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

**Overview**

**Overall Objective**

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

**Workshop Objectives**

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.

**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 hypothesise about future market dynamics.
- To evaluate the likely evaluation criteria HTAs will use to assess biosimilars.

**HTA Organisations**

**Role and Responsibilities**

- In GBR, NICE assesses a product’s additional value based on the incremental QALYs gained and adjusted through the incremental costs incurred.
- In FRA, the HAS evaluates a product’s clinical efficacy in order to help define how much the government wishes to pay.

**Background**

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**

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?

Source: ISA Proprietary Research
Today’s workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

**Agenda**

**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

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

**Biosimilar Competitive Landscape**

- **BIOSIMILAR OR BIOBETTER**
- **EMA PRODUCT DEFINITIONS**
  - BIOSIMILAR
  - BIOBETTER
  - FOLLOW-ON BIOLOGIC
  - SUBSEQUENT ENTRY BIOLOGIC

The EMA has defined biosimilar products as ‘a copy version of an already authorised biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise’

Therefore, the EMA has also clarified that ‘any copy version of a therapeutic protein, which has not been developed and assessed in line with the scientific principles of a strictly comparative development program against a reference product, should not be termed biosimilar’

Although the final definition remains to be seen, biobetters are expected to be approved as NMEs and be required to demonstrate improvements to the originator biologic molecules.

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.

**Biosimilars Market Landscape**

- MARKETED AND PIPELINE PRODUCTS, 2011

<table>
<thead>
<tr>
<th>Number of versions on-market</th>
<th>Number of versions under development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar “Low-Hanging Fruit”</td>
<td></td>
</tr>
</tbody>
</table>

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.

**Biosimilar Market Opportunity by Expected US Patent Expiration**

*Bolded agents are currently marketed biosimilars
*Biosimilars under development

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**

<table>
<thead>
<tr>
<th>COMMON CHARACTERISTICS</th>
<th>somatropin</th>
<th>insulin</th>
<th>epoetin alpha</th>
<th>filgrastim</th>
<th>interferon</th>
<th>rituximab</th>
<th>etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARKET- SPECIFIC PATENT EXPIRY</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>POTENTIAL MARKET SIZE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>MARKET-SPECIFIC LACK OF IP ENFORCEMENT</td>
<td>N/A</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>RELATIVE MOLECULAR SIMPLICITY</td>
<td>(hormone)</td>
<td>(hormone)</td>
<td>(cytokine)</td>
<td>(cytokine)</td>
<td>(mAb)</td>
<td>(fusion protein)</td>
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<tr>
<td>FAVORABLE SAFETY PROFILE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

**CURRENT MARKETS**

| EU, ASEAN, MENA, CAN, US | EU, ASEAN, MENA, JPN | EU, ASEAN, MENA, AUS | IPN | IND | CHN |

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**

<table>
<thead>
<tr>
<th>HQ</th>
<th>PIPELINE BIOSIMILAR PRODUCTS</th>
<th>STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELLTRON</td>
<td>infliximab, trastuzumab, rituximab, cetuximab, bevacizumab, palivizumab</td>
<td>mAb focus: development and manufacturing of products</td>
</tr>
<tr>
<td>biopartners</td>
<td>INF- alpha2A, etanercept</td>
<td>Biosimilar focus: Innovative formulations and novel delivery systems</td>
</tr>
<tr>
<td>Biocon</td>
<td>Undisclosed mAbs</td>
<td>Biosimilar, API, and innovative products: development, contract manufacturing, licensing, R&amp;D, commercialization</td>
</tr>
<tr>
<td>INTAS</td>
<td>Undisclosed biosimilar development programs</td>
<td>Broad focus: manufacture of biosimilars, API and animal health products, medical devices and novel delivery technology</td>
</tr>
</tbody>
</table>

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.

