TUNISIA : TOWARD A DRAFT GUIDELINE ON BIOSIMILARS IN 2016!

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Ministry of Health - Tunisia

Amman, 15th September 2015
Problem context

**International level**

- Beyond the High Cost of biological products
- Need for biosimilars as a real hope for patients (oncology)
- There was a Global development of biosimilars
- So different procedures were launched for biosimilars registration all over the world
Problem context

**National level**

1. Pharmaceutical industries portfolio continues to grow
2. Local biosimilars are emerging
3. With a particularity in their process: transfer of technology (a partnership with foreign referent laboratories)
4. During the registration procedure, we encountered the problem: Lack of a national regulation on biosimilars
Problem context

Guarantee quality, efficacy and safety

Supporting local production

Accelerate biosimilars marketing

**Tunisian Biosimilars guidelines**
DRUG REGISTRATION IN TUNISIA
Marketing authorization procedure

1. UPM (MoH)
   Application submission

2. Administrative information (Module 1)

3. NMCL (Module 3)
   - Assessment and Testing

4. Experts (Module 4 and 5)
   - Specialized Scientific Commission (SSC)

5. Technical Committee for Proprietary Medicinal Products
Assessment of Drug quality (Module 3)

National Medicines Control Laboratory

- Assessment of the pharmaceutical data
  - Teams of assessors (pharmacist and doctors)
  - Following the International Guidelines
Security and efficacy assessment (Module 4 and 5)

Experts / Specialized Scientific Commissions (SSC)

- Approximately 260 Experts appointed by The Minister of Health from different relevant specialties
- 17 Specialized Scientific Commissions
- Each one occurs once or twice per year
Technical Committee for Proprietary Medicinal Products

Committee composition:
- Experts representatives of different specialties
- College of pharmacists and physicians
- Representatives of relevant governmental structures (NMCL, DIP, NCPV, Central Pharmacy of Tunisia, National Health Insurance Fund/Ministry of Social Affairs, ministry of commerce)

Global evaluation
- Quality report (NMCL)
- SSC opinion
- Price negotiation

Approval or rejection of the MAA
REGISTRATION OF BIOSIMILAR IN TUNISIA
In case of a biosimilar, we are applying the procedure, following:

REGULATORY EXPECTATIONS AND RISK ASSESSMENT FOR BIOThERAPEUTIC PRODUCTS

Scientific Principles to Consider
Guidance for Industry

Clinical Pharmacology Data
to Support a Demonstration of
Biosimilarity to a Reference Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500, or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Biosimilars
Guideline on similar biological medicinal products
CHMP/437/04 Rev 1

Guideline on similar biological medicinal products
containing biotechnology-derived proteins as AS:
quality issues EMA/CHMP/BWP/247713/2012

Guideline on similar biological medicinal products
containing biotechnology-derived proteins as AS:
non-clinical and clinical issues
EMEA/CHMP/BMWP/42832/2005 Rev 1

Guideline on immunogenicity assessment of
biotechnology-derived therapeutic proteins
EMA/275542/2013

EMA genral and specific guidelines clarifying some requirements specially for
preclinical, clinical and immunogenicity issues
SITUATION IN TUNISIA
## Filgrastim (Timeframes of MA)

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<tr>
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NB: All the pending MAA are published in our website: www.dpm.tn
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## Monoclonal antibodies

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TUNISIAN GUIDELINES FOR BIOSIMILARs
Tunisian Guidelines on Biosimilars registration

Draft Redaction Group
Validation Group
Communication seminar
Adopted Guideline
Draft Redaction Group

Our project has started since April 2015

first draft before 2016:

- UPM
- NMCL
- NCPV
- Experts:
  - Clinicians
  - Analytical chemistry
  - Biotechnology
  - Pharmacology
  - Clinical trials
  - Pharmacovigilance
Draft Redaction Group

- Stakeholders (involved in the project) ➔ take their perspectives into account.
  - Delegates of the syndicate of local manufacturers (CNIP)
  - The Tunisian syndicate of research and development laboratories (SEPHIRE: multinational laboratories)
  - Investigators and clinical research associates (CRA) experienced in biosimilarity clinical trials
Decision: **To refer** to other guidelines, and not to redact a new one ➔ in order to benefit from the experiences of the other countries.

Guidelines from other countries (besides the WHO, FDA and EMA guidelines) were benchmarked.

