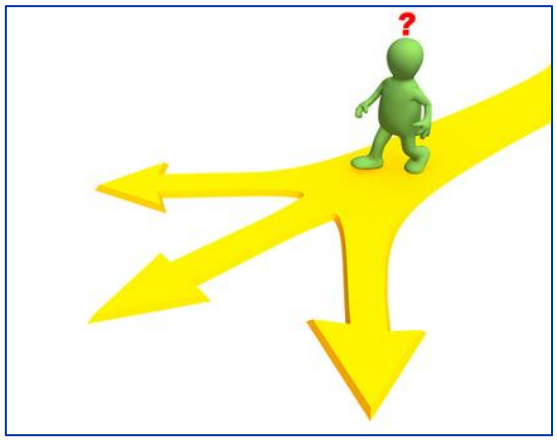
An SME perspective on the MAA process (including e-dossier preparation and submission)

Session 4: Regulatory issues in the run-up to dossier submission (part II)

Outline

1. Introduction
2. MAA process and SME Office
3. Unique challenges
4. Conclusion

Introduction



SME Initiative: SME Office & Incentives

How are the current incentives helpful to navigate the MAA process?

Regulatory Challenges of MAA Process for SME

Numerous procedures

- Need understanding of regulatory review process and its complexity
- Several committees involved during development
- Numerous contacts (PIP, ODD; MAA, SME, etc.)

Numerous documents

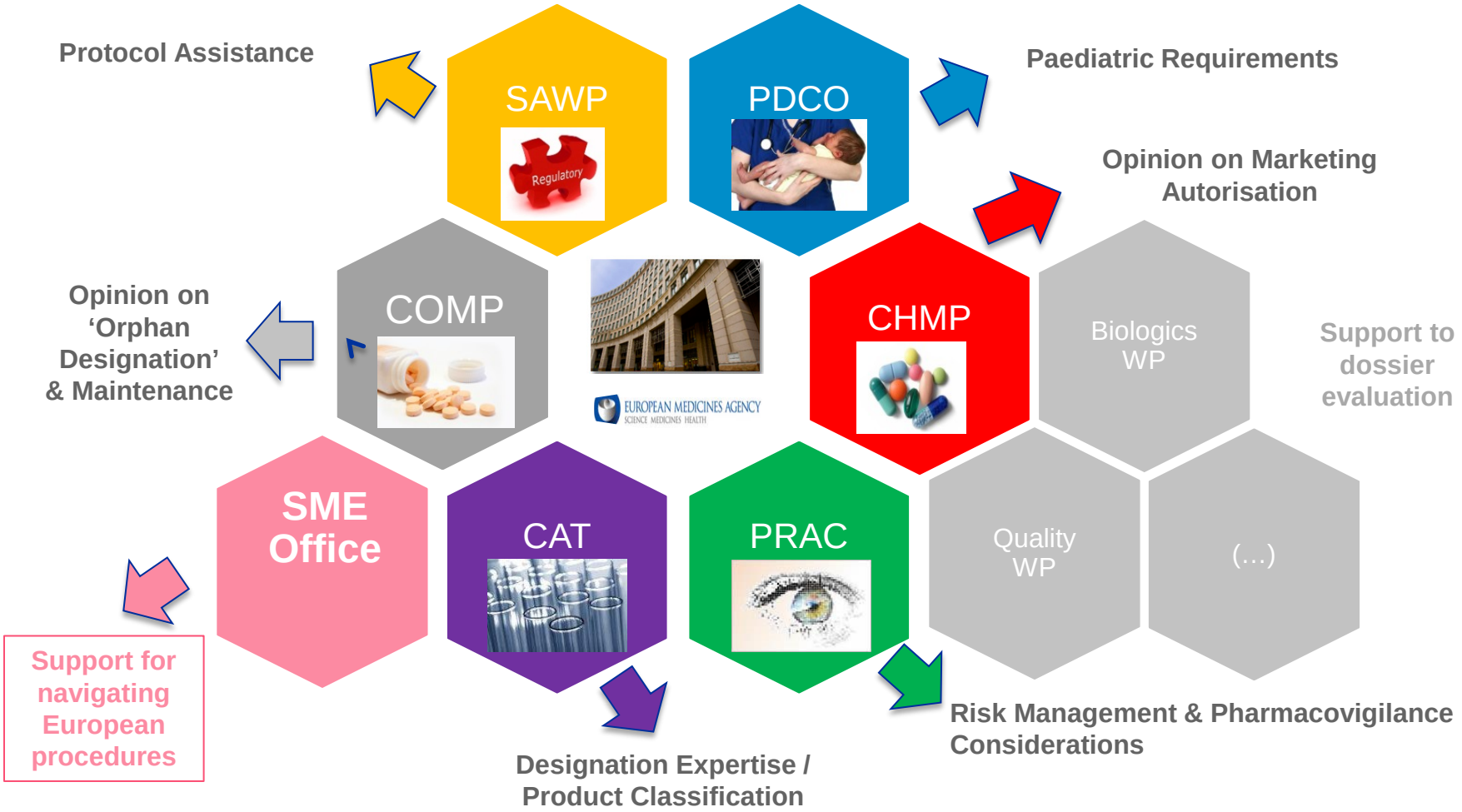
- Multiplicity of dossier requirements
- No or limited in house regulatory expertise
- No or limited knowledge of dossier content and format
- For PIP, requirements to submit per product

