Biosimilar market in context

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Roche: New growth opportunities

NMEs

- Alecensa
- Cotellic
- Venclexta

2015
- ocrelizumab
- lebrikizumab

2016
- Tecentriq
- lampalizumab

2017
- ACE910
- olesoxime

Post 2017
- gantenerumab
- crenezumab
- taselisib
- etrolizumab

Line extensions

- Herceptin + Perjeta
- Gazyva (GOYA)
- Gazyva (GALLIUM)

- Tecentriq + chemo

Category Legend:
- Orange: Oncology/hematology
- Light yellow: Neuroscience
- Light blue: Ophthalmology
- Dark blue: Immunology
Investigating tumor specific strategies

Size of bubble constitutes patient population

- Inflamed
- Non-inflamed

*TNBC mutation frequency is estimated
Strategies for long term growth

Anti-CD20 franchise

Protect. Replace. Extend.

Medical value

Rapidly and sustainably convert the market to SC

GALLIUM & await GOYA

Increase medical benefit with Venetoclax in NHL, CLL and expand into new diseases e.g. Multiple Myeloma

Venetoclax in collaboration with AbbVie; SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin’s lymphoma
Establishing Gazyva as new CD20 backbone

Pie chart shows 2014 Rituxan sales split according to indications; CLL=chronic lymphocytic leukemia; iNHL (FL)=indolent non-hodgkin's lymphoma; aNHL (DLBCL)=aggressive NHL; R/R=relapsed/refractory; Gazyva in collaboration with Biogen Idec
Biosimilars: Ten years in the making

Regulatory environment

Summary
Biosimilars: Ten years in the making

EU pioneered the BS concept
- Six products approved, including the first mAb BS (infliximab)
- Uptake did not achieve expected savings

WHO leading global efforts; many emerging countries implemented WHO BS Guidelines as a reference

US published final BS guideline
- FDA pathway operating

Differential adoption of WHO BS guidelines led to registration of Non-Comparable Biotherapeutic products (NCBs)*, driven by:
- Capacity issues at National Regulatory Agencies
- Local economic development policies

BS entry timelines delayed (incl. Herceptin & MabThera)

*For definition and industry position on NCBs please refer to IFPMA Policy Statement:
Current Biosimilar trends

MAT 1.7bn CHF (Mar 2016)
(CAGR 43.7 %)

*Excludes pegylated Biosimilars
Source: IMS Health. Based on Roche subscription of countries
Generics vs. Biosimilars

Clear divide in uptake; complex market drivers

Market share

- **Remicade**
- **Somatropin**
- **EPO**
- **Remicade (Norway)**
- **Filgrastim**
- **Diovan (Novartis)**
- **Zyprexa (Eli Lilly)**

**Driven by price and patient offering**
Efficacy visible only long(er) term

**Payer driven**
Efficacy visible immediately
High turnover of patients

**Small molecule**
Virtually disappear

Sources: IMS Health, IMS & Roche analysis

1 Volume market share based on EU5 average
2 Data based on % remaining sales in EU
Despite 10 years of experience in the EU, uptake of Biosimilars differ across countries

Payer environment is one of multiple drivers for Biosimilar uptake
Anti-TNF market is not a good analogue for oncology

Infliximab Biosimilar could expand beyond it’s accessible market and obtain market share from Enbrel® and Humira®

Biological products used to treat RA, IDB & Psoriasis

Other biologics

Roche
Small molecules and biologics

Not all the same

• Small molecule policies allow substitution → only the price counts

• For biologics, European Medicine Agency (EMA) do not provide guidance on interchangeability and substitution

• Most countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines
  – Biologics must be prescribed by brand name
  – Laws against substitution
  – Switching remains a physician decision
Biosimilar: 10 years in the making

Regulatory environment

Summary
Establishment of Biosimilar guidelines has increased driven by WHO efforts.
Requirements and study designs are different for the biosimilar vs. innovator

<table>
<thead>
<tr>
<th>Aspects of development</th>
<th>Biosimilar</th>
<th>Innovator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Sensitive and homogeneous (patients are <em>models</em>)</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Clinical design</strong></td>
<td>Comparative versus innovator, normally equivalence</td>
<td>Superiority vs standard of care (SoC*)</td>
</tr>
<tr>
<td><strong>Study endpoints</strong></td>
<td>Sensitive, clinically validated PD markers</td>
<td>Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Similar safety profile to innovator; no new findings</td>
<td>Acceptable benefit/risk profile versus SoC*</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Similar immunogenicity profile to innovator</td>
<td>Acceptable risk/benefit profile versus SoC*</td>
</tr>
<tr>
<td><strong>Extrapolation</strong></td>
<td>Possible if justified</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

* In some cases SoC may not exist
How should extrapolation risk be managed?  
*The regulator’s perspective*
How should extrapolation risk be managed?

*The physicians’ perspective*

I would like to see a phase III trial for each indication.
What is the right patient population to establish clinical similarity to Herceptin®?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Metastatic population (advanced)</th>
<th>Neoadjuvant/Adjuvant population (early)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK</td>
<td>✗ Affected by patients status &amp; tumor burden</td>
<td>✓ Homogeneous population can be selected</td>
</tr>
<tr>
<td>PD</td>
<td>✗ Clinically validated PD marker not available</td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy/safety</td>
<td>✗ • Difficult to select homogeneous group. • Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status…). • Population with heterogeneous characteristics affecting final clinical outcome.</td>
<td>✓ Populations less likely to be confounded by baseline characteristics and external factors</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>✗ Immune system affected by performance status and concomitant chemotherapies received</td>
<td>✓ Immune system impaired during chemotherapy cycles, but likely to recover to normal status thereafter</td>
</tr>
</tbody>
</table>
The regulatory thinking is evolving

The Herceptin® case

<table>
<thead>
<tr>
<th></th>
<th>mBC Phase III Start Date</th>
<th>Regulatory Filing</th>
<th>eBC Phase III Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celltrion</td>
<td>Q2 2010</td>
<td>X</td>
<td>Q1 2014</td>
</tr>
<tr>
<td>Mylan</td>
<td>Q4 2012</td>
<td>?</td>
<td>Q2 2014</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Q4 2013</td>
<td></td>
<td>Q2 2014</td>
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<td>Samsung</td>
<td>Q4 2013</td>
<td></td>
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<tr>
<td>Amgen</td>
<td></td>
<td></td>
<td>Q4 2013</td>
</tr>
</tbody>
</table>
Biosimilar: 10 years in the making

Regulatory environment

Summary
Generics, Biosimilars: Not all the same

• **Small molecules:** policies allow fast penetration of generics

• **Biosimilars:** countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines:
  
  – Biologics must be prescribed by brand name, laws against automatic substitution, switching remains a physician decision, EMA - no guidance on interchangeability
  
  – After 10 years of experience in the EU, uptake of Biosimilars differ heavily across countries

• **Regulatory environment:** still evolving with authorities in the process of finally establishing frameworks; case by case decisions likely
Doing now what patients need next