CP Extension to Croatia, Industry Perspective

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Content

- **Pre-accession challenges**
  - Case Study: PALC III at Pliva/Teva
- **Closer to the accession**
  - Case Study: switch from national to CP biosimilars
- **Post-accession challenges**
  - 3rd Party APIs
  - Zagreb as EU Production and Batch Release Site

PLIVA

- **The largest pharmaceutical company in Croatia**
- **10% of all granted MAs in Croatia belong to PLIVA**
- **The innovator of Azithromycin (Sumamed®, Zithromax®)**
- **Vertically integrated highly sophisticated products**
- **EU, US, JP GMP compliant**
- **3x100**
  - 100+ newly employed associates
  - $100+M investment into API development and production
  - $100+M investment into FDF (injectables, high-potency)
- **6 Billion tablet/capsule output to grow to 10 Billion**
- **Teva Global and EU Centers of Excellence**

Vision: Being the most indispensable medicines company in the world, executing on our obligation to our patients, customers, shareholders and employees

111 years	**46,000** employees	**$20.3B** 2012 revenues
1,000 molecules	**300+** APIs	**70B** tablets/annum

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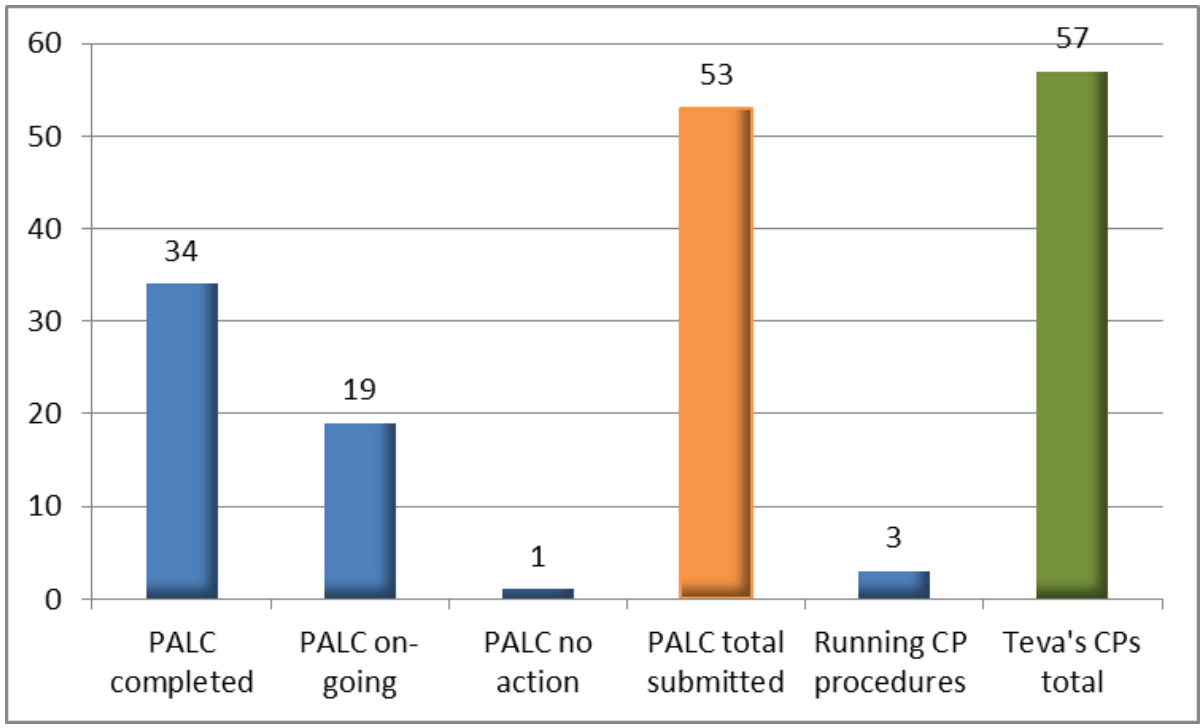
PLIVA Experience with PALC III (1)