Regulated environment

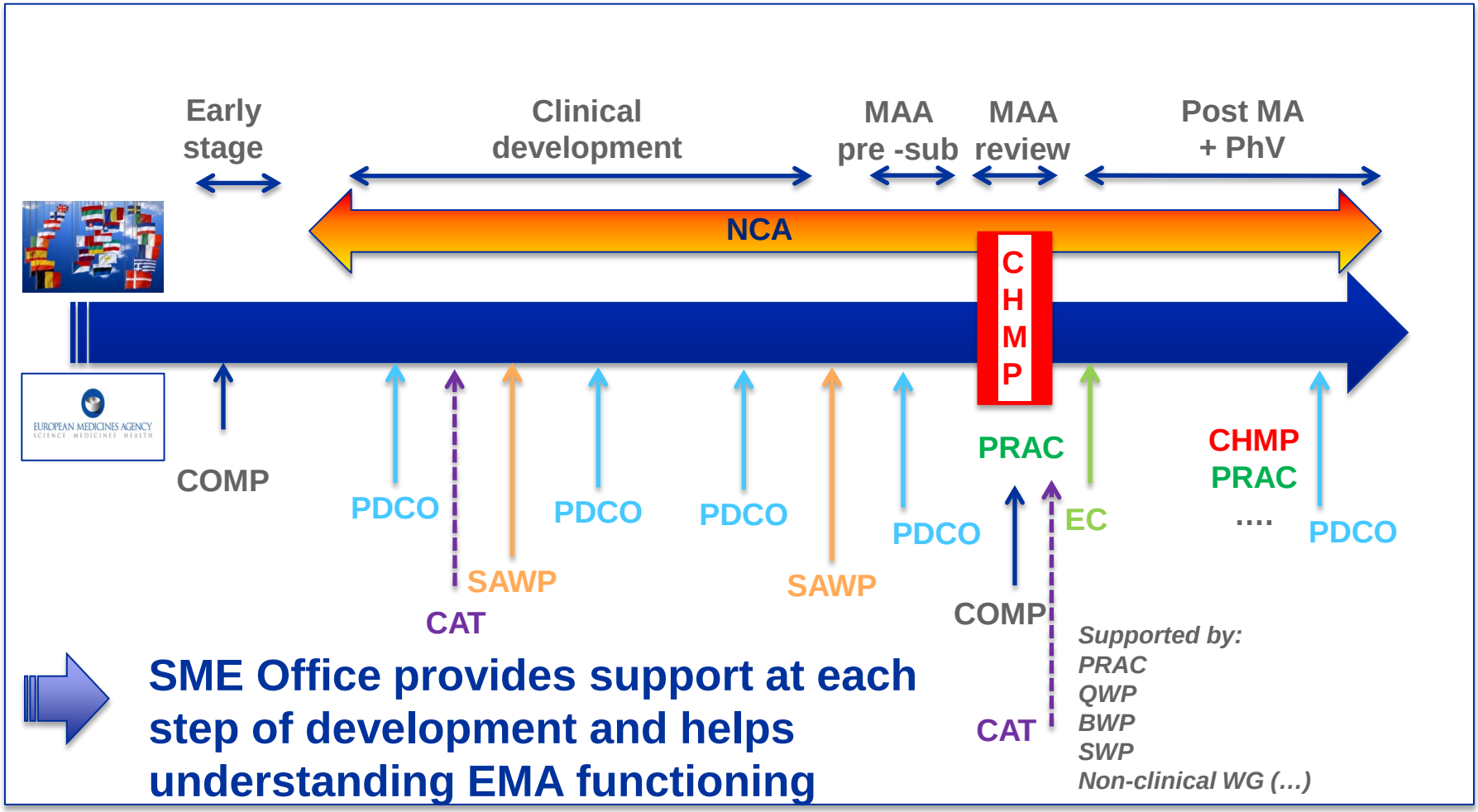
- No or limited in house knowledge of requirements, regulations, guidelines
- Limited information about changing regulatory requirements and legislation

