Review

- List in accordance with the approved indications for the treatment of RA, Ankylosing Spondylitis, plaque psoriasis and psoriatic arthritis.
  - For use in patients for whom infliximab is considered to be the most appropriate treatment option.
  - List in a manner similar to Remicade.
- Rationale
  - Two randomized controlled trials demonstrating similarity.
  - Extrapolation of data from RA and AS to psoriatic arthritis and psoriatic plaques is supported by similar pathophysiology.
  - Submitted price ($650 per 100 mg vial) is less costly than Remicade ($987.56 per 100 mg vial).

Canada - Provincial Decisions

- Approved in Quebec, Ontario, BC and Manitoba
- Under review in other provinces.
- In BC, only SEB reimbursed after Feb 19 for new patients.

Canada – Quebec

INFLIXIMAB F

Pd. Perf. I.V. 100 mg

02244016	*Remicade*	Janss. Inc	1	940,00	

INFLIXIMAB-POLYARTHRITE RHUMATOÏDE,SPONDYLITE ANKYLOSANTE, ARTHRITE PSORIASIQUE ET PSORIASIS EN PLAQUES F

Pd. Perf. I.V. 100 mg **PPB**

+	02419475	*Inflectra*	Hospira	1	➡	650,00
+	99101167	*Remicade*	Janss. Inc	1		940,00

Canada – Ontario

Indication	Inflectra		Remicade	
	Approved	Listed	Approved	Listed
Crohn's	X	X	√	√
Ulcerative colitis	X	X	√	√
Juvenile arthritis	X	X	√	√
Plaque psoriasis	√	√	√	X
Rheumatoid arthritis	√	√	√	√
Psoriatic arthritis	√	√	√	X
Ankylosing spondylitis	√	√	√	√