EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Active substances

from starting materials to ASMFs

SME Workshop – 04 April 2014

Ruben Pita
European Medicines Agency

General information - *contents, structure, guidance*

Requirements for Active Substance dossier submission:

- Annex I of Directive 2001/83/EC
- Notice to Applicants Volume 2B

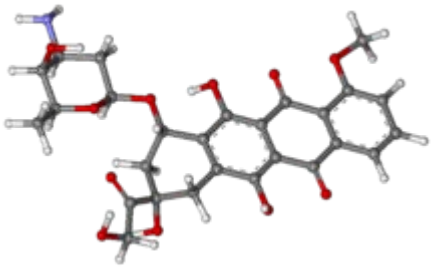
(...)

Quality standards and Guidance:

- QWP Guidance
- ICH guidance
- European Pharmacopoeia

(...)

Chemical entity - Definitions



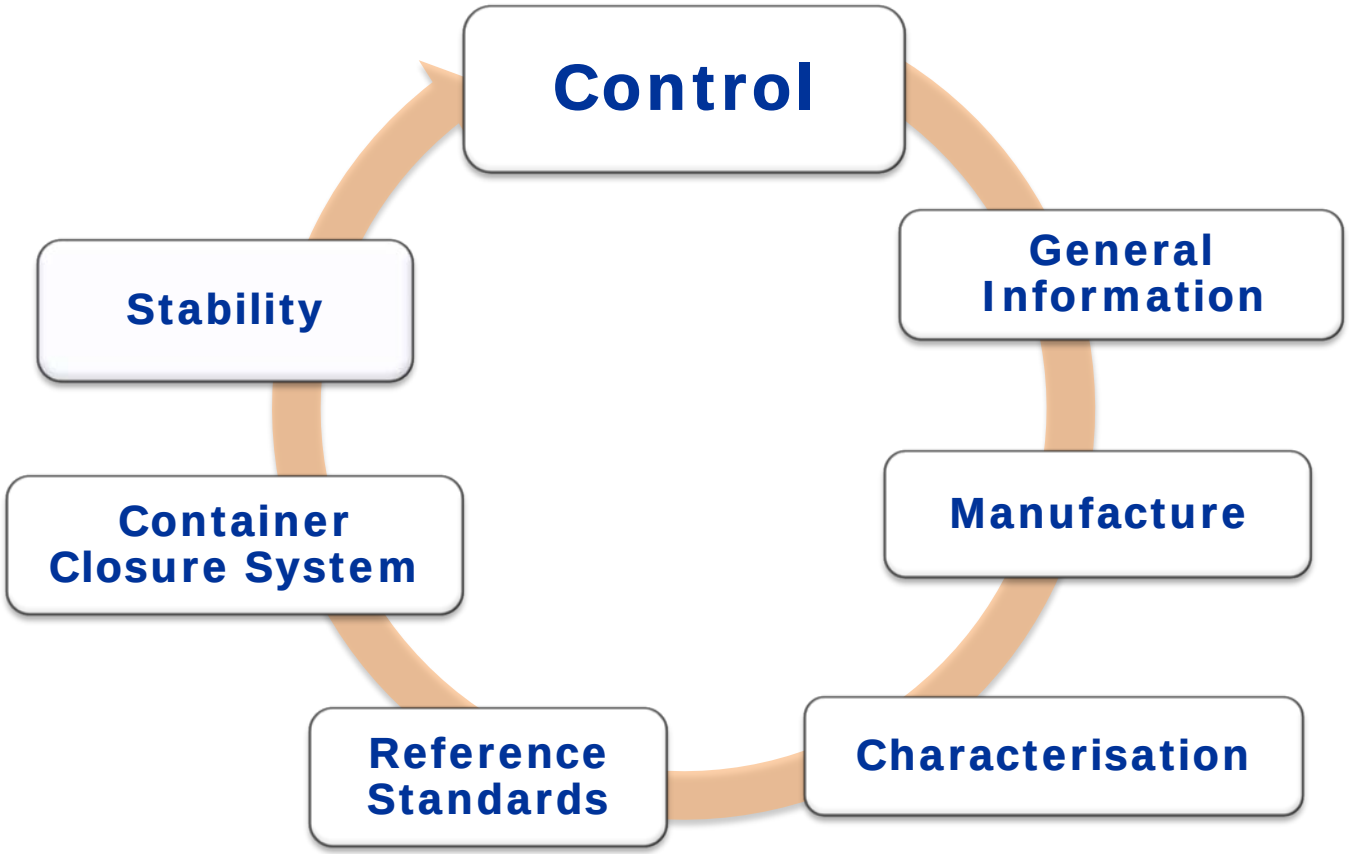
Not a biological

"A biological substance is a substance that is produced by or extracted from a **biological source** and that needs for its *characterisation* and the *determination of its quality* a combination of **physico-chemical-biological testing**, together with the **production process** and its **control"**