Navigating the European Regulatory Landscape

The EMA's scientific committees



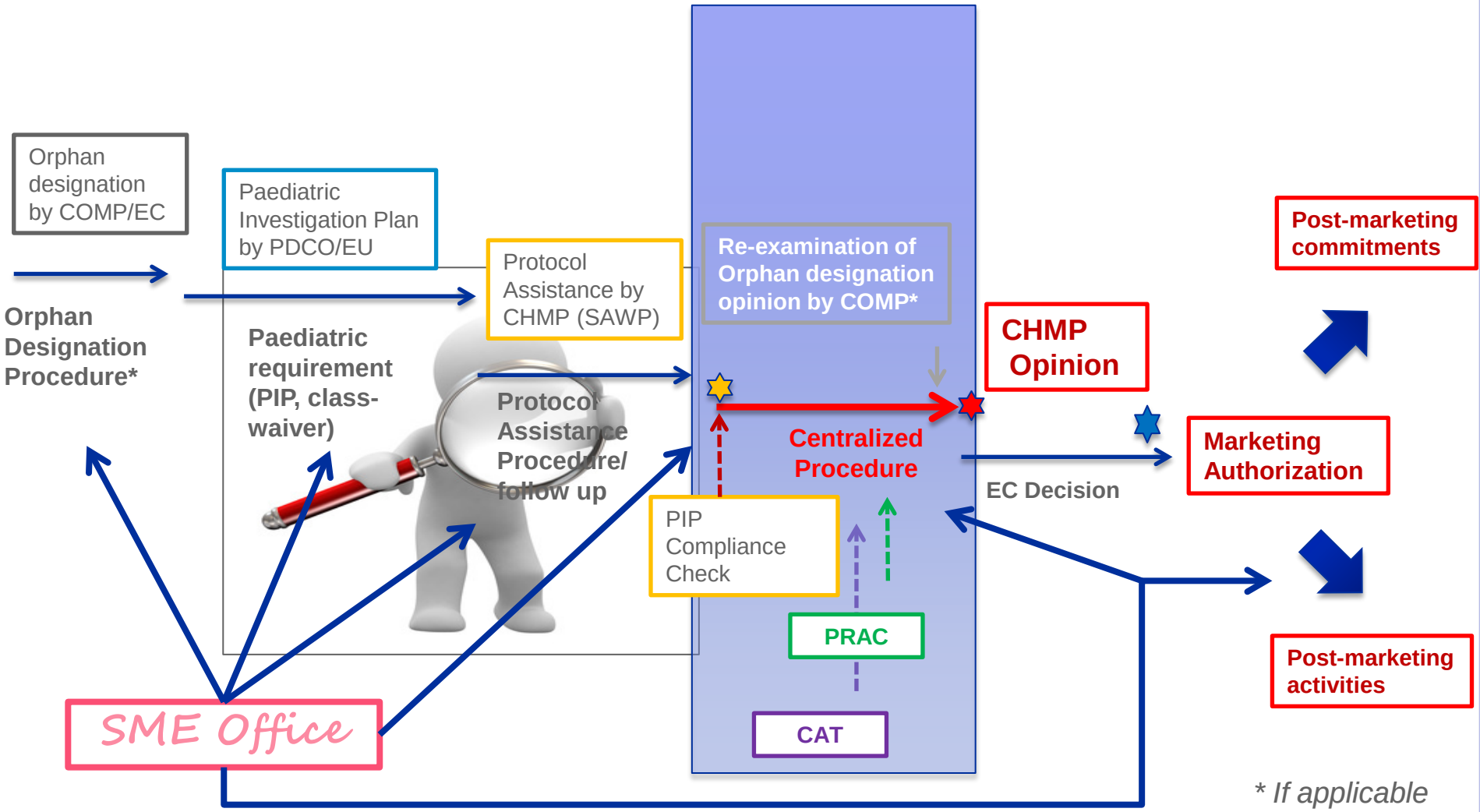
Diversity of Regulatory Interactions in Europe



