Country In-Focus Series 2: Regulations, Submissions and Registrations.

Algeria Case Study.

Lessons learnt from other emerging markets:
Development of a local biotech industry, what are the current challenges?

Dr. Yacine Sellam, Pharm.D., Ph.D.

Population: 39.7 million.
GDP: 164.8 Bn US$.
GDP/capita: 4,150 US$.
HE: 14,4 Bn US$ (8.7%/GDP).
HE/capita: 361,73 US$.

Pharma sales: 3.9 Bn US$ (2.4%/GDP).
Pharma sales/HE: 27,0%. 

Past growth (2010-15): 11,8%
Forecast growth (2015-20): 6.4%
Algeria: Pharma total market snapshot in 2015.

4196 authorized products.

Pharma total sales: 3,9 billion in current US$.

Locally manufactured products / Imported products; Non-originator products / Innovative products

Top 20 MNC / Top 10 local companies / Others

Algeria: Biologics market snapshot in 2015.

200 authorized Biologics (4.7%).

Biologics sales: 927 millions US$ (23.8%).

Top 5 biologic therapy areas:

- Diabetes 39%
- Oncology 26%
- Hematology 19%
- Infectiology 7%
- Endocrinology 2%
- Others 7%

Diabetology (insulins)
Oncology (mAb + cytostatic hormones)
Hematology (heparins + EPO + G-CSF + blood coagulation factors)
Infectiology (INF + immunoglobulins + vaccines)
Endocrinology (growth hormones)
Others (including anti-TNFα).

US & European MNC:

Other companies:

Roche SANOFI Amgen Merck Shire Mylan MSD Johnson & Johnson Biotest CSL Behring

Pfizer Novartis Lilly Perrigo Boehringer Ingelheim Astellas AstraZeneca CSL Behring Heber

Biocon

Pharmaceutical Regulations Summit
### Algeria: Biosimilar Market Landscape & Uncertainties (1/4).

<table>
<thead>
<tr>
<th>INN</th>
<th>Statut</th>
<th>Comments</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>🚫</td>
<td>No biosimilar registered, reference biologic approved and funded.</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>🟢</td>
<td>REMSIMA (Hikma/Celltrion) is under registration, reference biologic approved and funded.</td>
<td>🇰🇷</td>
</tr>
<tr>
<td>Etanercept</td>
<td>🚫</td>
<td>No biosimilar registered, reference biologic approved and funded.</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>🟢</td>
<td>KIKUZUBAM (Probiomed) was approved in 2012, and awarded the tender (-45%); however, it was later removed from the market after the licence was revoked in Mexico during 2014.</td>
<td>🇲🇽</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>🟢</td>
<td>CANMAB (Abdi Ibrahim/Biocon) &amp; HERTRAZ (Mylan) were approved in 2015, and awarded the last tender (-20%).</td>
<td>🇮🇳</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>🚫</td>
<td>No biosimilar registered, reference biologic approved and funded.</td>
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</tr>
<tr>
<td>Cetuximab</td>
<td>🚫</td>
<td>No biosimilar registered, reference biologic approved and funded.</td>
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</tr>
<tr>
<td>Filgrastim</td>
<td>✅</td>
<td>IOR LEUKOCIM (El Kendi/CIM) approved in 2009, and awarded the last tender (-30%) + ZARZIO (Sandoz) approved in 2017.</td>
<td>🇨🇺</td>
</tr>
</tbody>
</table>
Algeria: **Biosimilars market landscape & Uncertainties (2/4).**

**November 10th, 2016.**
Out of stock of HERCEPTIN, a drug for cancer patients, at CPMC.

**PROFESSOR BOUZID RAISES THE ALARM BELL. (T0)**

**November 12th, 2016.**
Despite availability of 14,000 boxes stock at the PCH.
SHORTAGE OF HERCEPTIN CONTINUES. (?)

**November 23th, 2016.**
THE ROCHE LABORATORY AND ITS ALGERIAN RELAYS WANT TO FORCE THE HAND OF THE STATE! (?!)

**November 24th, 2016.**
They had meeting yesterday with Ministry of Health and PCH officers.
ONCOLOGISTS WON THE BATTLE OF HERCEPTIN. (?)

**November 12th, 2016.**
ANTI-CANCER MEDICINES: THE INTERCHANGEABILITY OF TREATMENTS AUTHORIZED BY THE LEGISLATION.

**November 14th, 2016.**
PROFESSOR BOUZID: “THE PCH TAKES MY PATIENTS AS HOSTAGES”.

**November 18th, 2016.**
M'hamed Ayad. General Director of the Central Pharmacy of Hospitals (PCH)
I DID NOT TAKE ANY PATIENT AS HOSTAGE.

Local newspapers.
Trastuzumab: biosimilars versus originator timeline.

