WHAT DO MANUFACTURERS AND IMPORTERS HAVE TO DO TO PREPARE FOR EU MEMBERSHIP ?

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EU: BEATEN TRACK

- land of contrasted peoples, languages, religious practices and strong beliefs, knowledge and powers, confronted thoughts and values

- land of uniform understanding of common objectives and approaches to achieve them, which must be open also to individual needs.

WELCOME

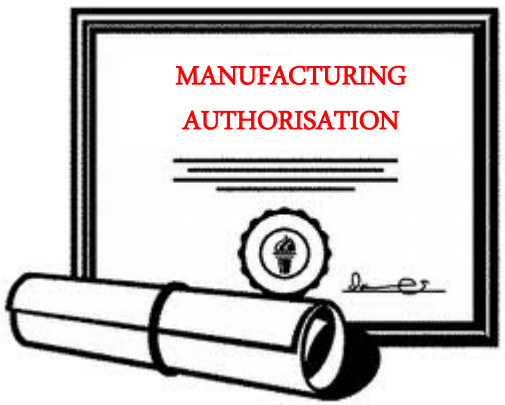
WHAT DO MANUFACTURERS AND IMPORTERS HAVE TO DO TO PREPARE FOR EU MEMBERSHIP ?

- To fulfill EU requirements and obligations
  - Dir 2001/83/EC; 2001/82/EC; 2010/84/EC: 2011/62; 2003/94/EC(COM); 2005/28/EC(COM)…
  - GMP…
  - …
- To accept the difference between being a manufacturer/importer in 3rd Country and in EU MS
- To cope with derogation: upgrading of old files by the end of transitional period and its consequences
- …

FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC

- **Manufacture and importation**
- Manufacturing authorisation is required for:
  - Total & partial manufacture including IMP
  - Various processes of dividing up, packaging …(exceptions)
  - Imports from 3rd countries

Compilation of Community Procedures on Inspections and Exchange of Information



ANNEX 1

ANNEX 2

Manufacturing operations

Importation of MP

Manufacturing Operations of IMP

Importation of IMP

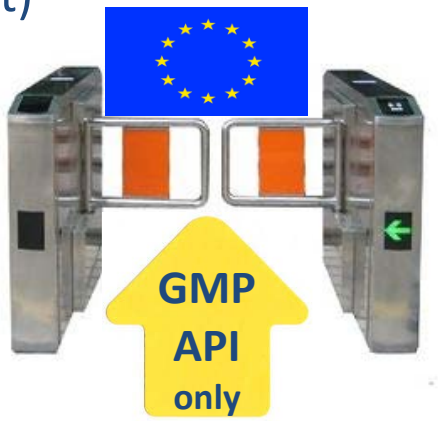
FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC

- Requirements to be fulfilled:
  - To specify medicinal products and pharmaceutical forms which are to be manufactured/imported
  - To specify the manufacturing place and/or place for control
  - To have suitable and sufficient premises, technical equipment and control facilities for manufacture and storage of medicinal products
  - To have staff in line with legal requirements concerning education and experience
  - To have Qualified Person (+ 

requirements concerning API)
  - All changes of the requirements concerning premises, equipment, control of facilities and QP are to be authorised by CA

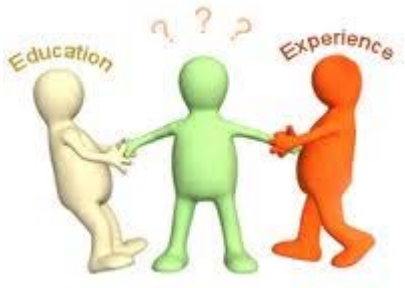
FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC

- Obligations of the holder of manufacturing authorisation
  - To comply with principles/guidelines of GMP
  - To dispose of authorised medicinal products only in accordance with national legislation
  - To allow inspection access to premises at any time
  - To enable QP to carry out his/her duties
  - To use API and certain excipients manufactured in line with GMP for API (includes total or partial of manufacture/import)



FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC

- Requirements for QP
  - Qualifications recognised by MS bearing upon listed basic subjects in the directive
    - 4y of university degree (pharmacy, medicine, chemistry, technology, biology) or
    - 3,5y of university degree + 1y of training (at least 6m in pharmacy)
  - 2y experience in manufacturing, analysing or control of medicinal products (may be reduced to 1y if university studies last 5y or more)



FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC

- QP responsibilities
  - Ensures that each batch of medicinal products has been manufactured and checked in compliance with the relevant laws
  - Ensures that each batch of medicinal products imported in the EU from 3rd countries (irrespectively if it was manufactured in the EU or not) has undergone full qualitative analysis and quantitative analysis of at least API and other tests necessary to ensure quality of medicinal product in line with MA except in case of MRA
  - Ensures traceability of medicinal products and enables efficiant recall
  - QP Declaration concerning GMP compliance of API and verification of its supply chain 

FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC (2011/62)

QP Declaration on GMP compliance of API and verification of its supply chain

- Verifies the GMP compliance of all parties in the supply chain and that all sources are in accordance with relevant authorisations.
- Demonstrates full understanding and control of the supply chain of active substances used by manufacturer (including brokers, re-labellers and re-packagers) and taken steps to shorten the supply chain wherever possible.
- Clearly demonstrates that each batch of active substance accepted by manufacturer for use in the manufacture of medicinal products has been sourced through this supply chain.

FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC (2011/62)

QP Declaration on GMP compliance of API and verification of its supply chain: 5 parts

A - Concerned manufacturing site

B – Declaration of GMP Compliance (single or multiple) (Art. 46(f) Dir. 2001/83/EC & Art. 50(f); Dir 2001/82/EC)

C - Basis of Declaration (audit & supportive info)

D – Verification of the API supply chain (Art. 46a Dir. 2001/83/EC & Art. 50a Dir 2001/82/EC)

E - Attestation of the Responsible QP

FULFILLING EU REQUIREMENTS AND OBLIGATIONS: DIRECTIVE 2001/83/EC (2011/62)

Manufacturer‘s obligations 

- To verify the compliance of the API manufacturer with GMP requirements
- To perform audit in order to confirm API manufacturer‘s complience with GMP/GDP
- To ensure that the excipients are suitable for use in medicinal products
- To verify that economic operators are registered with the competent authority of the Member State in which they are established
- To verify the authenticity and quality of the API

FULFILLING EU REQUIREMENTS AND OBLIGATIONS: PLACING MEDICINAL PRODUCTS ON THE MARKET

Directive 2001/83/EC and Regulation 726/2004 require

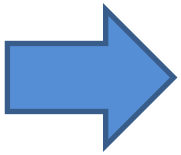
- Contract with marketing authorisation holder
- Required labeling and package leaflet
- Responsibilities for marketed product

- Classification
- P&R

CHANGING RELATION TO EU & 3rd COUNTRIES

- Manufacturers become ⇒ EU manufacturers
- Importers become ⇒ EU importers:
  - Import = from non EU countires/3rd countries only
  - transfer = from EU countries
- Parallel import and parallel distribution → within EU only
- …

