CURRENT STATUS AND FUTURE OUTLOOK FOR BIOSIMILARs

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Conflict of Interest Disclosure
Jos Kosterink, Pharm D, PhD

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• Contracted Research: Amgen, Genentech, Pfizer
Figures, Facts and Future Outlooks
Biosimilars

- Where are we talking about; biotech market
  - in general and especially in oncology
- Biosimilars: some definitions
- Biosimilars: development, authorization and regulations
- Interchangebility, substitution
- “The” biosimilar does not exist
- Economic implications and Drug selection
- In summary
Global spending 2014 US$ 1000 billion
Biotech approx. 20%
Table 7  Top-ten-selling biologic drugs of 2012

<table>
<thead>
<tr>
<th>Name</th>
<th>Lead company</th>
<th>Molecule type</th>
<th>Approved indication(s)</th>
<th>2012 (worldwide sales)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira (adalimumab)</td>
<td>AbbVie</td>
<td>mAb</td>
<td>Rheumatoid arthritis (RA), juvenile rheumatoid arthritis, Crohn’s disease, psoriatic arthritis (PA), psoriasis, ankylosing spondylitis, ulcerative colitis (UC), Behçet syndrome</td>
<td>9,266</td>
</tr>
<tr>
<td>Enbrel (etanercept)</td>
<td>Amgen</td>
<td>Protein</td>
<td>RA, psoriasis, ankylosing spondylitis, PA, juvenile rheumatoid arthritis</td>
<td>7,967</td>
</tr>
<tr>
<td>Remicade (infliximab)</td>
<td>J&amp;J</td>
<td>mAb</td>
<td>RA, Crohn’s disease, psoriasis, UC, ankylosing spondylitis, Behçet syndrome, PA</td>
<td>6,564</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Manufacturer</td>
<td>Type</td>
<td>Indications</td>
<td>Sales</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>Roche</td>
<td>mAb</td>
<td>Breast cancer, gastric cancer</td>
<td>6,188</td>
</tr>
<tr>
<td>Avastin (bevacizumab)</td>
<td>Roche</td>
<td>mAb</td>
<td>Colorectal cancer, non-small cell lung cancer, renal cell cancer, brain cancer (malignant glioma; anaplastic astrocytoma, glioblastoma multiforme)</td>
<td>6,059</td>
</tr>
<tr>
<td>Neulasta (pegfilgrastim)</td>
<td>Amgen</td>
<td>Protein</td>
<td>Neutropenia/leukopenia</td>
<td>4,092</td>
</tr>
<tr>
<td>Lucentis (ranibizumab)</td>
<td>Roche</td>
<td>mAb</td>
<td>Wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion</td>
<td>4,003</td>
</tr>
<tr>
<td>Avonex (interferon beta-1a)</td>
<td>Biogen IDEC</td>
<td>Protein</td>
<td>Multiple sclerosis</td>
<td>2,913</td>
</tr>
<tr>
<td>Rebif (interferon beta-1a)</td>
<td>Merck</td>
<td>Protein</td>
<td>Multiple sclerosis</td>
<td>2,408</td>
</tr>
</tbody>
</table>

mAb, monoclonal antibody. Source: BioMedTracker.
Figure 1  FDA new molecular entities and biological license approvals 1998–2013.
Total Care expenditures The Netherlands
bron CBS 2011, 2012 en 2013

- 2013: €94.2 billion
- 15.6% GDP
- Hospital care: €24.8 billion
- Drugs: €7 billion
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• Economic implications and Drug selection

• In summary
<table>
<thead>
<tr>
<th>Term(s)</th>
<th>Definition</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar</td>
<td>Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.</td>
<td></td>
</tr>
<tr>
<td>Second-generation (next-generation) biological/biologic</td>
<td>Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance.</td>
<td>Usually stand-alone developments with a full development program.</td>
</tr>
<tr>
<td>Biobetter</td>
<td></td>
<td>Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>From a regulatory perspective, a claim for 'better' would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.</td>
</tr>
</tbody>
</table>

*aComparable terms defined by the same/similar scientific principles include the WHO’s 'similar biotherapeutic products' and Health Canada’s (Toronto) 'subsequent-entry biologicals’*
# Currently Approved Biosimilars in Europe

