Biologics and Subsequent Entry Biologics:

HTA perspectives

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IHE SYMPOSIUM ON BIOLOGICS AND BIOSIMILARS

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CADTH

Who and what is CADTH?

- Private, not-for-profit corporation
- Major producer of HTA for drugs, devices, diagnostics, and procedures
- Recognized globally as a leader in HTA
- Funded by Health Canada, Provinces and Territories

CADTH supports informed decisions by providing impartial, evidence-based research and advice on drugs and other health technologies.

Biologics

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Content

- Biologics and Subsequent Entry Biologics (SEBs) – Landscape
- HTA perspectives – are biologics different?
- Developing the CDR SEB review Process
  - SEB Submission Requirements
  - Structure and Content of the Template
  - Additional Submission Requirements
  - Next Steps

Biologics: landscape

- The biologics market is expanding rapidly
- US FDA approved 16 biologics in the year 2009 compared to 9 in 2007, and the trend is continuing
- Global spending on biologics increased from US$93 billion in 2006 to US$157 billion in 2011. It is expected to climb to between US$200 and US$210 billion by 2016.
- Therapeutic areas and indications are growing
- Biosimilars or SEBs are expected to be marketed for several reference biologics

The global use of medicines: outlook through 2016 [Internet].: IMS Institute for Healthcare Informatics; 2012 Jul. Available from: http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global%20Use%20of%20Meds%202011/Medicines_Outlook_Through_2016_Report.pdf

Biologics Reviewed by CADTH's Common Drug Review (CDR)

- 76 biologic drugs have been reviewed
- The most frequent indications submitted include:
  - adult or juvenile rheumatoid arthritis (8 submissions),
  - psoriasis (7 submissions), and
  - adult or pediatric diabetes type 1 and/or 2 (6 submissions)

HTA perspectives: are biologics different from other drugs (small molecule drugs)?

- No difference with regard to the methodology used for the clinical and economic assessments
- Important considerations
  - lack of the use of appropriate comparators in clinical trials
  - Significant price premium compared with the historic or current standard of care
  - lack of long-term clinical data, particularly the lack of ‘on-market’ efficacy or safety data
  - multiple indications across same or different therapeutic areas

Biologics Reviewed by CADTH's CDR- Listing Recommendations

- As of May 2014, there have been 64 CDEC recommendations issued for biologics:
  - 27 Do Not List recommendations,
  - 8 List in a similar manner recommendations, and
  - 29 List with clinical criteria and/or conditions recommendations

Subsequent Entry Biologics (SEBs)

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Biologics with SEBs in Development

Table 4: Biologics with SEBs in Development-		
Drug (Brand Name)	Global Sales in 2012 (US$ billions)	# SEBs in Development
Adalimumab (Humira)	$8.4	13
Etanercept (Enbrel)	$7.5	21
Infliximab (Remicade)	$7.3	9
Insulin Glargine (Lantus)	$6.6	5
Rituximab (Rituxan/MabThera)	$6.0	30
Bevacizumab (Avastin)	$5.4	14
Trastuzumab (Herceptin)	$5.0	24
Pegfilgrastim (Neulasta)	$4.3	14
Ranibizumab (Lucentis)	$4.1	2
Epoetin Alfa (Epogen/Procrit)	$3.7	69
Darbepoetin Alfa (Aranesp)	$3.0	4
Filgrastim (Neupogen)	$1.4	52

As cited in Ndegwa S, Quansah K. Subsequent Entry Biologics — Emerging Trends in Regulatory and Health Technology Assessment Frameworks [Environmental Scan, Issue 43, ES0284]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014. http://www.cadth.ca/en/products/environmental-scanning/environmental-scans/environmental-scan-43

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SEBs Pipeline

Reference Drug (Brand Name)	Patent Expiry	SEB (Manufacturer)	Disease/ Indication	Current Status
SEBs in Clinical Development				
Rituximab (Rituxan/ MabThera)	2020 (CAN) 2013 (EU) 2016 (US)	BI 695500 (Boehringer Ingelheim)	Rheumatoid arthritis	Phase III
		BI 695500 (Boehringer Ingelheim)	Non-Hodgkin's lymphoma	Phase III
		SAIT-101 (Samsung)	Rheumatoid arthritis	Phase III
		MK-8808 (Merck)	Follicular lymphoma	Phase III
		GP 2013 (Sandoz)	Follicular lymphoma	Phase III
		GP 2013 (Sandoz)	Rheumatoid arthritis	Phase II
		BCD-020 (CJSC Biocad)	Rheumatoid arthritis	Phase III
		PF-05280586 (Pfizer)	Rheumatoid arthritis	Phase II
Trastuzumab (Herceptin)	2021 (CAN) 2015 (EU) 2019 (US)	ABP-980 (Amgen)	Breast cancer	Phase III
		CT P06 (CT-P6) (Celltrion/ Hospira)	Breast cancer Gastric cancer	Phase III
		BCD-022 (CJSC Biocad)	Breast cancer	Phase III