ALEXION

Marketing Authorization Process in EU

A step-wise approach



ALEXION

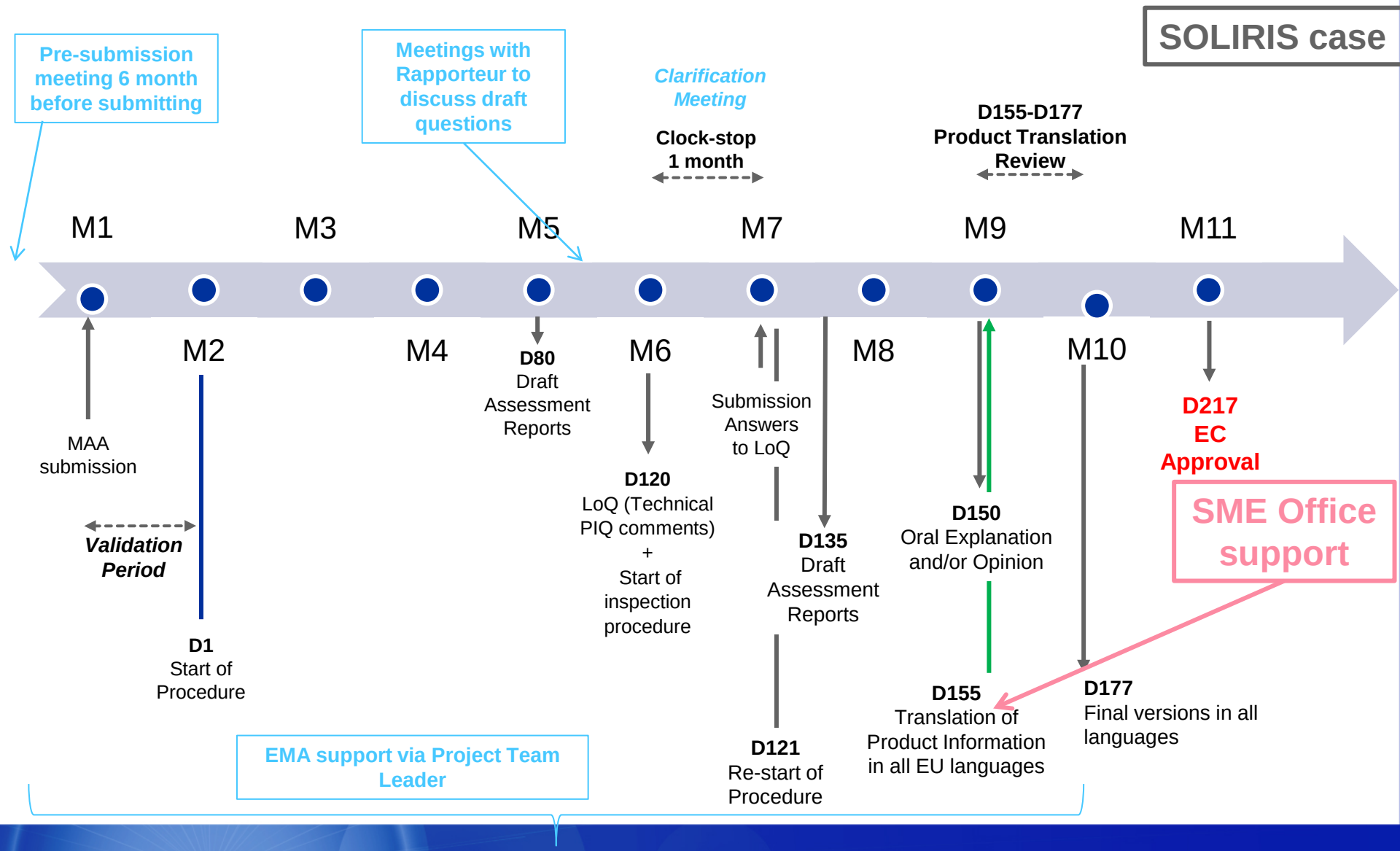
Pre-MAA Activities

- Accelerated Assessment Procedure request
- Eligibility for CP request
- Letter of intent to submit
- Pre-submission meeting request
- Rapporteur / Co-rapporteur meeting requests
- Compliance check
- ATC code request
- Invented name request
- Fee reduction request

SME Office is providing helpful support

→ Soliris case: frequent informal interactions

MAA Accelerated Assessment Procedure



ALEXION

Product Information Translation

D1 to D155 **Product Information Review (English version)**	• Final draft submitted with initial MAA • First set of comments D120 (+ PIQ comments) • Revised version submitted at D121 • Second review D121-150 – frequent interactions with EMA/Project Manager • Final text adopted D150 (positive opinion)
D150 to D155 Generation of translated versions	22 European languages + IS and NO (+ CR) **SME Office support**
D155 to D177	Translation Review by Member States

Remaining Challenges Post-Authorization

- National steps to be performed:
  - European Article Numbering code
  - Blue-box
  - Risk Management Plan implementation

→ **Time- and resources-consuming process, lots of variability, lack of up to date information**

No specific support to date to expedite national process (guidance information provided in SME User Guide)

- Navigating post-marketing regulations

→ **Close regulatory surveillance needed**

SME Office publication

Remaining Challenges Post-Authorization

23 Issue 23
March 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SME Office
NEWSLETTER

Information for SMEs in the EU regulatory environment for medicines.
Published four times a year by the European Medicines Agency.

An agency of the European Union

IN THIS ISSUE

Pharmaceutical development guidance

Two annexes to ICH guidance Q4B which recommend that analytical procedures described in the official pharmacopoeial texts can be used interchangeably in the ICH regions were announced on:

- Bulk density and tapped density of powders (EMA/CHMP/ICH/405290/2010), which will come into effect in January 2013.
- Bacterial Endotoxins (Ph.Eur.2.6.14. Bacterial Endotoxins, JP 4.01 Bacterial Endotoxins Test, and USP General Chapter <85> Bacterial Endotoxins Test) (EMA/CHMP/ICH/529785/2010). It will come into effect in May 2013.