<table>
<thead>
<tr>
<th>Class</th>
<th>Product</th>
<th>Brand Name</th>
<th>Active Substance (INN)</th>
<th>Authorisation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetins</td>
<td>HX575</td>
<td>Abseamed</td>
<td>epoetin alfa</td>
<td>28/08/2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Binocrit</td>
<td>epoetin alfa</td>
<td>28/08/2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epoetin alfa Hexal</td>
<td>epoetin alfa</td>
<td>28/08/2007</td>
</tr>
<tr>
<td></td>
<td>SB-309</td>
<td>Retacrit</td>
<td>epoetin zeta</td>
<td>18/12/2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Silapo</td>
<td>epoetin zeta</td>
<td>18/12/2007</td>
</tr>
<tr>
<td>Follicle Stimulating Hormones</td>
<td>XM17</td>
<td>Ovaleap</td>
<td>follitropin alfa</td>
<td>27/09/2013</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>bemfola</td>
<td>follitropin alfa</td>
<td>27/03/2014</td>
</tr>
<tr>
<td>Granulocyte-colony stimulating factor (G-CSF)</td>
<td>XM02</td>
<td>Biogranstim</td>
<td>filgrastim</td>
<td>15/09/2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ratiogranstim</td>
<td>filgrastim</td>
<td>15/09/2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tevagranstim</td>
<td>filgrastim</td>
<td>15/09/2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filgrastim ratiopharm</td>
<td>filgrastim</td>
<td>withdrawn</td>
</tr>
<tr>
<td></td>
<td>EP2006</td>
<td>Filgrastim Hexal</td>
<td>filgrastim</td>
<td>06/02/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zarzio</td>
<td>filgrastim</td>
<td>06/02/2009</td>
</tr>
<tr>
<td></td>
<td>PLD108</td>
<td>Nivestim</td>
<td>filgrastim</td>
<td>08/06/2010</td>
</tr>
<tr>
<td></td>
<td>Apo-filgrastim</td>
<td>Grastofil</td>
<td>filgrastim</td>
<td>18/10/2013</td>
</tr>
<tr>
<td>Human growth Hormone</td>
<td>NA</td>
<td>Omnitrope</td>
<td>somatropin</td>
<td>12/04/2006</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Valtropin</td>
<td>somatropin</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Infliximab</td>
<td>CT-P13</td>
<td>Inflectra</td>
<td>infliximab</td>
<td>10/09/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Remsima</td>
<td>infliximab</td>
<td>10/09/2013</td>
</tr>
</tbody>
</table>

INN, International non-proprietary name
Monoclonal Antibodies: Key Therapies for Several Diseases

• Cancers
• Hematologic diseases
• Autoimmune diseases
The Number of Therapeutic Monoclonal Antibodies Is Constantly Increasing

Number of therapeutic antibodies entering clinical study per year

# mAbs Approved in the US and EU for Cancer Management

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Format</th>
<th>Target</th>
<th>Therapy Area</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan (rituximab)</td>
<td>Chimeric IgG1</td>
<td>CD20</td>
<td>NHL, CLL</td>
<td>1997, 2010</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>Humanized IgG1</td>
<td>HER-2</td>
<td>Met breast cancer</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early breast cancer</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Met gastric cancer</td>
<td>2010</td>
</tr>
<tr>
<td>Mylotarg (gentuzumab ozogamicin)</td>
<td>Humanized IgG1</td>
<td>CD33</td>
<td>AML</td>
<td>2000</td>
</tr>
<tr>
<td>Campath (alemtuzumab)</td>
<td>Humanized IgG1</td>
<td>CD52</td>
<td>CML</td>
<td>2001</td>
</tr>
<tr>
<td>Zevalin (ibritumomab tiuxetan)</td>
<td>Mouse IgG1 conj to 90Y</td>
<td>CD20</td>
<td>NHL</td>
<td>2002</td>
</tr>
<tr>
<td>Bexxar (tositumumab)</td>
<td>Mouse IgG1 conj to 131I</td>
<td>CD20</td>
<td>NHL</td>
<td>2003</td>
</tr>
<tr>
<td>Avastin (bevacizumab)</td>
<td>Humanized IgG1</td>
<td>VEGF</td>
<td>mCRC, NSCLC</td>
<td>2004, 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRCC; GBM</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ovarian cancer (EU only)</td>
<td>2011</td>
</tr>
<tr>
<td>Erbitux (cetuximab)</td>
<td>Chimeric IgG1</td>
<td>EGFR</td>
<td>mCRC</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Head and neck cancer</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mCRC (first-line)</td>
<td>2012</td>
</tr>
<tr>
<td>Vectibix (panitumumab)</td>
<td>Human IgG2</td>
<td>EGFR</td>
<td>mCRC</td>
<td>2006</td>
</tr>
<tr>
<td>Arezera (ofatumumab)</td>
<td>Human IgG1</td>
<td>CD20</td>
<td>CLL</td>
<td>2009</td>
</tr>
<tr>
<td>Removab</td>
<td>Mouse/rat hybrid IgG</td>
<td>EpCAM X CD3</td>
<td>Malignant ascites (EU only)</td>
<td>2009</td>
</tr>
<tr>
<td>Yervoy (ipilimumab)</td>
<td>Human IgG1</td>
<td>CTLA-4</td>
<td>Metastatic melanoma</td>
<td>2011</td>
</tr>
<tr>
<td>Adcetris (brentuximab)</td>
<td>Chimeric IgG1</td>
<td>CD30</td>
<td>ALCL and HL</td>
<td>2011</td>
</tr>
<tr>
<td>Perjeta (pertuzumab)</td>
<td>Humanized IgG1</td>
<td>HER2</td>
<td>Metastatic breast cancer</td>
<td>2012</td>
</tr>
</tbody>
</table>