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SEBs Pipeline- Continued

Reference Drug (Brand Name)	Patent Expiry	SEB (Manufacturer)	Disease/ Indication	Current Status
SEBs in Clinical Development				
Bevacizumab (Avastin)	2018 (CAN) 2022 (EU) 2019 (US)	BI 695502 (Boehringer Ingelheim)	Cancer	Phase I
		BCD-021 (CJSC Biocad)	Lung cancer	Phase III
Etanercept (Enbrel)	2023 (CAN) 2015 (EU) 2028 (US)	SB4 (Samsung Bioepis)	Rheumatoid arthritis	Phase III
		GP 2015 (Sandoz)	Plaque psoriasis	Phase III
Infliximab (Remicade)	2017 (CAN) 2015 (EU) 2018 (US)	BOW-015 (Epirus)	Rheumatoid arthritis	Phase III
		SB2 (Samsung Bioepis)	Rheumatoid arthritis	Phase III
Adalimumab (Humira)	2017 (CAN) 2018 (EU) 2016 (US)	ABP 501 (Amgen)	Plaque psoriasis	Phase III
		ABP 501 (Amgen)	Rheumatoid arthritis	Phase III

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Why are SEBs reviewed by CDR?

- The CDR-participating drug plans have requested that SEBs should undergo review through the CDR process for the following reasons:
  - SEBs are not generic versions of the reference product
  - Avoids duplication of reviews by multiple drug plans
  - Cost and cost-effectiveness of SEBs are not reviewed by Health Canada
  - Some uncertainty may exist regarding issues related to extrapolation

CDR Experience with SEBs

10/2009: CADTH initiated a pilot program for SEBs

- Determine CDR requirements for SEB submissions; establish the evaluative framework; and gain an increased understanding of regulatory approach to assessing SEBs.

12/2009: Only CDR SEB submission reviewed

- Omnitrope (recombinant human growth hormone)

2013: CADTH environmental scan on SEBs

- Large increase in the number of SEBs in Canada is expected in the next few years

2013: CADTH initiated consultations on SEBs

- Need to establish a clear process and procedure for submitting and reviewing SEBs

Steps in developing a CDR process for SEBs

9/2013: CADTH engaged stakeholders on SEBs

- Single vs. separate submissions for each indication
- Use of a tailored-review approach CDR
- Critical elements to be included in a CDR submission
- Use of cost-comparison approach for most reviews
- issue of interchangeability and substitutability of SEBs

10/2013 to 02/2014: CADTH approach for SEBs finalized

- Consultation with CDR-participating drug plans, Health Canada, and CDEC

03/2014: CADTH SEB guidance published

- CDR submission guidelines and procedure for SEB submissions is posted on the CADTH website

Challenges with SEBs (CDR Perspective)

- An SEB relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference biologic and which influences the amount and type of original data required.
  - Reduced clinical data package can be acceptable for NOC.
  - Indications can be granted based on extrapolated data.
  - RCT evidence is minimal or absent for many indications.
  - Lack of robust evidence to assess comparative efficacy, safety, and cost-effectiveness using traditional HTA approaches.
- CADTH anticipates submissions for multiple SEBs of the same reference biologic
- Stakeholders expect CADTH to comment on issues of interchangeability and substitutability that are keys issues at the decision making level

Why a Tailored-review Approach?

- CDR will review SEBs using a tailored-review approach
  - **Tailored Review:** review template will be completed jointly by the applicant and the CDR review team

- Advantages of the tailored-review approach
  - Offers the most efficient use of CDR resources without compromising quality
  - Template created to address the unique aspects SEBs
    - Justification for the reduced clinical data package
    - Rationale and regulatory opinion regarding extrapolation

CDR Submission Requirements for SEBs

- In addition to the completed “tailored review” template, applicants will also be required to submit all necessary requirements
  - Includes additional sections of the CTD that are not currently required for other CDR reviews.
- Cost comparison
  - Table and explanatory text providing the cost differential between the SEB compared with the reference product
- Re-evaluate process after the first few submissions
  - Not a pilot project, but we will continuously seek feedback to make sure the template is effective and the requirements are sufficient

CDEC Recommendations for SEBs will be based On:

- Patient and public perspectives on the impact of the drug
- Safety, Efficacy and Effectiveness of the drug compared to alternatives
- Therapeutic advantages relative to current accepted therapy
- Cost and cost-effectiveness relative to current accepted therapy

Patient Group Input for SEBs

- Development of Patient Group Input Template for SEB submissions informed by:
  - CADTH - Patient Community Liaison Forum (PLF)
- Modified Template
  - Some information about SEB and Reference Product
  - Section specific to inputs for use by drug plans
- Next Steps
  - Open consultation (all stakeholders) – May 2014
  - Template finalised based on feedback – June 2014

25 years of supporting informed decisions.

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