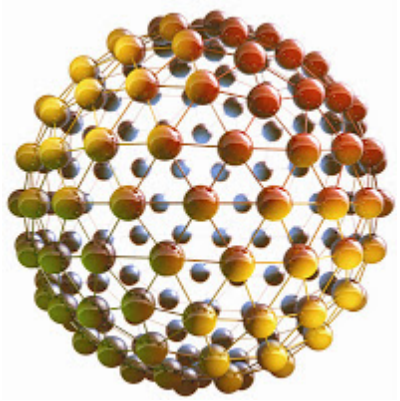
Not a herbal

"(…) whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh"
not subject to any step of chemical synthesis

General information – *Sections of Module 3.2.S*



Defining the active substance



- Different polymorphic forms
- Chiral substances
- Multicomponent active substances
- Other relevant properties, e.g. nanomaterials
- Mixtures (active + active or excipients)
- Expression of Strength (active moiety vs salt/hydrate)
- *in situ* formation

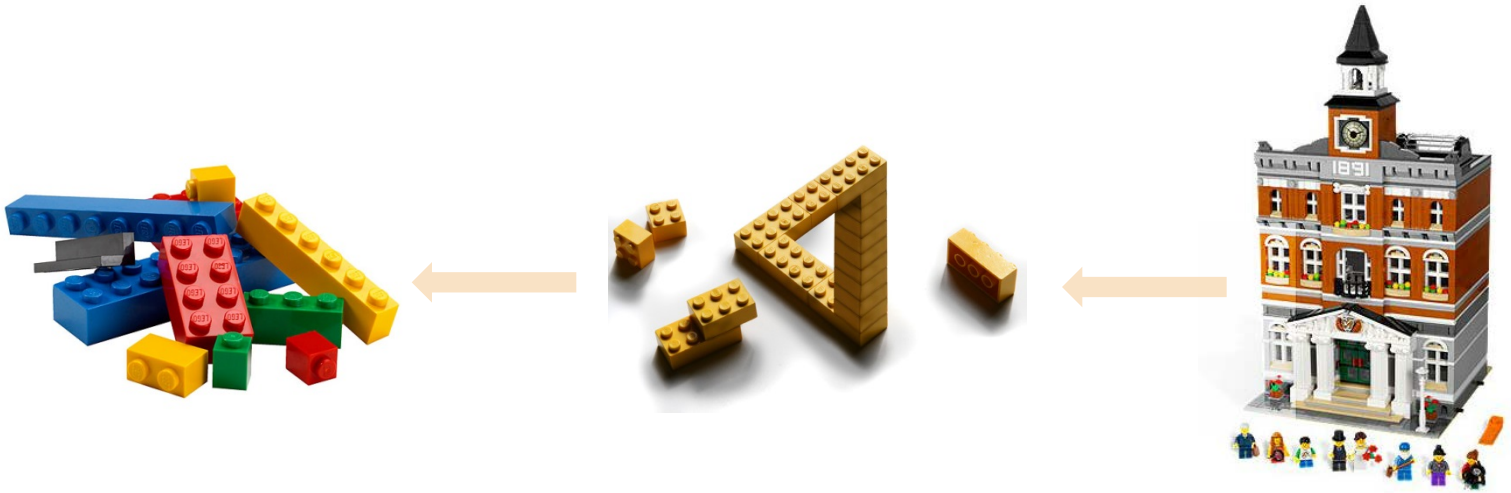
Manufacture - Manufacturing process

- Declaration of all manufacturing sites involved, in which steps, with which synthetic options
- Description of the manufacturing in the form of a flow diagram and sequential procedural narrative, see ICH M4Q
- Guideline on process validation, principles also valid for active substances