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**

| NORTH AMERICA | APTOPEX, BIOTECHNOLOGIES, BISTROPHARMACOTHERAPIES CANADA, CELL THERAPEUTICS, KRONOS BIOTECH | HOSPIRA, JOER BIOPHARMA, MEDECA, MOMENAT PHARMA, MYLAN, PFIZER, SINENSIS, SORIN, ZERIES, IHS, JANDER, BIER INDIAN 
| ASIA | ASIA, BIOLOGICS, BIOTECH, CYPRIOT, GETZ PHARMA, HIKMA, Israel group, KNO BIOLOGICS, INNOGENE, JCPHARMA, LG life SCIENCES, MBCI, AMERICAN BIOTECH, PROTEKAW, SANDERS, SUGEN, HANGZHOU CELEGEN, SHANGHAI GUOJIAN |
| LATAM | AMBI, TEVA, CINNAFARM, HAMAM, LAMARE | MEX, CN, US, MENA, JPN |

Summary

- 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.
- 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.
- Key influencing factors for biosimilar development in developed markets include date of patent expiry as well as potential market size.
- Potential future market leader biosimilar MFGs vary in their revenue stream diversification and consequently in their choices of agents for development.
- Increasing influence on development decision: potential size, safety profile, patent expiry, market and competitive landscape, regulatory environment.
- Relative few MFGs are currently developing mAb biosimilars, potentially making this class a more attractive target than simpler biosimilar molecules.

Source: ISA Proprietary Research
Today’s workshop will focus on exploring the need for HTA for biosimilars / biobetters, and the various considerations for establishing value of these agents.

**HTA Development Landscape**

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

**HTA RIGOUR AND INFLUENCE**

*SELECT MARKETS*

Decisions by the HAS and NICE are publicly available and well established, as are the access repercussions emanating from the decisions.

**LEVEL OF ANALYTICAL RIGOUR**

- HIGH
- LOW

**MARKET ACCESS INFLUENCE**

- HIGH
- LOW

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

- 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

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

**Automatic Substitution**

**Unallowed**

- FRA
- GER
- ITA
- ESP

**Allowed with Limits**

- FIN
- DNK
- HUN
- NOR

**MD-Prohibited**

- CZE

- AUT

**Biosimilar Substitution**

**HTA RIGOUR IS PRODUCT SPECIFIC**

Although HIRA and CITEC are not completely transparent about their HTA processes and the level of rigour with which they examine products is less than that of NICE, the direct influence of their decision over a product's reimbursement corroborates their high level of influence.

**Illustrative: Influence and Rigour is Product Specific**

**International HTA and Influence**

*Markets selected represent a sampling of global HTA organisations and are not comprehensive*
The EU has led the creation of biosimilar legislation approvals, which many markets have looked to in the creation of their guidance.

**Biosimilar Approval Pathways**

### Global Adoption Landscape

<table>
<thead>
<tr>
<th>Year</th>
<th>EU</th>
<th>BU</th>
<th>JAP</th>
<th>AU</th>
<th>Canada</th>
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<th>WHO</th>
<th>MYS</th>
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The EU published one of the first developed biosimilars regulatory approval pathways.

#### Reference Product Selection
- The EU demands the reference product to be already approved in the EU.

#### Quality & Characterisation
- Full quality data and comparability assay
- **Pre-Clinical:** Toxicity – head-to-head repeat dose study and on a case-by-case basis additional in vitro / in vivo study
- **PK/PD (PH I):** Recommended single-dose, cross-over study
- **Safety & Efficacy (PH II):** Trial demonstrating equivalence with at least 300 patients
- Pharmacovigilance (PH IV): a risk management plan is mandatory before approval, case-by-case requirements for additional long-term safety data (e.g. immunogenicity)

#### Pre / Post Approval Studies
- As more governments develop follow-on biologic pathways, the EU’s established regulations will continue to serve as a template, as demonstrated by the WHO; this is further evidenced by AUS’ unadulterated adoption of the EU guidelines.

### Efficacy

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Safety</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Innovator</strong></td>
<td>Not likely to be approved by EMA</td>
<td>Not likely to be approved by EMA</td>
</tr>
</tbody>
</table>

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

### PHIII Trial Design

- **Non-Inferiority vs Equivalence**

- **EMA Accepted Trial Design**
- **May Demonstrate Superiority**
- **Smaller Patient Population**

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.

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

**Biosimilar Opportunity**

ERBITUX has achieved positive recommendations from both NICE and SMC for mCRC and HN, but only with radiotherapy.
HERCEPTIN achieved a positive recommendation from NICE for its BC and mGC patient populations, while the SMC has been less generous.

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

**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.
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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.

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