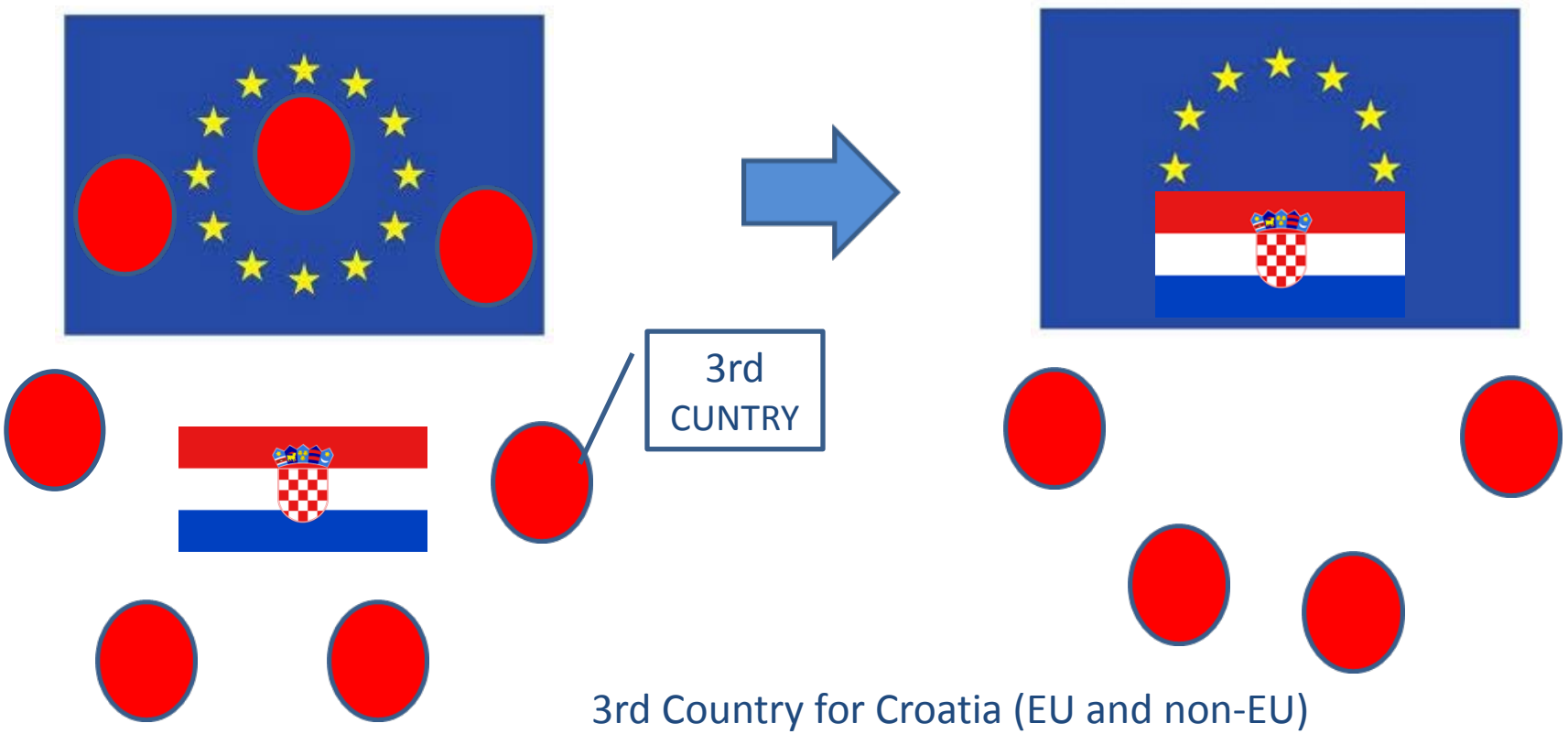
CHANGING RELATION TO EU & 3rd COUNTRIES



If placed in Croatia
Non-EU manufacturer

EU manufacturer

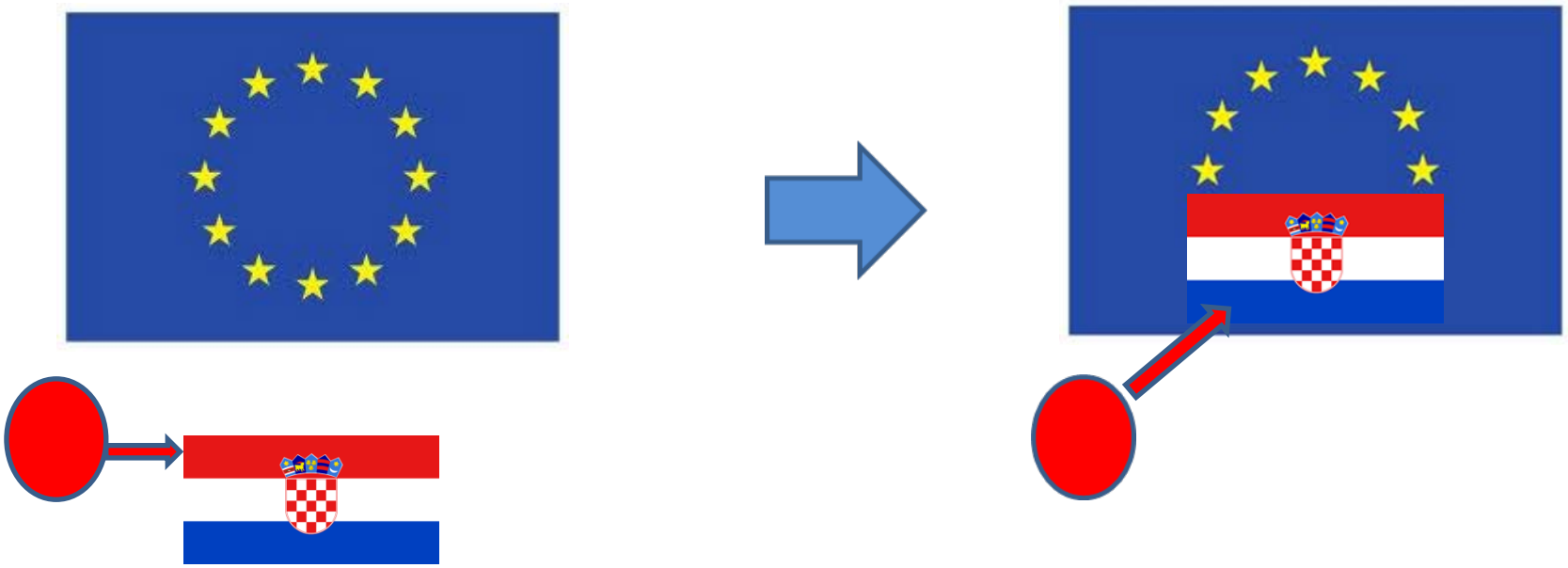
CHANGING RELATION TO EU & 3rd COUNTRIES



3rd Country for Croatia (EU and non-EU)

3rd Country for EU (non-EU)