“information on validation of non-sterile active substances is not required in the dossier”

Manufacture - Selection of Starting Materials

- Definition of the beginning of the regulated synthesis and selection of starting materials - ICH Q11



- Driven by the understanding of all critical steps of the manufacturing process that may impact on the impurity profile of the active substance

Manufacture - Selection of Starting Materials

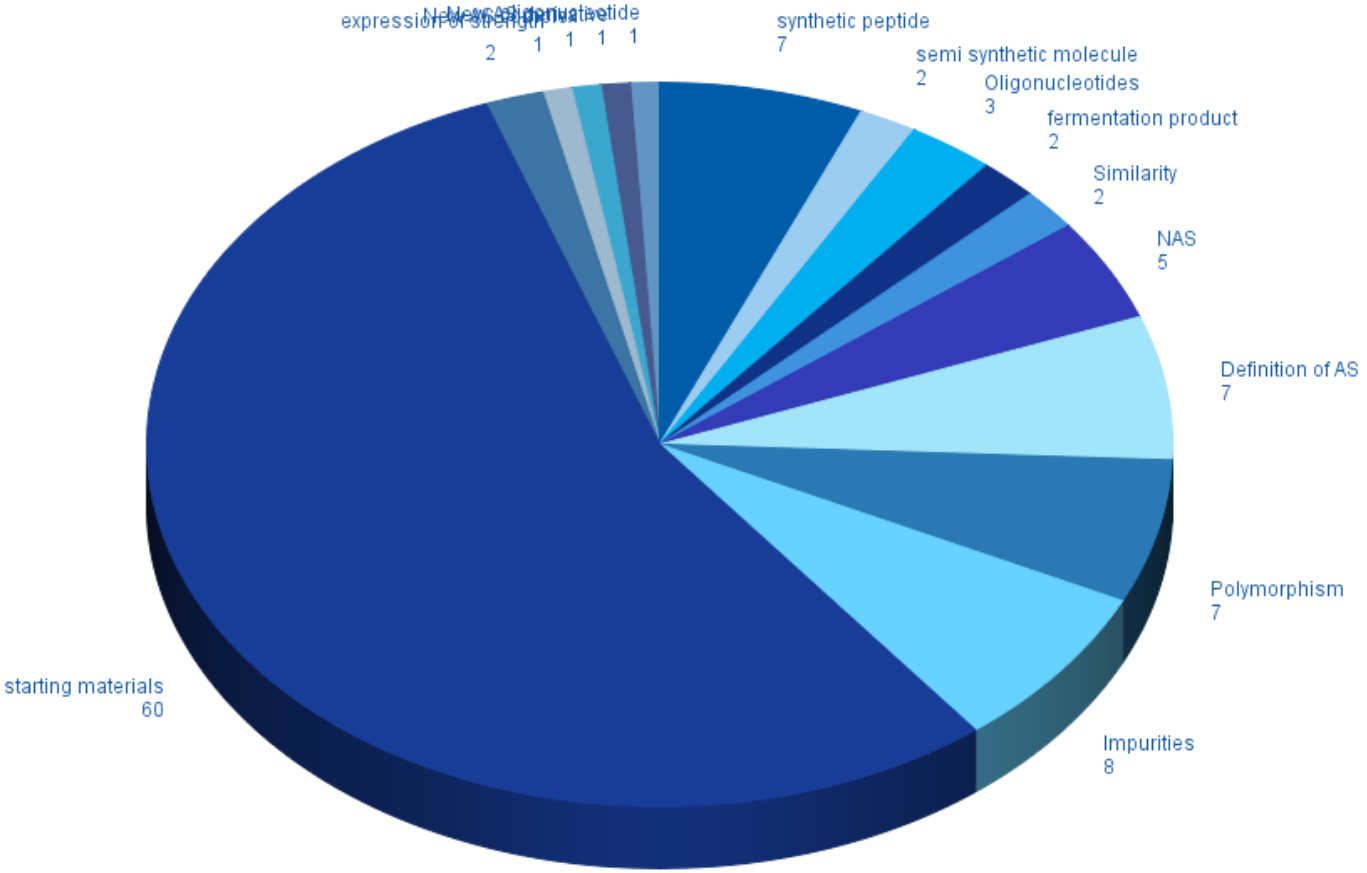
GMP (ICH Q7) starts with the first use of a starting material