Biosimilars

• The patents for many first-generation antibodies will expire in the next few years, allowing for the creation of copy, or ‘biosimilar’ versions.

• Only copy versions that have been approved through a legal framework (eg, EMA) can be called ‘biosimilar’.

EMA, European Medicines Agency
Figures, Facts and Future Outlooks
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- Economic implications and Drug selection
- In summary
## Small Chemical Drugs vs Biologics

<table>
<thead>
<tr>
<th></th>
<th>Small Chemical Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Unstable</td>
</tr>
<tr>
<td><strong>Modification</strong></td>
<td>Well defined</td>
<td>Many options</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>• Predictable chemical process</td>
<td>• Unique line of living cells</td>
</tr>
<tr>
<td></td>
<td>• Identical copy can be made</td>
<td>• Impossible to ensure identical copy</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Easy to characterize fully</td>
<td>Difficult to characterize fully due to a mixture of related molecules</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Nonimmunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>
Monoclonal Antibodies Are More Complex Than ‘Simple’ Biologics

Small molecule drug

‘Simple’ biologics

‘Complex’ biologics
Manufacture of Biologic Drugs: Unique and Complex Process

Even if a biosimilar uses the same human gene as its innovator, it will differ in other parts of the process.

It is impossible to make an exact copy.
Post-translational Modifications May Impact Antibody Activity

Even Small Glycosylation Differences May Have Significant Effects on Immune Effector Functions

- Both amino acid sequence and glycosylation pattern of $C_H^2$ influence FcR binding and ADCC activity
- The presence or absence of one fucose residue can affect the biological activity (killing of target cells via ADCC)
- Even very small differences in fucosylation may have significant effects on in vitro ADCC
The process is the product

Each company has its own unique cell line, process and manufacturing platform

<table>
<thead>
<tr>
<th>Company</th>
<th>Expression system</th>
<th>Expressed molecule</th>
<th>Pro-Insulin (35 AA bridge)</th>
<th>Leader sequence</th>
<th>Other sequences as needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly &amp; Co</td>
<td>E. Coli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>S. Cerevisiae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Talk Inger Mollerup, Novo Nordisk A/S Joint EMEA/DIA Workshop on Biosimilars, Paris 2005
Processes are very different

And processes are very different!

Eli Lilly & Company: Unfolding and refolding
- Biomass
  - Cell harvesting
  - Cell disruption
- Inclusion Bodies
  - IB recovery
  - IB dissolution
- Trp-Leu-Met-Proinsulin
  - CNBr cleavage
- Proinsulin (unfolded)
  - Oxidative refolding
- Proinsulin S503
  - Folding, S-S bond formation
- Proinsulin (refolded)
  - Enzymatic conversion
- Human Insulin (crude)
  - Purification
- Purified Human Insulin

Novo Nordisk: Secreted with correct folding
- Biomass
  - Cell removal
- Clear broth with secreted insulin precursor
  - Capture process
- Purified insulin precursor
  - Enzymatic conversion
- Insulin ester
  - Purification
- Insulin ester
  - Hydrolysis
- Human Insulin (crude)
  - Purification
- Purified Human Insulin

Source: Talk Inger Mollerup, Novo Nordisk A/S Joint EMEA/DIA Workshop on Biosimilars, Paris 2005
EMA Guidelines

Similar biological medicinal products*

Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*

- Follicle-stimulating hormone
- Monoclonal antibodies
- Erythropoietins
- Interferon beta
- Interferon alpha*
- Granulocyte-colony stimulating factor
- Somatropin
- Human insulin and insulin analogues*
- Low-molecular-weight heparins*

Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues*

- Immunogenicity guidelines
  - Immunogenicity assessment of biotechnology-derived therapeutic proteins*
  - Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use
Development of a biosimilar

How much similarity do we need?

