

BIOSIMILAR ACCESS

The Future of Value Assessment

Workshop

For Distribution to ISPOR Europe Attendees
November 07, 2011

Cyrus A. Chowdhury – Vice President and Practice Leader, Global Market Access – Insight Strategy Advisors
Corinna Sorenson – Research Fellow in European Health Policy – London School of Economics
Monica Martin de Bustamante – Principal, Global Market Access – Insight Strategy Advisors

Today's workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

17:15 – 17:25

Introduction & Objectives

1. Introduction
2. Meeting Objectives

17:25 – 17:40

Biosimilar Situation Analysis

1. Biosimilar Definitions
2. Biosimilar Competitive Landscape

17:40 – 18:00

Potential HTA Repercussions

1. HTA Landscape
2. Current Biosimilar Management Examples
3. HTA Biosimilar Evaluation Criteria

18:00 – 18:15

Discussion and Questions

1. Discussion
2. Questions

The objective of this workshop is to explore the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

OVERALL OBJECTIVE

To explore the **need for HTA for biosimilars / biobetters**, and the various considerations for **establishing value of these agents**

WORKSHOP GOALS

- ✓ To better **understand the current** global development and regulatory **landscape** for biosimilars
- ✓ To explore the **policies** that have been drafted for biosimilars and the hypothesise about **future market dynamics**
- ✓ To **evaluate** the likely evaluation criteria HTAs will use to assess biosimilars

Historically, the implementation of HTA in a given market has been viewed negatively, but cost-containment is not the only role these organisations have.

**HTA ORGANISATIONS
ROLE AND RESPONSIBILITIES**



GBR

In GBR, NICE assesses a product's additional value based on the incremental QALYs gained and adjusted through the incremental costs incurred



FRA

In FRA, the HAS evaluates a product's clinical efficacy in order to help define how much the government wishes to pay

Although cost-containment is an outlined goal for HTA organisations, providing the **best product for the least amount of money** is ultimately the aspiration

BIOSIMILARS



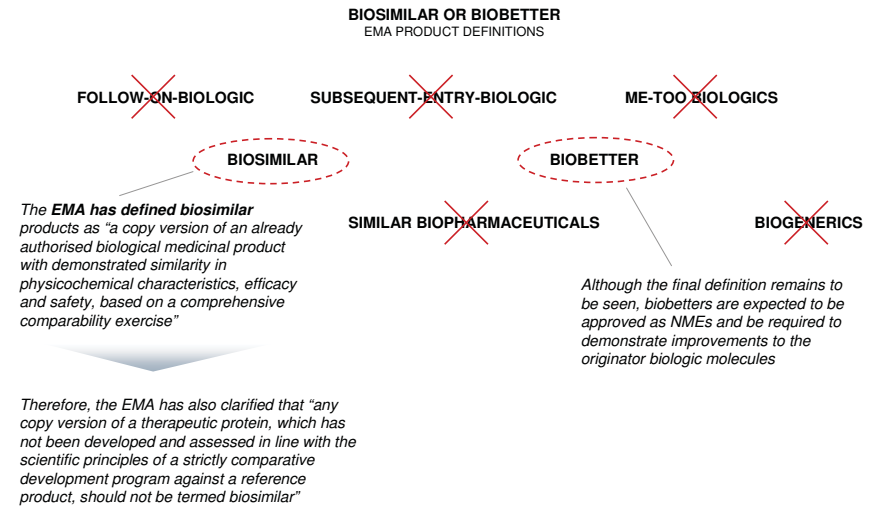
BIOLOGICS

Biosimilars are **not expected to be exact replicas of biologics** due to the complex manufacturing processes, therefore, **should they not be fully evaluated through an HTA process?**

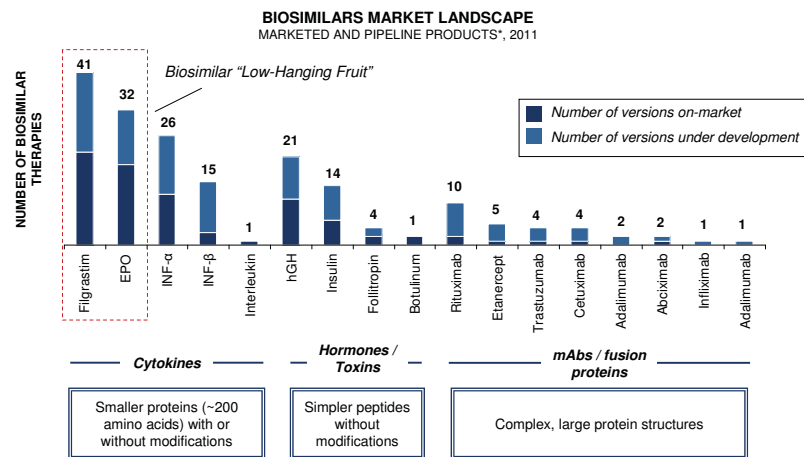
Today's workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