A draft guideline on the pharmaceutical development of medicines for paediatric use was released for consultation (EMA/CHMP/QWP/805880/2012 Rev. 1). Specific sections of the document on e.g. handling of oral solid preparations to facilitate administration, mixing with food and drinks and patients acceptability were revised following a first round of consultation. The guideline is now open for further comments until 1 April 2012.

A draft guideline on the use of porcine trypsin in the manufacture of human biologics was released for consultation until 31 August 2013 (EMA/CHMP/BWP/814397/2011). Porcine trypsin is a reagent widely used in the manufacture of vaccines and recombinant proteins. It is extracted from the pancreas of pigs, and carries the risk of contamination with adventitious agents such as viruses.

A draft ICH guidance on the photosafety evaluation of pharmaceuticals was published on 17 December 2012 (CHMP/ICH/752211/2012). The document should be read in conjunction with the photosafety testing section of ICH M3 (R2). It applies to new active substances and

SME support in monitoring newly released or changed regulatory requirements

How are SMEs handling the electronic submission requirement?

Fundamentals of eCTD

eCTD

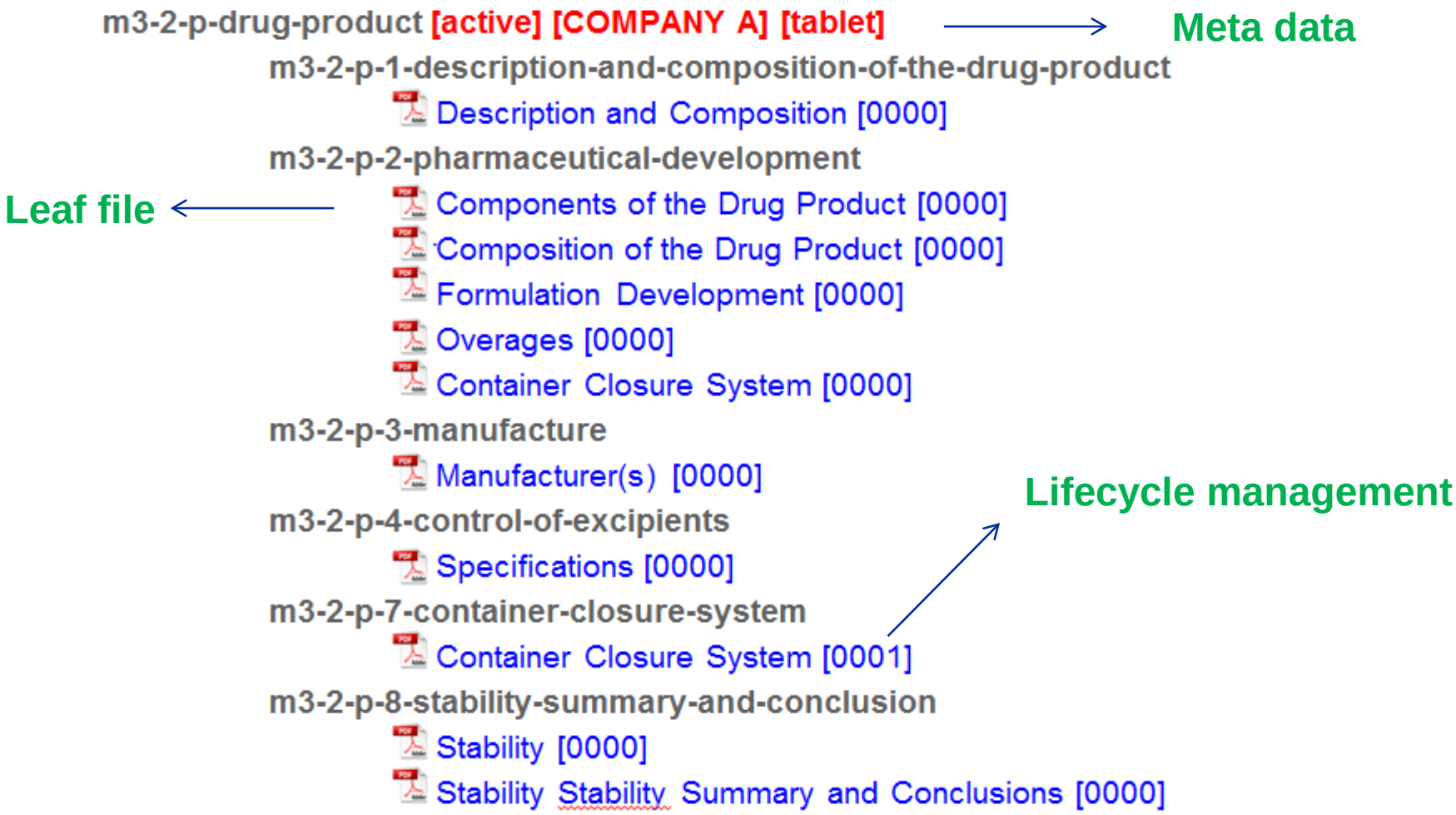
- Offers a standard format of submission to different agencies
- Improves lifecycle management
- Enhances the transfer of information between sponsor, outsourcing partners and authorities
- Offers ability to rapidly find the components, re-use some documents
- Allows transparency of changes/variations amending the MAA dossier