How much do we need to know?
A comprehensive set and combination of orthogonal analytical methods revealing structure-function relationships, delivering in depth comparability information and allowing extrapolation towards non-measured attributes.

From J. Goncalves; TOPRA meeting
Dossier Requirements for Biosimilars are Reduced

Stepwise comparability approach Q → NC → C

Source: Dr Falk Ehmann (EMA)
Development of a biosimilar

Step-wise approach is the key principle in biosimilar development

• Mainstay is an extensive physicochemical and biological characterisation:
  Form and function of the molecule
  – Same primary, secondary and tertiary structure
  – Comparable post-translational profile

• Pre-clinical tests
  – Extensive *in vitro* characterization of biological activity
  – *In vivo* only in case of remaining uncertainties based on physicochemical and biological characterization and *in vitro* studies and animal studies should add valuable information (=exceptional)
EMA Guidelines for Biosimilar Antibodies

• Preclinical: *in vitro* pharmacodynamic (PD) and pharmacokinetic (PK) studies; *in vivo* animal studies if necessary and when an appropriate model system exists
  – PD studies should include antigen binding, FcR and complement binding, and Fab and Fc activity

Clinical efficacy

- The aim of a biosimilar development programme is not to establish benefit of a treatment for the patient (this had been done before for the reference product!)

- The aim is to establish biosimilarity!

- This means:
  - The clinical study follows the idea that patients are „models“
  - The clinical study is selected to represent the most sensitive model to study differences
  - Thus, trial design might be (entirely) different from the normal guideline principles!
  - Scientifically not „abridged“, but rather „tailored“ development
EMA Guidelines for Biosimilar Antibodies

- **Clinical:** Comparative clinical studies between the biosimilar and reference antibody should always be conducted
  - **Human PK and PD:**
    - PK comparability in a sufficiently sensitive and homogenous population (healthy volunteers)
    - PD comparability studies if possible
  - **Efficacy:** If PD studies cannot convincingly show comparability, clinical efficacy should be demonstrated in adequately powered randomized comparative trials (double-blind, normal equivalence trials). The most sensitive patient population and clinical endpoint should be used in these studies.
    - Considerations for anticancer indications: demonstrate similar efficacy and safety, not patient benefit; primary endpoint that measures clinical activity (eg, ORR, pCR); survival data should be recorded and novel endpoints may be tested
  - **Safety:** At all steps of clinical evaluation, comparable safety (type, frequency, and severity of AEs) and immunogenicity should be demonstrated

Clinical safety

- Safety profile should be comparable
- Immunogenicity should specifically be studied
- Higher immunogenicity would question biosimilarity
- However, lower immunogenicity might be acceptable
Immunogenicity: The Key Issue for Protein Drugs

Factors Contributing to Immunity

- **Host related**
  - Genetic predisposition (major histocompatibility complex alleles)
  - Concomitant therapy (interferon)
  - Immunosuppression (cancer)
  - Activated immune system due to infection
  - Ethnic sensitivity
  - Prior treatments

- **Product related**
  - Structural properties
  - Glycosylation
  - Impurities
  - Formulation
  - Storage
  - Aggregates

- **Treatment related**
  - Route of administration
  - Dose
  - Length of treatment
Immune Reactions to Biologic Therapeutics May Lead to Altered Efficacy or SAEs


Draft agreed by Similar Biological Medicinal Products Working Party | October 2010
Adoption by CHMP for release for consultation | November 2010
End of consultation (deadline for comments) | May 2011
Final agreed by BMWP | March 2012
Adoption by CHMP | 24 May 2012
Date for coming into effect | 1 December 2012

“The immunogenicity of mAbs is complex and there are a number of often poorly understood factors which makes it difficult to predict with any certainty whether a therapeutic or diagnostic monoclonal antibody is likely to provoke a clinically relevant immune response”
Patient Population for Immunogenicity Testing