<p>17:15 – 17:25</p> <p>Introduction & Objectives</p> <ol style="list-style-type: none"> 1. Introduction 2. Meeting Objectives 	<p>17:25 – 17:40</p> <p>Biosimilar Situation Analysis</p> <ol style="list-style-type: none"> 1. Biosimilar Definitions 2. Biosimilar Competitive Landscape 	<p>17:40 – 18:00</p> <p>Potential HTA Repercussions</p> <ol style="list-style-type: none"> 1. HTA Landscape 2. Current Biosimilar Management Examples 3. HTA Biosimilar Evaluation Criteria 	<p>18:00 – 18:15</p> <p>Discussion and Questions</p> <ol style="list-style-type: none"> 1. Discussion 2. Questions
--	--	--	--

Many terms have been used to define the entry of non-innovative versions of biologics, but slowly definitions for 'biosimilars' versus 'biobetters' are emerging.

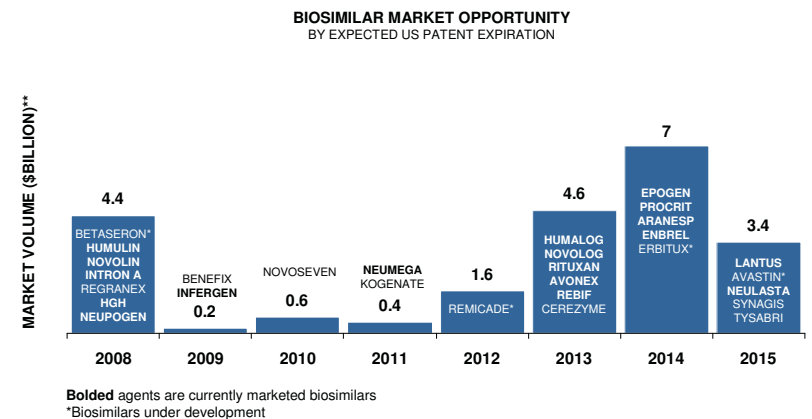


Two agents stand out as having been the most extensively commercialised to date, likely due to their relatively simple structure and date of patent expiry.



The EPO and filgrastim markets are becoming saturated with biosimilar competitors, at least in developed markets

The likelihood of a biosimilar having been developed and marketed correlates strongly with its date of patent expiration in the US / EU.



Most biologics coming off US patent by 2015 are already marketed or under development; with the exception of certain agents with less favourable safety profiles (e.g. TYSABRI)

Key influencing factors for biosimilar development in developed markets include date of patent expiry as well as potential market size.

CURRENTLY MARKET BIOSIMILARS
COMMON CHARACTERISTICS

	somatropin	insulin	epoetin alpha	filgrastim	interferon	rituximab	etanercept
MARKET-SPECIFIC PATENT EXPIRY	✓	✓	✓	✓	✓	~2013	~2014
POTENTIAL MARKET SIZE*	✓	✓	✓	✓	✓	~\$6 billion USD	~\$7 billion USD
MARKET-SPECIFIC LACK OF IP ENFORCEMENT	N/A	N/A	N/A	✗ - US N/A - RoW	✓ (IRN only)	✓ (IND only)	✓ (CHN only)
RELATIVE MOLECULAR SIMPLICITY	✓ (hormone)	✓ (hormone)	✓ (hormone)	✓ (cytokine)	✓ (cytokine)	✗ (mAb)	✗ (fusion protein)
FAVORABLE SAFETY PROFILE	✓	✓	✓	✓	✗	✗	✗
CURRENT MARKETS	EU, ASEAN, MENA, CAN, US, JPN, AUS	EU, ASEAN, MENA, CAN, US	EU, ASEAN, MENA, JPN	EU, ASEAN, MENA, AUS	IRN	IND	CHN

Source: ISA Proprietary Research



*worldwide sales for reference brand in USD, most recent year available; Source: medtrack.com

India is the country with the largest number of biosimilar MFGs, likely due in part to the relaxed IP environment and the lower cost of manufacturing in this country.

BIOSIMILAR MFGs OF INTEREST



Source: ISA Proprietary Research

Potential future market leader biosimilar MFGs vary in their revenue stream diversification and consequently in their choices of agents for development.