*ie*: Egyptian, Jordanian guidelines ...
Main sections of the Guideline

the same as most of the biosimilar guidelines

Scope
Reference biotherapeutic product
Registration procedure
Quality
Non-clinical evaluation
Clinical evaluation
Pharmacovigilance
Interchangeability
Transfert of technology
Legal basis
TUNISIAN GUIDELINES : CHALLENGES
First Challenge

- **Scope**
- **Reference biotherapeutic product**
- **Registration procedure**
- **Quality**
- **Non-clinical evaluation**
- **Clinical evaluation**
- **Pharmacovigilance**
- **Interchangeability**
- **Transfert of technology**
- **Legal basis**
To shorten the MA timeframes

Adapt the registration procedure in order to allow a **combined evaluation** of the comparability exercises:

- Quality (NMCL)
- Efficacy and security (Specialized Scientific Commission)
LOCAL MANUFACTURED biosimilars registration procedure

**STEPWISE APPROACH**

- Quality assessment
- Preclinical studies
- Clinical trials
- SSC - TC
- MA

→ To shorten the MA timeframes

Define a « fast and wise » stepwise approach

→ we decided to implement a fast track procedure for the quality assessment before going to the preclinical and the clinical studies
## Challenges

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<td>Legal basis</td>
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Challenges

Quality, preclinical and clinical issues:

- The working group was split into 3 taskforces to discuss the choice of the suitable guideline that would be adopted in each section.
- In some sections, most of the guidelines are in a complete concordance.
- In others, many disparities were highlighted.
Challenges

- Shall we choose/adopt the guidelines that are more drastic, specially about:
  - The necessity of a clinical trial for some biosimilar classes?
  - The design of the clinical trial?
  - The timing of the immunogenicity assessment?
  - … ???

- How to choose the reference product when it is not registered in Tunisia and there is no access to its pharmaceutical data to assess its quality comparability?
Challenges

- **Pharmacovigilance:**
  In Tunisia, we have already adopted a main part of the Guideline on good pharmacovigilance practices (GVP) For Arab Countries, since July 2015.

- **The interchangeability:**
  In Tunisia, we follow the “call for tenders” mode to import most of the hospital drugs ➔ the medicine could be substituted every one or 2 years.
THE BIG Challenge

- Scope
- Reference biotherapeutic product
- Registration procedure
- Quality
- Non-clinical evaluation
- Clinical evaluation
- Pharmacovigilance
- Interchangeability
- Transfer of technology
- Legal basis
THE BIG Challenge

- In case of a transfer of technology: the most frequent case for locally manufactured biosimilars in Tunisia
- Local manufacturer has a partnership with a foreign referent laboratory:

  Same active substance

  Same formulation process

  Can we consider the local finished product is the same FP already marketed as a biosimilar in the country of the referent laboratory?

???
THE BIG Challenge

- Transfer of technology:
  - In this case, regarding to all the published guidelines, shall we require preclinical studies for the local biosimilar?
  - Could the partner clinical trials be sufficient to demonstrate biosimilarity of the Tunisian product?

ICH Harmonised Tripartite Guideline
Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
Q5E

© World Health Organization

Annex 7
WHO guidelines on transfer of technology in pharmaceutical manufacturing

Current Step 4 version
dated 18 November 2004
A STEPWISE or A COMBINED APPROACH???

And which approach will be applied??
PERSPECTIVES
Perspectives

- We have to Guarantee quality, efficacy and safety of biosimilars
  - Pre-marketing
  - Post marketing monitoring +++
- Accelerate the marketing of biosimilars to access to patients developed therapies with a great economic benefit
Economic Benefit

**Cost in MD of REMICADE vs biosimilar (at least -30%)**

- **2012**: REMICADE $6 M, BIOSIMILAR $4 M
- **2013**: REMICADE $7 M, BIOSIMILAR $5 M
- **2014**: REMICADE $8 M, BIOSIMILAR $5 M
- **Estimation 2015**: REMICADE $8 M, BIOSIMILAR $5 M

**Cost in MD of HERCEPTIN vs Biosimilar (at least -30%)**

- **2012**: HERCEPTIN $15 M, BIOSIMILAR $10 M
- **2013**: HERCEPTIN $25 M, BIOSIMILAR $15 M
- **2014**: HERCEPTIN $35 M, BIOSIMILAR $20 M
- **Estimation 2015**: HERCEPTIN $45 M, BIOSIMILAR $30 M
Conclusion

- To Guarantee quality, efficacy and safety of biosimilars
  - Pre-marketing
  - Post marketing monitoring +++
- Accelerate the marketing of biosimilars to access to patients developed therapies with a great economic benefit

TO ESTABLISH A CLEAR REGISTRATION PROCEDURE TOWARD A REGULATORY HARMONIZATION
"The courage of the water drop is to fall into the desert." Lao She

Thank you!