- The same therapeutic protein will induce different levels of immune response in different patient populations
- Immunogenicity testing should be done in the most sensitive patient population, ie, patients who are most likely to develop an immune reaction to treatment

Extrapolation of indications is a key aspect in the approval of biosimilars

- Additional data needed if:
  - Different receptors in different indications
  - Differences in immunogenicity
  - Differences in co-medication
  - Etc.
EMA Guidelines for Biosimilar Antibodies

- **Extrapolation**: Is possible if biosimilarity is confirmed in the comparability studies and the mechanism of action is known to be the same.
The Mode of Action of mAbs is complex and may involve Contributions from multiple Mechanisms

- Inhibition of Signal Transduction or Receptor Activation
  - Inhibition of Ligand Binding (Example: Cetuximab)
  - Induction of Receptor Internalization (Example: IGF-1R-Abs)
  - Inhibition of Receptor Dimerization (Example: Pertuzumab)
  - Inhibition of Receptor Shedding (Example: Trastuzumab)

The in-vivo net contribution of different modes of action described for one mAb is often incompletely understood and may also be different in different indications.
Pharmacovigilance and Traceability

• Post approval, biosimilars must undergo at least one year of post-marketing surveillance to detect incidence of immunogenicity and other adverse events

• This includes detailed risk management plans that should be followed by both physicians and pharmacists

• Because biosimilars are given the international nonproprietary name (INN) as the originator, additional information including brand name should be used when prescribing
Risk-Management Plan (RMP)

• Risk Management Plan of the biosimilar is required to guide PV activities (as for all biologics)

• Enhanced PV monitoring is important for biosimilars due to limited size of the pre-marketing clinical trial population

• Safety-related post-marketing commitments:
  – Safety in indications that are claimed on extrapolation
  – Rare and SAEs predicted based on pharmacology of reference product
  – Detection of new safety signals
  – Activities to obtain additional immunogenicity data (immunogenicity testing)
Where are we talking about; biotech market
- in general and especially in oncology

Biosimilars: some definitions

Biosimilars: development, authorization and regulations

Interchangebility, substitution

“The” biosimilar does not exist

Economic implications and Drug selection

In summary
Interchangeability/Automatic Substitution of Biosimilars

• EMA has refrained from providing guidance on interchangeability and substitution

• Biosimilars are similar to the originator drugs, not identical, and there is currently no scientific basis to substitute different products

• The decision on automatic substitution of medicines falls under national authority

• The ultimate therapeutic responsibility has to remain with the treating physician
“The” biosimilar does not exist (1)

how similar are biosimilars

- First generation: replacement therapies
  - pharmacological effect almost instantaneous or within days
  - simple dose-effect relation
  - eg hormones, clotting factors, (hematopoietic) growth factors
“The” biosimilar does not exist (2)

how similar are biosimilars

• Second generation: proteins with distinct pharmacological effect
  - no mimic of biological function
  - antagonistic effect; binding circulation protein, receptor blocking
  - eg TNF-alpha inhibitors (infliximab, etanercept, adalimumab,…)

“The” biosimilar does not exist (3) how similar are biosimilars

• Third generation: proteins with different clinical effects
  - targeted therapies in oncology
  - clinical efficacy in future (survival)
  - not always clear mechanism of action
  - extrapolation different kind of cancers

• Not yet on the market
• Knowledge and education
• Selection criteria; matrix models
“The” biosimilar does not exist (4)
how similar are biosimilars

• Fist generation
  - proven efficacy and safety
• Second generation
  - (become) available
  - current experience and knowledge are promising
  - discussion on extrapolation and interchangeability
• Third generation
  - still a lot of discussion and uncertainties
Figures, Facts and Future Outlooks

**Biosimilars**

- Where are we talking about; biotech market
  - in general and especially in oncology
- Biosimilars: some definitions
- Biosimilars: development, authorization and regulations
- Interchangeability, substitution
- “The” biosimilar does not exist
- **Economic implications and Drug selection**
- In summary


Economic Implications

- With generics, the price reduction from the originator is up to 80%.
- Similar numbers are not expected for biosimilars, as there are higher development costs.
  
  - Development time 6-9 years with biosimilars, as compared to 3 years with generics.
  
  - Biosimilars require phase I and large phase III trials, whereas generics only require bioequivalence studies.
  