BIOSIMILAR PIPELINE LEADERS
BY DEVELOPMENT STRATEGY

	HQ	PIPELINE BIOSIMILAR PRODUCTS	STRATEGY
CELLTRION	KOR	infliximab, trastuzumab, rituximab, cetuximab, bevacizumab, palivizumab	mAb focus: development and manufacturing of products
biopartners	CHE	IFN-alpha2A, etanercept	Biosimilar focus: innovative formulations and novel delivery systems
Biocon	IND	Undisclosed mAbs	Biosimilar, API, and innovative products: development, contract manufacturing, licensing, R&D, commercialization
INTAS	IND	12 undisclosed biosimilar development programs	Broad focus: manufacture of biosimilars, API and animal health products, medical devices and novel delivery technology

As more mAb biosimilars enter the market, these companies are likely to pose a threat to the current market leaders in terms of revenue-generating potential

Source: ISA Proprietary Research



Relatively few MFGs are currently developing mAb biosimilars, potentially making this class a more attractive target than simpler biosimilar molecules.

SUMMARY

- **Epoetin alpha** and **filgrastim** are the innovator agents with the largest number of biosimilars already on-market, a space which is fast becoming saturated with competitors
- Most biologics with US patents expiring by 2015 have already been targeted by biosimilar MFGs for development programs
- Factors influencing the decision to develop a biosimilar compound include:
 - Patent Expiry in developed markets
 - Annual worldwide revenues of >\$1 billion US for the reference compound
 - Lack of IP enforcement in emerging markets
 - Relative molecular simplicity to maximize manufacturing ease and minimize preparation heterogeneity and immunogenicity
 - Favourable safety profile
- **Generic MFGs** (SANDOZ, TEVA, HOSPIRA) are the current key players in the biosimilar market, and are attempting to secure this position by the development or acquisition of in-house biologic manufacturing capabilities
- **Big Pharma** has been relatively slow to enter the biosimilar space, with only MERCK and PFIZER having made significant acquisitions or licensing deals with biotech or generic MFGs
- **Biotech / specialty firms** (CELLTRION, CIMAB) with especially robust pipelines may be increasingly manufacturing subclasses of biosimilars only (e.g. mAbs) or developing biosimilars as part of a broad spectrum of products (INTAS)



Today's workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

17:15 – 17:25

Introduction & Objectives

1. Introduction
2. Meeting Objectives

17:25 – 17:40

Biosimilar Situation Analysis

1. Biosimilar Definitions
2. Biosimilar Competitive Landscape

17:40 – 18:00

Potential HTA Repercussions

1. HTA Landscape
2. Current Biosimilar Management Examples
3. HTA Biosimilar Evaluation Criteria

18:00 – 18:15

Discussion and Questions

1. Discussion
2. Questions

Although the HTA landscape is continuously evolving, new organisations are consistently developing, Europe remains where the majority of HTAs are located.

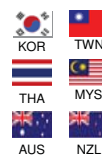
HTA DEVELOPMENT GLOBAL ADOPTION LANDSCAPE

EUROPE

Although many European markets currently have HTA systems in place, some like **ESP and ITA** only use the evaluations at the **sub-national level and for select therapeutic areas**



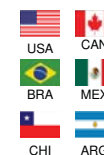
ASIA



AFRICA & MIDDLE EAST



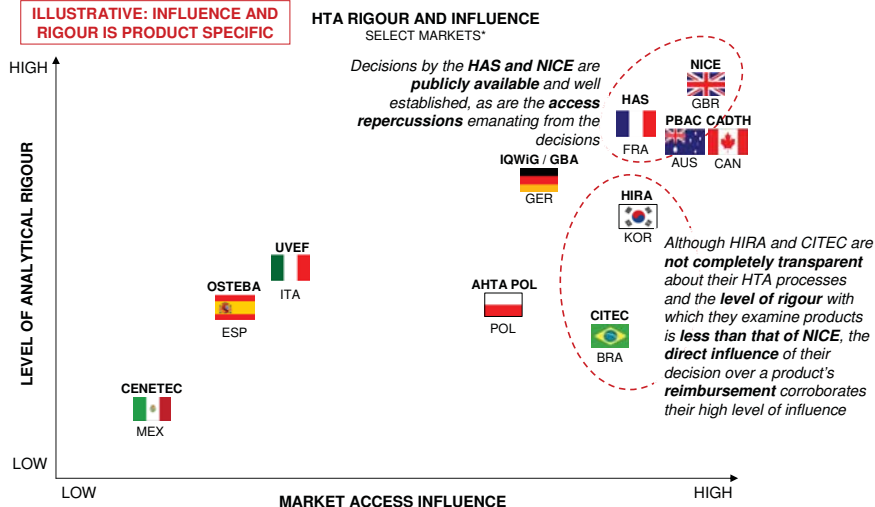
AMERICAS



HTA throughout **Asia and the Americas** is in its **beginning stages**, but some **advanced organisations like HIRA and CADTH** currently exist

However, the threat of HTA is not equivalent for each market where an organisation has been established, as some organisations do not influence access decisions.