GMP compliance together with an appropriate control strategy provides assurance of quality of the drug substance

- Defined chemical properties and structure, not a non-isolated intermediate
- Significant structural fragment
- Adequate specification
- Representative of the overall synthetic process

Declaration of all sites - **GMP compliance** (QP declaration)

Discussions at QWP CT on Starting Materials



Manufacturing process development

- Critical Quality Attributes of the active substance in the finished product (manufacturing and in vivo aspects)
- Manufacturing changes during pharmaceutical development and clinical trials
  - potential impact to the safety/efficacy profile of the product
  - supported by adequate in vitro/in vivo data, as appropriate
- Satisfactory control of the manufacturing process, particularly when end testing may not fully control all attributes of the active substance

Characterisation - Impurities

- Origin of materials – e.g. TSE, DNA
- Understanding the origin and fate of all potential impurities
    - Reagents
    - Residual solvents
    - Process intermediates
    - Metal catalysts
    - By-products and Carry-over impurities from raw materials
    - Degradation products
- Limits and approach dependent on the type of product

  (synthetic, semi-synthetic, fermentation, e.g. antibiotics, radiopharmaceuticals)
- Genotoxic impurities

Control – Specification & Methods

- Description
- Identification
- Impurities
- Assay and/or potency

- Polymorphism
- Chirality
- Water content
- Microbiological quality
- Additional properties

active substance/finished product development data, pharmacopoeial standards, test data used in toxicology/clinical studies, and stability studies

- Substances for Pharmaceutical Use, Ph.Eur no. 2034
- Control of Impurities for Pharmaceutical Use, Ph.Eur. 5.10
- NtG Test procedures and Acceptance Criteria for New Drug Substances and New Drug Products
- NfG Validation of Analytical Procedures: Text and Methodology

Control – Batch Analyses

- Batch data from pre-clinical and clinical studies
- At least 3 consecutive batches of not less than 10 % of the commercial scale
- Demonstrate compliance with limits using the proposed analytical methods

Stability

- Forced degradation studies
- Stress conditions
- Accelerated, intermediate and long-term data
- Others (e.g. climatic zones outside Europe)

Which batches?

What container closure system? (identical/representative/different)

Special labelling requirements? (e.g. store in original package)

Link to QWP stability guidance

Submission of data

- Open file
- Active Substance Master File (ASMF)
- Certificate of Suitability - EDQM

eSubmission Guidance

Active Substance Master File (ASMF)

- Protection of confidential intellectual property or 'know-how' of the manufacturer of the active substance
- **Scope** - only for well-defined active substances, such as:
  - New active substances
  - Existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State
  - Pharmacopoeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State
  - Chemical or Herbal
- Biologicals, excipients and finished products **excluded**

Active Substance Master File (ASMF)