However, …

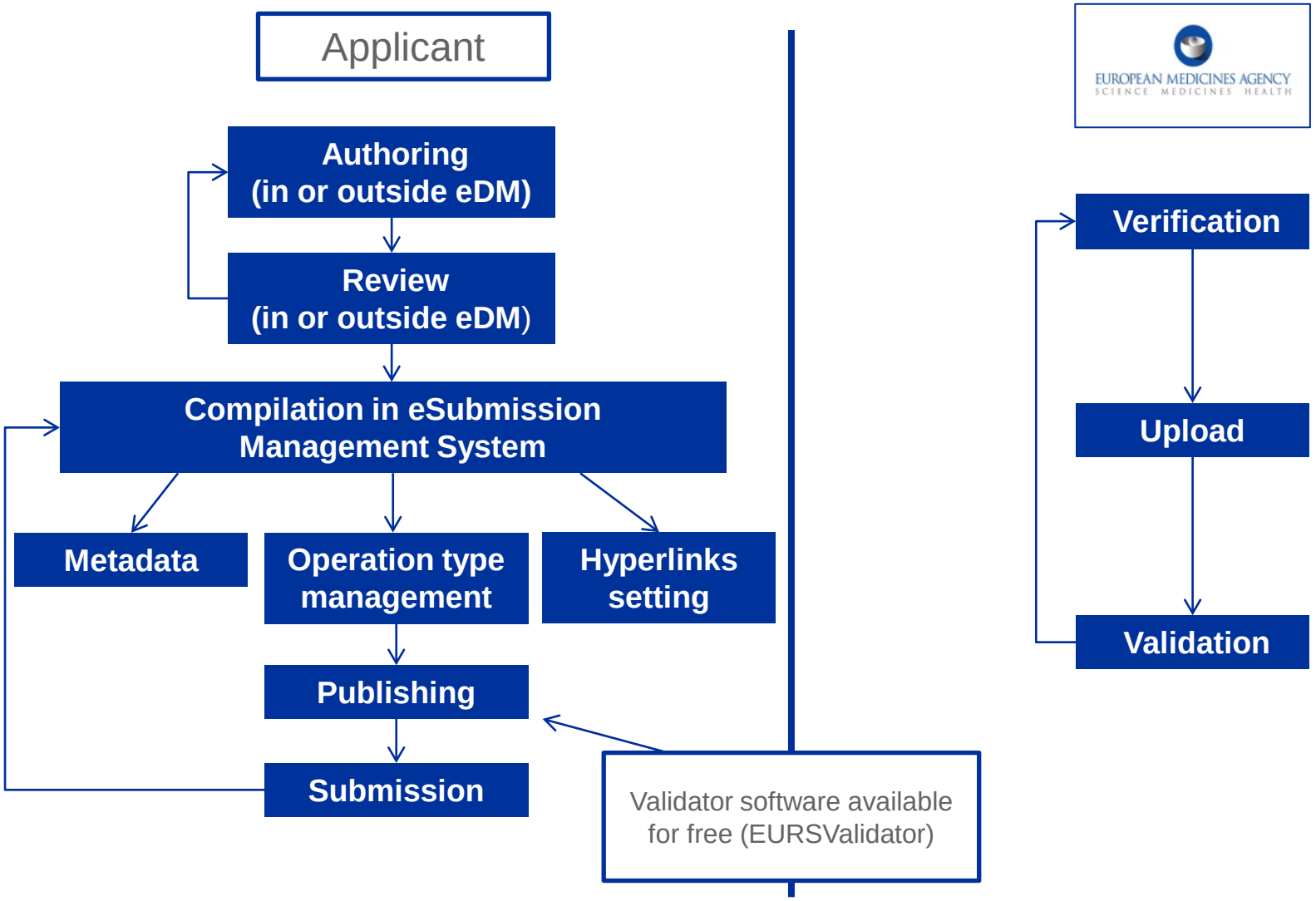
eCTD requirement → Additional complexity