ILLUSTRATIVE: INFLUENCE AND RIGOUR IS PRODUCT SPECIFIC



* Markets selected represent a sampling of global HTA organisations and are not comprehensive

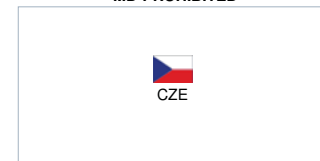
Most large European markets have moved in the direction of limiting automatic substitution for biosimilars.

- High **molecular complexity** and **micro-heterogeneity**
- Sensitive to **manufacturing process changes**, including the choice of the **cell type**, along with **production, purification and formulation** processes
- **No two biotech medicines can be exactly the same**
- Many believe that **substitution should be ruled out for reasons of patient safety**

AUTOMATIC SUBSTITUTION UNALLOWED



AUTOMATIC SUBSTITUTION MD-PROHIBITED



AUTOMATIC SUBSTITUTION ALLOWED W/ LIMITS

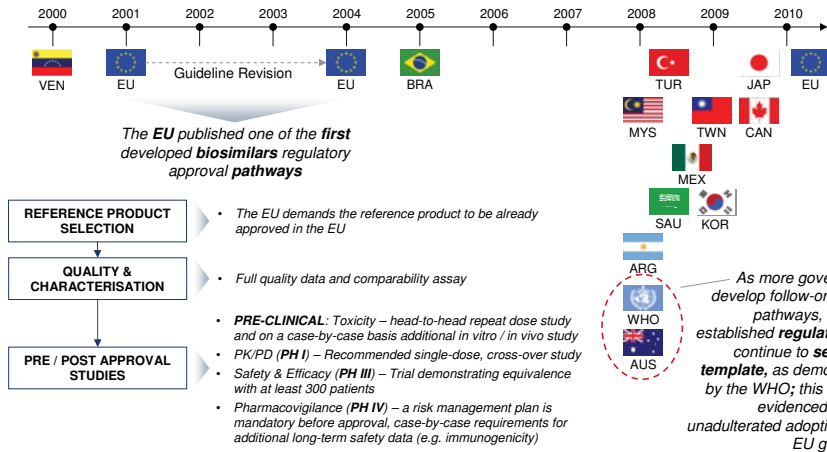


BRAND-PRESCRIPTION ONLY ALLOWED



The EU has led the creation of biosimilar legislation approvals, which many markets have looked to in the creation of their guidance.

BIOSIMILAR MARKET AUTHORIZATION
GLOBAL ADOPTION LANDSCAPE



Source: ISA Proprietary Research

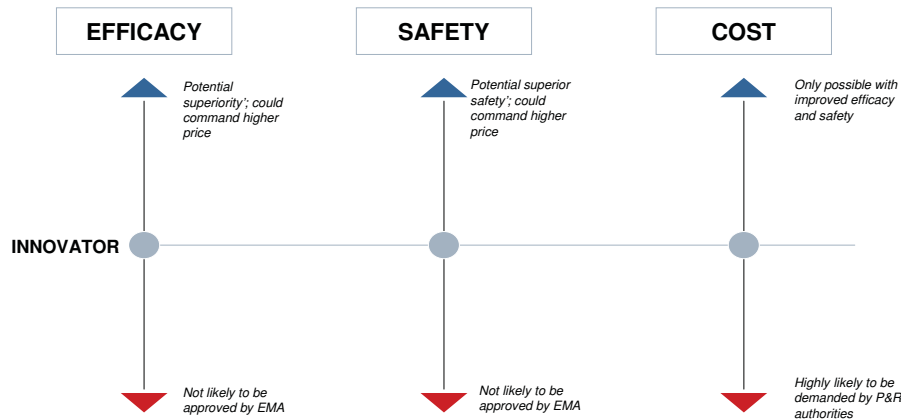
Phase III trials can be either non-inferiority trials or equivalence trials, however the result can directly impact future HTA assessment.