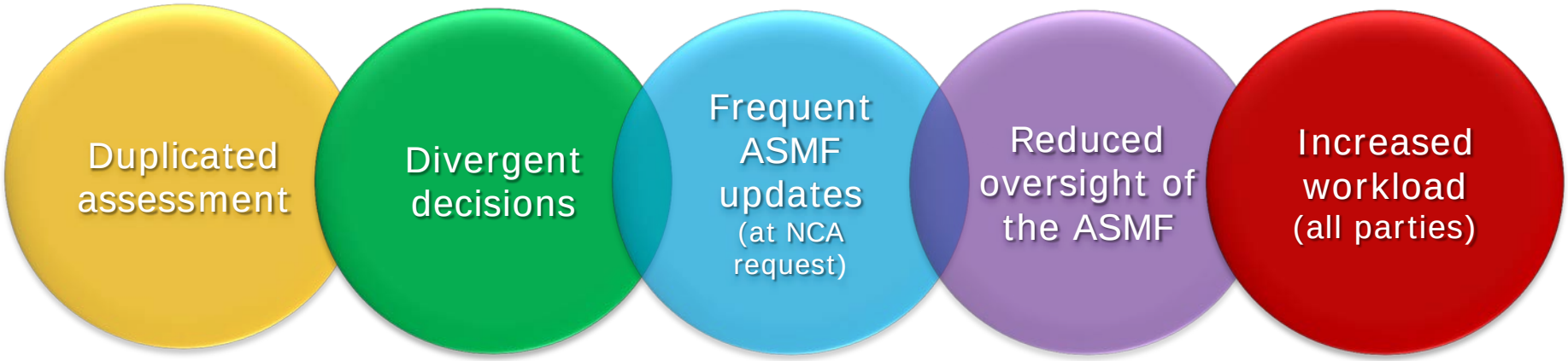
- Same information as in an open file but data divided in two parts
  - **A**pplicant's **P**art (also included in Module 3.2.S)
  - **R**estricted **P**art (only available to Competent Authorities)

- In case of more than one supplier of the active substance, a consolidated specification should be submitted in Module 3.2.S

- Strongly recommended to consult the available submission guidance:
  - EMA Pre-submission guidance, Q&A no. 24
  - Joint ASMF WG, Q&A

Active Substance Master File (ASMF)

Recognised that the **same ASMF** is used in **different products** & across **different procedures**



CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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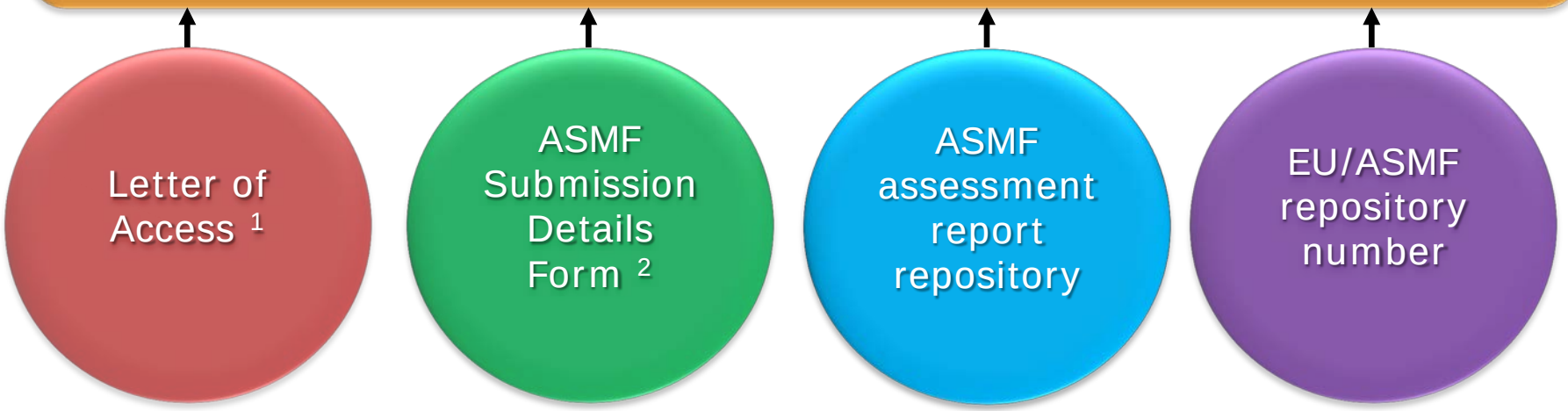
CMDv
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