- **HERCEPTIN 150 registration in Algeria**
- **HERCEPTIN 150 new price (2,93 US$/mg rather than 6,02 US$/mg)**
- **CANMAB 440 & HERTRAZ 150 tender winner (1,84 US$/mg)**
  - **70% of market**
  - **30% of market**
- **Tender: Savings of 65M US$/year**
- **HERCEPTIN 150 second position (2,34 US$/mg)**
- **HERTRAZ 150 Submission for registration accepted for review by EMA**
- **HERTRAZ 150 Submission for registration accepted for review by US FDA**
- **Interchangeability arbitration in Algeria (new patients will receive biosimilars)**
- **« Droit de Substitution » law does not applicable for Biologics.**

Date timeline:
- **07/2006**
- **07/2015**
- **09/2015**
- **12/2015**
- **08/2016**
- **11/2016**
- **11/2016**
Algeria: **Biosimilars** market landscape & Uncertainties (4/4).

**Current situation.**
- Originator
- New patient

**Future situation...**
- Originator (Or New Biologic)
- Old patient ??
- Biosimilar
Algeria: Local pharma manufacturing environment.

- **80** operational manufacturing plants (+70 in the next three years).

- Mainly for solid oral dosages (only **05** plants for sterile injectables).

- **357** products (in INN) forbidden for importation in 2015 (official decree).

- Governmental objective to cover **70%** of national needs in value by 2018.

- **49/51 rule** remains applicable for foreign investments.

Prioritized areas for localisation:

- Sterile injectable
- APIs
- Plasma derived products
- Bioequivalence Centers
- Biosimilars
- Vaccines

Top 10 local manufacturers:
Algeria: Investment and local manufacturing incentives.

**Taxes:**

During Construction phase: for 03 years.
- Customs duties exemption.
- Value-added tax exemptions.
- Real-estate transfer tax exemption.

During operating phase: for 05 years.
- Corporate income tax exemption.
- Tax on professional activity (1% of turnover) exemption.

**Pricing:**

- Higher prices level for locally manufactured products.
- No historical price reduction for local products after 5 years.

**Tenders:**

- Hospital call for tenders dedicated to local products.
- **25% bonus** on price for local products (international tenders).

ANDI
National Agency of Investment Development.
Examples of local Biologics manufacturing projects (1/5).

SANOFI new industrial complex in the new city Sidi Abdellah:

- Investment of 100M US$.
- Area of 66,000 square meters.
- Production of 80% Sanofi portefolio.
- The biggest SANOFI production complex in Middle-East and Africa.
- Operational by the end of 2017.

Future extension of 10,000 square meters for:
- Assembly of disposable Solostar® insulins pens for additional investment of 20M US$ (the 4th SANOFI site in the world after Germany, China and Russia);
- Filling and finishing of vaccines for additional investment of 30M US$.
Examples of local Biologics manufacturing projects (2/5).

Tech transfer agreement (80M US$): a plant for insulins production both conventional and analogs + a plant for assembly of disposable Flexpen® insulin pens (the 1st in Africa and the 2nd in MENA after IR Iran).

Tech transfer agreement for G-CSF joint production in Algiers (started in Q4 2016).

Tech transfer agreement for several mAbs production in Sidi Abdellah (in progress).

Tech transfer agreement for EPO joint production in Algiers (in progress).

Tech transfer agreements for BCG vaccine & DT based combined vaccines production.
Examples of local Biologics manufacturing projects (3/5).

MENA biotechnology hub in the new city of Sidi Abdellah (1/3):

- Investment of **12 Bn US$** for the 4th biotech regional hub in the world (after Boston, Dublin & Singapore).

**Year 2011:**

- USA / Algeria Health Forum & Expo on biotech R&D (Algiers): MoU 1 PhRMA-MoH on **Algeria regulatory environment study (Vision 2020 report).**
- **Innovative Pharmaceutical Study Tour** (Boston / Washington): organized by the U.S.-Algeria Business Council.

Sixteen MNC partners:
**Examples** of local Biologics manufacturing projects (4/5).

**MENA biotechnology hub in the new city of Sidi Abdellah (2/3):**

**Year 2012:**

- **Algeria guest of honor** of BIO International Convention (Boston): *Official launch of Algeria 2020 Initiative*, an investment & development program focused on health sector.

- **Education / training agreements** with:
  
  ![Harvard Medical School](image)
  ![NIH](image)
  ![Dana-Farber Cancer Institute](image)

Sixteen MNC partners:
Examples of local Biologics manufacturing projects (5/5).

MENA biotechnology hub in the new city of Sidi Abdellah (3/3):

**Year 2014:**
- (San Diego) MoU 2 « Vision 2020 » PhRMA-MoH on regulatory policies reform to strengthen Algeria competitiveness in R&D and manufacturing of innovative biotech products.

**Year 2016:**
- (Algiers) Local private companies commitment to participate in funding the project of MENA-wide biotechnology hub...