- Specific technical knowledge required, staff training, implementation of tools to meet e-submission criteria
- Strict compliance with defined formatting requirements required for a successful validation

XML backbone: Different Components



eCTD – Basic Process Flow



eCTD – Looking into the Future

- Requirements will continue to change / mount
  - ➡ leading to refinement and improvement of eCTD specification and harmonization of the standards
- Adequate processes required to keep pace with Regulation changes
- e-submission expertise CRITICAL
- Interest of managing eCTD dossier using a web-based approach → working in a “cloud” environment

Different Approaches to Consider for SMEs

Outsourcing solution or in-house production, which direction to go ?

Critical components to be considered:

- *eCTD ready documents*
- *fully compliant eCTD document management system*

Different Approaches to Consider for SMEs

Advantages of OUTSOURCING

- To avoid the purchase and maintenance of expensive tools
- To avoid the training of employees not familiar with the production of eCTD-compliant dossiers
- To take advantage of global experience built on a large client database
- To avoid delays in producing high quality work

Different Approaches to Consider for SMEs

Drawbacks of OUTSOURCING

- Intensive preparatory work cannot be avoided
- Loss of business control of the company's operations
- Cost (or/and hidden cost)
- Total dependence on the outsourcing company
- "Know-how" not developed within the company
- Assure that each individual vendor involved in document preparation can deliver compliant-eCTD documents as part of their services

Different Approaches to Consider for SMEs

Is the IN-HOUSE production a right direction to go for SMEs ?

Specific considerations:

- Can you hire Regulatory Operations professionals?
- Acquisition of viewing software to enable people to review submission
- List all Software to purchase for eCTD compilation & consider their costs
  - Templates for authors
  - Desktop tools to create and manipulate PDF files
  - Publishing software to create & validate the xml backbone

Different Approaches to Consider for SMEs

What about a Combined Approach (Hybrids) ?

Examples:

- Develop in house eCTD document templates & share them
- Outsource fully integrated and compliant document management system
- Outsource first submission, bring the rest in-house
- Services “à la carte”: chose vendors and consultants according to specific needs (networking solution)
- In-house publisher, with contractors for document formatting
- In-house formatting, with contract publishers

Conclusions

- MAA process currently well supported by EMA/SME Office
- SME initiative has been helpful supporting Soliris review process & supporting SMEs in general
- Specific considerations for eCTD:
  - Technical requirements increase dossier preparation complexity
  - Hybrid solution may be the right answer

Thank you for your attention