- **Pliva as MAH was requested to prepare and submit the linguistic version in the Croatian (HR) language reflecting the English (EN) reference text.**
- **Croatian translations were sent for checking twice a month, first sending date: March 2011, last sending date: April 2013**



PLIVA Experience with PALC III (2)

Positive experience

- **The process was well managed and coordinated within TEVA.**
  - Deadlines for preparing texts for slots were realistic and feasible.
  - Colleagues from TEVA EU shared their knowledge, experience and information
- **Excellent cooperation with the Croatian Agency**
- **A great experience for everybody in the local regulatory team**

Issues we faced

- The process of receiving English texts from TEVA started later than expected (April 2012)
- No experience in Croatia (both Agency and MAHs)
- All the rules for preparing Croatian PALC texts were not clearly defined at the beginning of the process
- Deficiencies of PALC as a concept:
  - Waiting for the originator prolonged the whole process
  - Should we wait or be the first to submit the text for the generic

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Switch Biosimilars (1)

Eporatio (erythropoetin theta)

- **Launch in Croatia based on national MA prior to the accession**
- **National MA will be cancelled and CP MA will come into affect**
- **Pliva harmonised the product name, packaging and PIL between national and CP Products to make sure there will be no confusion of either patients or healthcare professionals**

- **Regulatory Issue: Ongoing Regulatory Activity**
  - Type II variation submitted in April, expected approval in May, i.e. within two months prior to the accession
  - Pliva to submit HR text
  - Since the PALC process for Eporatio is finished, all changes should be highlighted
  - No notification is required after the accession date

Switch Biosimilars (2)

Tevagrastim (filgrastim)

- **Launch in Croatia based on national MA prior to the accession**
- **National MA will be cancelled and CP MA will come into affect**
- **Pliva harmonised the product name, packaging and PIL between national and CP Products to make sure there will be no confusion of either patients or healthcare professionals**

- **Regulatory Issue: No Ongoing Regulatory Activity**
  - Notification in July 2013 according to Article 61(3) to include Pliva as local representative (PIL and Blue Box)
  - Croatian text approved
  - PALC will be brought in line with the EU
  - Introduction of HR into the CP will be done with the first change of Product Information after July 2013

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Falsified Medicines Directive (1)

PLIVA

- **Main Themes**

Directive covers all players in the Supply Chain

Legal requirement GMP/GDP for API's manufactured in the EU and imported

Requirement for the Manufacturer to assess GMP for excipients

Safety features for drug products. Unique identifier and tamper evidence.

GDP regulations for drug product and API's strengthened

Requirements for internet trade

Falsified Medicines Directive (2)

- **New requirements for QP GMP declaration**
  - Requires verification of **pedigree** of the API
  - Impacts on GMP status of key intermediates and starting materials
  - More audits needed with limited resources to perform them
  - Many intermediate suppliers will not accept audits from finished product manufacturers

- **Importation of API from outside EU**
  - Countries can sign up for equivalence in GMP standards
    - CH (approved), Israel, Australia, Singapore, Brazil, Japan, US (all under assessment)
  - Implement a systems for written confirmation
    - In place in Korea, Israel, Mexico, Canada, Taiwan, Ukraine and South Africa

- **Pliva imports 48 APIs from non-EU**

- **Real potential to cause shortfalls in medicinal products in Europe**

Manufacturing in Croatia

Situation today

- **Manufacturing site for Teva for EU, US, RoW**
  - Retest and release within EU for commercial supply

Main challenge ---

- **Ensuring batch release is possible for EU on Day 1 of accession, but.....**

  .....minimise regulatory impact

  - Already manufacturing commercial products for EU
  - Has potential to create many variations to existing MAs
  - Simplification of supply chain possible post-accession


At the
heart
of Teva
We bring safe and effective medicines to the world through
the quality of our people,
the quality of our products and
our commitment to the patient.
You matter. **We** care.