  - Manufacturing costs of $250-$450 million for complex biosimilars.
  
  - Postapproval pharmacovigilance programs.

- A price reduction of 15%-30% is expected with biosimilars.

- However, presence of biosimilars will likely result in competitive decrease in the price of the originator.

Biosimilar selection criteria

- European/Dutch biosimilar expert panel
- Rational selection
- Many selection criteria possible
- What is dealt with by authorities?
- Crazy to re-invent the wheel in every hospital!

Boone et al Eur J Hosp Pharm 2013
Biosimilar selection criteria

- A Production process/Manufacturer
- B Product specifications
- C Reliability of supply
- D Good handling practice
- E Clinical efficacy
- F Clinical safety and tolerability
- G Pharmacovigilance

Acquisition cost was NOT taken into account

Select drugs on quality aspects
Next round: only cost taken into consideration
Summary

• Biosimilars have high quality
• Good regulation and authorization system
• Unless authorized biosimilars can be prescribed for therapy naive patients or patients on an innovator in a controlled way
• First generation biosimilars have proven efficacy and safety profiles
• Extrapolation of indications and interchangeability especially within the group of third generation biosimilars is still under debate
• Knowledge cap, education is necessary
• Selection criteria, decision support matrix
• Improve rational and cost-effective use by monitoring, personalized medicine and good purchase practice
Thank you for your attention
Questions?
Development of a biosimilar

- Proving “highly similar” to reference product often requires multiple iterations of process change and physicochemical characterization
- Clinical Trials
- PK/PD
- Preclinical
- Biological characterization
- Physicochemical characterization
- Design specification
- Validation

Analytics
Process development
Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Includes Recommendations for:

**Nonclinical studies**
- *In vitro* PD studies
- *In vivo* animal studies

**Clinical studies**
- Human PK and PD studies
- Efficacy studies
  - Endpoints
- Extrapolation
- Safety
- Pharmacovigilance

---

<table>
<thead>
<tr>
<th>Draft Agreed by Similar Biological Medicinal Products Working Party</th>
<th>October 2010</th>
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<tbody>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>18 November 2010</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 May 2011</td>
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<td>Final agreed by BMWP</td>
<td>March 2012</td>
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<td>30 May 2012</td>
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<td>Date for coming into effect</td>
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**Keywords**
- Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, non-clinical studies, in vitro studies, clinical use, clinical endpoints, extrapolation
Currently Approved Biosimilars in Europe

<table>
<thead>
<tr>
<th>Class</th>
<th>Product</th>
<th>Brand Name</th>
<th>Active Substance (INN)</th>
<th>Authorisation date</th>
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<tr>
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<td>SB-309</td>
<td>Retacrit</td>
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<td>Silapo</td>
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<tr>
<td>Follicle Stimulating Hormones</td>
<td>XM17</td>
<td>Ovaleap</td>
<td>follitropin alfa</td>
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<tr>
<td></td>
<td>NA</td>
<td>bemfcola</td>
<td>follitropin alfa</td>
<td>27/03/2014</td>
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<td>Granulocyte-colony stimulating factor (G-CSF)</td>
<td>XM02</td>
<td>Biogranstim</td>
<td>filgrastim</td>
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<td>Ratiogranstim</td>
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<td>Filgrastim ratiopharm</td>
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<td>Inflectra</td>
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<tr>
<td></td>
<td></td>
<td>Remsima</td>
<td>infliximab</td>
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INN, International non-proprietary name
# mAbs Approved in the US and EU for Cancer Management

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Format</th>
<th>Target</th>
<th>Therapy Area</th>
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<tbody>
<tr>
<td>Rituxan (rituximab)</td>
<td>Chimeric IgG1</td>
<td>CD20</td>
<td>NHL, CLL</td>
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<td>Herceptin (trastuzumab)</td>
<td>Humanized IgG1</td>
<td>HER-2</td>
<td>Met breast cancer</td>
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<td>Early breast cancer</td>
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<td></td>
<td></td>
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<td>Met gastric cancer</td>
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<td>Mylotarg (gentuzumab ozogamicin)</td>
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<td>AML</td>
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<td>Zevalin (ibritumomab tiuxetan)</td>
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<td>Bexxar (tositumumab)</td>
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<td>CD20</td>
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<td>mRCC; GBM</td>
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<td>mCRC (first-line)</td>
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<td>Vectibix (panitumumab)</td>
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<td>EGFR</td>
<td>mCRC</td>
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<td>Arezera (ofatumumab)</td>
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<td>Removab</td>
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<td>Yervoy (ipilimumab)</td>
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</table>