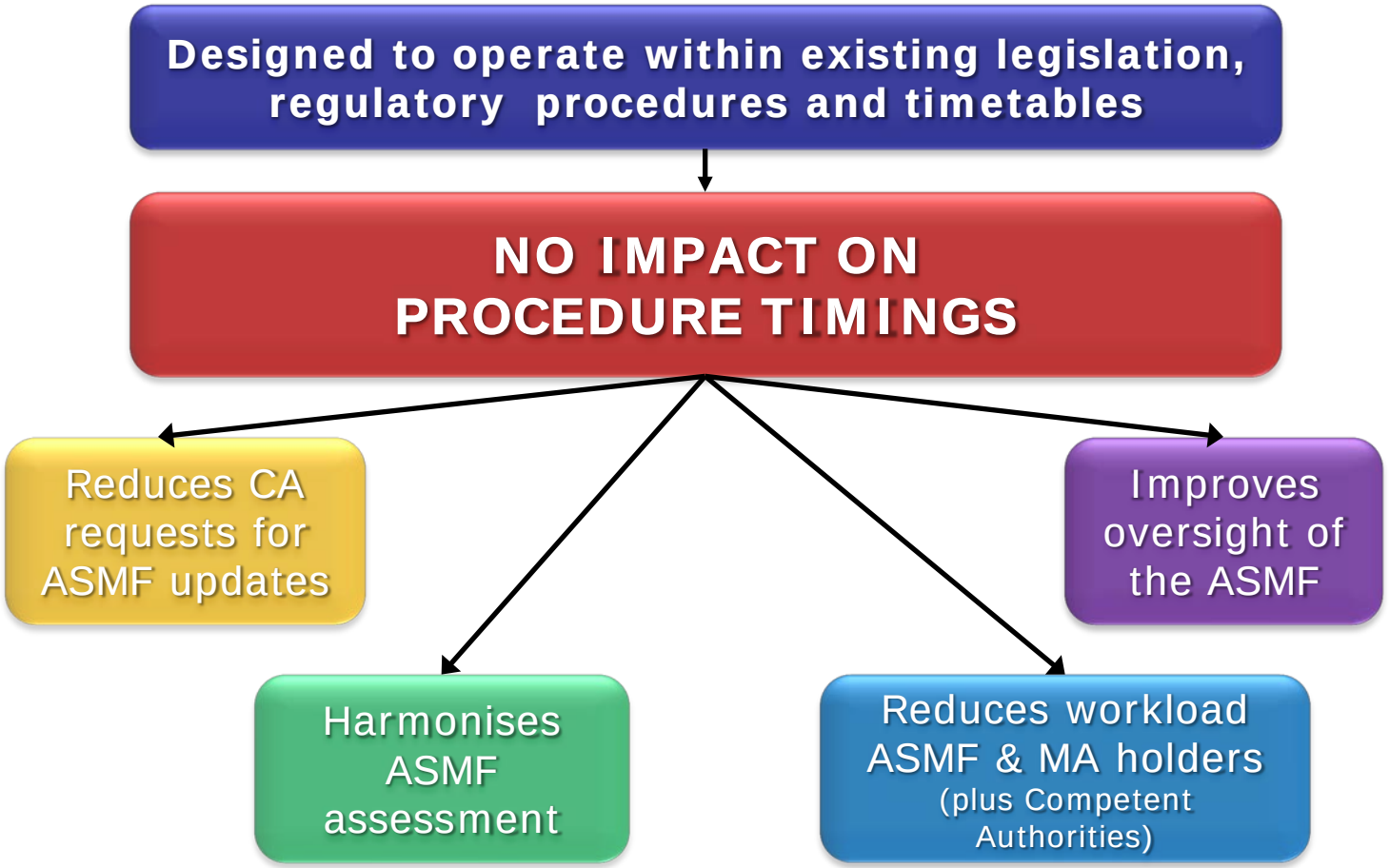
ASMF Assessment Worksharing Procedure

A simple way for Competent Authorities to share assessment report for the same version of the ASMF



[1] Annex 2 and [2] Annex 3 of CHMP/QWP/227/02 Rev 3/Corr Guideline on the ASMF procedure

ASMF Worksharing



Questions ?