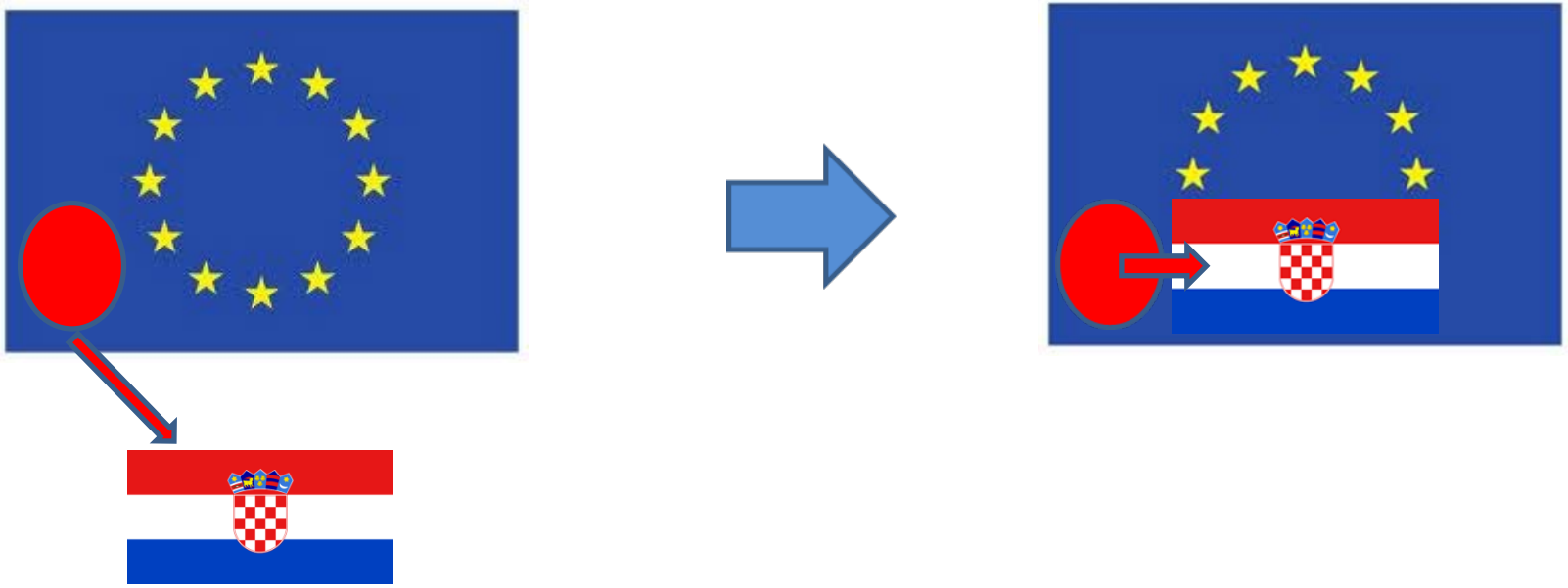
CHANGING RELATION TO EU & 3rd COUNTRIES



Import to Croatia

Import to EU

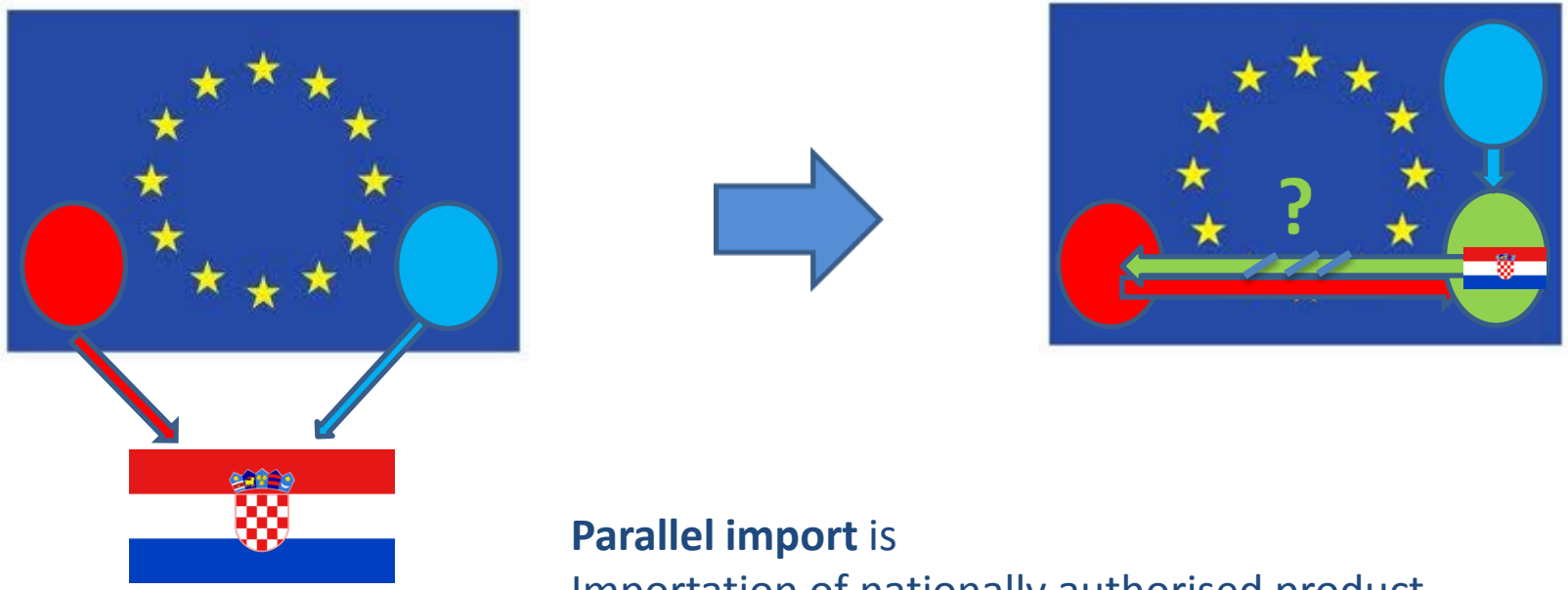
CHANGING RELATION TO EU & 3rd COUNTRIES



Import to Croatia from EU

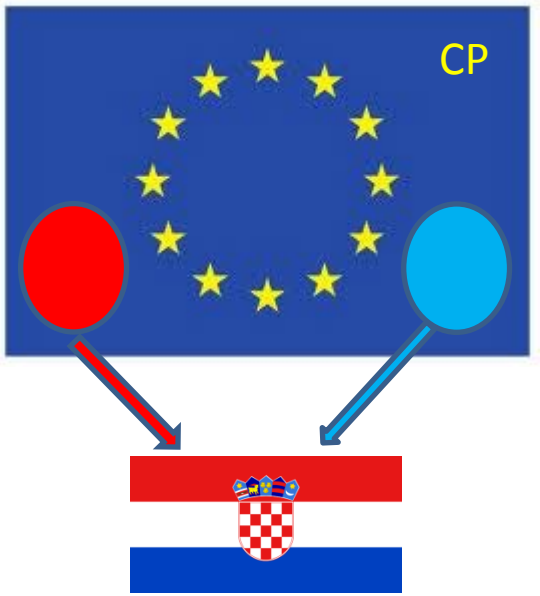
Distribution between MSs

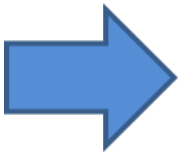
CHANGING RELATION TO EU & 3rd COUNTRIES

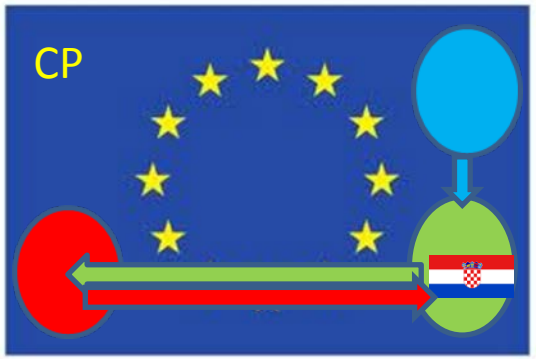


Parallel import is
Importation of nationally authorised product into MS (A) from MS(B), but where the importation is carried out by someone other than a person appointed by the manufacturer/ holder of the marketing authorisation
(will PI be blocked from CRO by 2017 ?)