Sixteen MNC partners:
Algeria on **Priority Watch List** of PhRMA Special 301 in 2017.

"This submission focuses on the most urgent barriers and threats in **18 countries** that are significant and increasingly important markets for medicines invented, developed and manufactured in the US."

Biopharmaceutical environment \textit{competitiveness}?

- **Scientific Capabilities & Infrastructure.**
  - Ability to leverage personnel, technologies and facilities in biopharmaceutical research forums to translate discoveries into products.

- **Clinical Research Framework.**
  - Ability of research institutions to conduct clinical research in a high quality and efficient manner.

- **Intellectual Property Protections.**
  - Ability to fully realize required terms of intellectual property protections for biopharmaceutical products.

- **Regulatory System.**
  - Ability of the regulatory system to ensure that only high quality, safe biopharmaceutical products enter the market, yet do so in a timely manner.

- **Market Access & Financing.**
  - Ability of new biopharmaceutical products to access the market via the pricing, reimbursement and procurement system in an efficient manner and at an acceptable price.
Local biopharmaceutical environment competitiveness (1/5).

Scientific capabilities & Clinical research & IP protections.

- R&D capabilities at a basic level, and lacking adequate investment.
- Efforts to strengthen the science base and R&D, including as part of Algeria Vision 2020.
- Limited level of collaboration between the industry and research institutions.

- Fairly developed capabilities among hospitals and CROs.
- Conducting clinical trials is considered to be relatively low cost.
- Improved timeframe for approval, still ways to reach government target of 60-90 days.

- Effective patenting process for biopharmaceuticals.
- Lack of effective enforcement mechanisms of patents and other IP rights.
- Lack of regulatory data protection is particularly limiting investment attractiveness.
Local biopharmaceutical environment competitiveness (2/5).

Regulatory System: Strengths versus Weaknesses.

- Gaps in review capacity in relation to innovative drugs.
- Lack of biosimilars and innovative drugs fast-track pathways.
- Burdensome procedures and delays for imported products.
- Linking of registration with pricing reinforces delays and uncertainty.
- Strong quality control standards and compliance.
- Relatively good pharmacovigilance framework.
- New independent drug regulatory agency, ANPP (February 2017).

Average delay from NCE first global launch (years)

<table>
<thead>
<tr>
<th>Country</th>
<th>Delay (years)</th>
</tr>
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<tbody>
<tr>
<td>US</td>
<td>0.7</td>
</tr>
<tr>
<td>Germany</td>
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</tr>
<tr>
<td>UK</td>
<td>2.0</td>
</tr>
<tr>
<td>Canada</td>
<td>2.6</td>
</tr>
<tr>
<td>Spain</td>
<td>2.7</td>
</tr>
<tr>
<td>Italy</td>
<td>2.9</td>
</tr>
<tr>
<td>Japan</td>
<td>3.9</td>
</tr>
<tr>
<td>Brazil</td>
<td>4.0</td>
</tr>
<tr>
<td>Argentina</td>
<td>4.2</td>
</tr>
<tr>
<td>S. Korea</td>
<td>4.6</td>
</tr>
<tr>
<td>S. Africa</td>
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<tr>
<td>Colombia</td>
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<tr>
<td>Turkey</td>
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<tr>
<td>Thailand</td>
<td>5.5</td>
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<tr>
<td>Indonesia</td>
<td>5.9</td>
</tr>
<tr>
<td>Russia</td>
<td>6.2</td>
</tr>
<tr>
<td>India</td>
<td>6.4</td>
</tr>
<tr>
<td>Venezuela</td>
<td>7.1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
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<tr>
<td>Pakistan</td>
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<tr>
<td>China</td>
<td>7.7</td>
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<tr>
<td>Vietnam</td>
<td>8.9</td>
</tr>
<tr>
<td>Egypt</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Includes NCE’s launched locally 1995-2014.
Local biopharmaceutical environment competitiveness (3/5).


BioS pathways in place.

BioS pathways under development.

No BioS pathways.
Local biopharmaceutical environment competitiveness (4/5).

Regulatory System: Facilitated Regulatory Pathways.

FRP in place.
FRP under development.
No FRP.

Local biopharmaceutical environment competitiveness (5/5).

- **Strong public reimbursement system coverage (2 Bn US$), and public funding for all hospital products (0,65 Bn US$).**

- Pricing & procurement systems prioritize cost over value and preferential treatment to local products.

- **International reference pricing system limiting competitiveness significantly.**

- Limited reimbursement of innovative drugs and reimbursement system increasingly convoluted and uncertain.

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: "Neither Greece nor Turkey are appropriate reference countries."
Enhancing local R&D, clinical research and IP protections are prerequisites for establishing local biotech manufacturing.

Fast track pathways for innovative products and biosimilars are perceived as the pillars of regulatory system reform.

Investments in biosimilars are undermined by regulatory uncertainties and the rise of new innovative therapies.
Thank you for your attention.

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