PHIII TRIAL DESIGN
NON-INFERIORITY vs EQUIVALENCE

	EMA ACCEPTED TRIAL DESIGN	MAY DEMONSTRATE SUPERIORITY	SMALLER PATIENT POPULATION
NON-INFERIORITY			
EQUIVALENCE			

Although the ability to demonstrate superiority exists in a "non-inferiority" trial, the EMA has specified that only the lower bound of the confidence interval will be considered for this trial design, indicating that superiority claims will likely not be accepted for biosimilars

Pending trial outcomes, a biosimilar can achieve any of a variety of efficacy, safety, and cost outcomes.



ERBITUX has achieved positive recommendations from both NICE and SMC for mCRC and HN, but only with radiotherapy.

	mCRC	HN + RADIOTHERAPY	HN + PT
NHS (National Institute for Health and Clinical Excellence)			
NHS SCOTLAND			

HERCEPTIN achieved a positive recommendation from NICE for its BC and mGC patient populations, while the SMC has been less generous.



	BC – EARLY	BC – ADVANCED – COMBINATION	BC – ADVANCED – MONOTHERAPY	mGC
NHS	Green	Green	Green	Green
NHS SCOTLAND	Green	Red	Red	Red

ERBITUX's current access seems to indicate many cost-based opportunities for biosimilars.



£121,367 ICER; pricing likely to play a role

	mCRC			HN + RADIOTHERAPY			HN + PT		
	EFFICACY	SAFETY	COST	EFFICACY	SAFETY	COST	EFFICACY	SAFETY	COST
NHS	Green	Green	Green	Green	Green	Green	Red	Red	Red
NHS SCOTLAND	Green	Green	Green	Green	Green	Green	Red	Red	Red

Patient Assistance Scheme was implemented to promote approval (under mCRC COST for NHS and NHS SCOTLAND)
Never submitted by manufacturer (under HN + PT for NHS and NHS SCOTLAND)

■ Currently Financed / Biosimilar Opportunity for Differentiation
■ Currently Unfinanced / Biosimilar Opportunity for Differentiation
■ Currently Financed / Low Biosimilar Opportunity for Differentiation
■ Currently Unfinanced / Low Biosimilar Opportunity for Differentiation

HERCEPTIN, however, has both cost and safety opportunities, particularly for the originator's cardiotoxicity profile.



Cardiotoxicity could pose potential advantages against HERCEPTIN

	BC – EARLY			BC – ADVANCED – COMBINATION			BC – ADVANCED – MONOTHERAPY			mGC		
	EFFICACY	SAFETY	COST	EFFICACY	SAFETY	COST	EFFICACY	SAFETY	COST	EFFICACY	SAFETY	COST
NHS	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
NHS SCOTLAND	Green	Green	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red

£16k ICER is already low; discounted option may have limited returns (under BC – EARLY COST for NHS and NHS SCOTLAND)
Rejection due to choice of comparator (under mGC for NHS and NHS SCOTLAND)

■ Currently Financed / Biosimilar Opportunity for Differentiation
■ Currently Unfinanced / Biosimilar Opportunity for Differentiation
■ Currently Financed / Low Biosimilar Opportunity for Differentiation
■ Currently Unfinanced / Low Biosimilar Opportunity for Differentiation

Currently, biosimilars are unlikely to be automatically substituted, but will need evaluation processes to understand which new agents should be financed.

SUMMARY

- Most major European governments have indicated that biosimilars cannot be directly substitutable for originator molecules, thus prompting the need for evaluation of biosimilars
- Current opportunities for biosimilars to demonstrate value for money include cost, safety, and new patient population arguments
- Cost-based arguments will be the easiest to uphold
- Superior safety may not be possible to demonstrate due to non-inferiority trial designs

Today's workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

17:15 – 17:25

Introduction & Objectives

1. Introduction
2. Meeting Objectives

17:25 – 17:40

Biosimilar Situation Analysis

1. Biosimilar Definitions
2. Biosimilar Competitive Landscape

17:40 – 18:00

Potential HTA Repercussions

1. HTA Landscape
2. Current Biosimilar Management Examples
3. HTA Biosimilar Evaluation Criteria

18:00 – 18:15

Discussion and Questions

1. Discussion
2. Questions

If you would like a copy of these slides, please contact us.

Cyrus A. Chowdhury

Vice President and Practice Leader,
Global Market Access
Insight Strategy Advisors

- o +1 212 702 4690 (NYC)
- o +41 225 331 276 (GVA)
- m +1 347 221 9536

e cyrus.chowdhury@insightstrat.com

Monica Martin de Bustamante

Principal, Global Market Access
Insight Strategy Advisors

- o +1 212 702 4693 (NYC)
- o +41 225 331 275 (GVA)
- m +1 650 823 9568

e monica.bustamante@insightrat.com