CHANGING RELATION TO EU & 3rd COUNTRIES



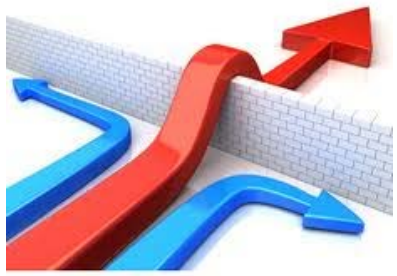




Parallel distribution is
Distribution of **centrally authorised** medicinal product transported into MS (A) from MS(B), but where the distribution is carried out by someone other than the person appointed by the manufacturer/holder of the MA

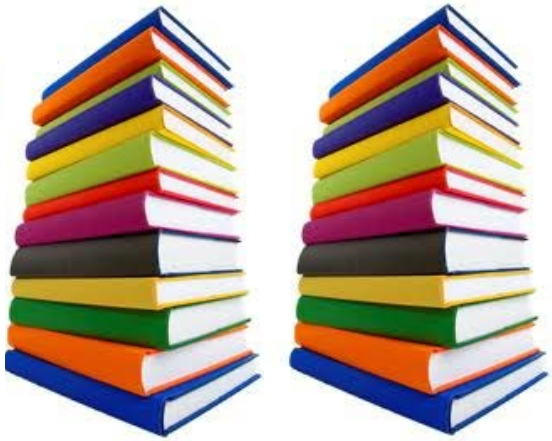
UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD (2017)

- Challenges:
- Art. 6 of Dir. 2001/83/EC: No medicinal product may be placed on the market of a Member State unless a MA has been issued by the CA of that MS in accordance with this directive or an authorisation has been granted in accordance with CR 726/2004/EC
- No „minimum requirements“ ➡ „hard law“ to be followed
- Availability of medicinal products



UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD

- Derogation: upgrading of old documentation by the end of transitional period
- Preparing documentation:
  - strategy (manufacturer‘s priorities vs. availability)
  - timing (renewals or not, deadline)
  - regulatory dilemmas (generic application vs. WEU…)



UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD

The role of the list of products to be upgraded

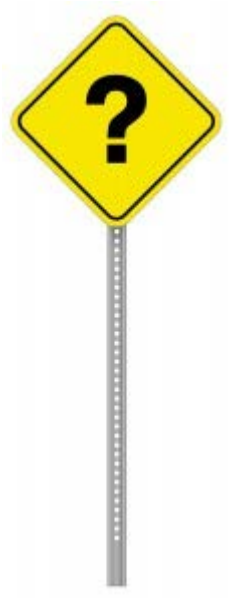
- additional document provided to the EC during negotiations for the transitional period as a picture of the scope of the problem?

or

- leading document linked to the granting of the transitional period?

UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD

What is the understanding of the requirements for the upgrading?



- should the structure and the content of the file be followed (or does CA's discretion right to decide about the upgraded dossier start only after all missing parts of the dossier have been submitted)?
- should hard law requirements be followed?

UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD

What is the understanding of the requirements for the upgrading?

- should the same MP with non-upgraded documentation and actually marketed in the EU
  - remain on other MSs‘ market and
  - be withdrawn from Croatian markets after the day of accession?

- ECJ CASE C-527/07:….“*placing of the product on the market in a Member State was not authorised in accordance with the applicable Community law, cannot be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of Directive 2001/83/EC …*

  (no further marketing ban)

UPGRADING OF OLD DOCUMENTATION BY THE END OF TRANSITIONAL PERIOD

- effects of upgrading of old dossiers
  - withdrawal of old products of a good quality?
  - higher prices for newer products not always with added value?
  - investing in upgrading!
  - upgrading exercise & maintaining the access to existing medicinal products of a good quality !!
  - working together !!!

THANK YOU !
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