Immunogenicity Testing: A Tiered Approach

Screening assays: for ‘identification’ of all antitherapeutic binding antibodies

- Enzyme-linked immunosorbent assays (ELISAs): direct, bridging, other formats
- Radioimmunoprecipitation assays (RIPA)
- Surface plasmon resonance (SPR)
- Other technologies

Confirmatory assays: for confirming antibodies

Neutralization assays: for distinguishing neutralizing & non-neutralizing antibodies

- Cell-based assay
- Non-cell-based ligand binding assay
Regulatory history of mAbs in EU

Final set of relative selection criteria (1)

A  Production process/Manufacturer

1  Is the manufacturer of the API and the medicinal product experienced in the production of biopharmaceuticals?

2  How long has the biopharmaceutical been on the market?

3  How extensive is the clinical experience with biosimilar? Expressed as the number of patient-days worldwide

B  PRODUCT SPECIFICATIONS

4  Are there any differences in drug formulation and administration in comparison to the reference product or other biosimilars?

5  What is the number of registered indications for the biopharmaceutical/biosimilar?
Final set of relative selection criteria (2)

- **E**  CLINICAL EFFICACY
  - 6  Are there different results in comparison to the reference product?

- **F**  CLINICAL SAFETY AND TOLERABILITY
  - 7  Which (serious and mild) adverse events and in which frequency were reported in clinical trials with the biopharmaceutical?
  - 8  Are there any contraindications, precautions or warnings which are different compared to the reference product?
  - 9  Is immunogenicity, as far as known, caused by a homogeneous type of antibody or is there a high intra- or interindividual variability? Is there a difference between biosimilar products regarding drug antibody homogenicity?
  - 10  Are there differences in the incidence and severity of drug interactions?
The approach to clinical testing of mAb biosimilars should build upon the principles used for simpler proteins:

- Identical amino acid sequence and high similarity with regard to chemical, physical, and biological characteristics should first be demonstrated in laboratory/non-clinical testing
- Clinical similarity may then be tested head-to-head
- Extrapolation across endpoints, populations, or diseases should be justified scientifically

However, application of those principles should take into account particular properties of monoclonal antibodies:

- Monoclonal antibodies are large and complex
- Multiple features determine clinical activities
- Different activities may depend on different features
- Critical structure-function relationships are often not well understood
- mAbs are generally used to treat serious and/or life-threatening diseases
Pharmacovigilance

• Same rules apply to biosimilar as to all biologicals:
  - Biosimilar companies should submit a risk management plan
  - Collect spontaneously reported adverse events
  - Submit Periodic Safety Update Reports

Traceability is of high importance for all biologicals

*(this is specifically addressed in the pharmacovigilance legislation)*
RMP for Biosimilar Antibodies

- Proactive PV activities
  - Targeted questionnaire
  - Phase IV studies
  - Registries
  - Specialized follow-up for long-term use
- Individual RMPs are available in the European public assessment report (EPAR)
- Physicians should be informed about RMPs (close collaboration with hospital pharmacists)
Position papers
Scientific and professional societies

- Quality and safety criteria
- Decision support matrix
- Multidisciplinary guidelines
- Naive patients no problem
- Switching not yet recommended for good responding patients
- Unless under controlled conditions
- Registry; efficacy, safety, pharmacovigilance
- Tracebility
Absolute set of criteria

- **A10** Is the reference medicinal product authorised in the European Community?

- **C1** Does the supplier reliably guarantee the supply of the biosimilar over a long time period?

- **G1a** Does the MAH has a 24-hour phone number equipped with adequate personal to report adverse events?
Conclusions (mAbs in oncology)

- Therapeutic antibodies in oncology:
  - vastly altered treatment strategies
  - improved patient outcomes for many diseases

- Patents several first-generation antibodies will expire soon, allowing the creation of copy versions

- Developing biosimilar antibodies will be more difficult and expensive:
  - Altered composition (eg, glycosylation) may lead to different efficacy or function \textit{in vivo}
  - Minor changes in antibody structure will lead to the development of immune responses that may limit therapeutic efficacy

- Regulatory guidelines for biosimilar antibodies are evolving:
  - discussion about clinical endpoints, study population, extrapolation, and automatic substitution