EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Implementation of Article 57(2), second subparagraph of Regulation (EC) No. 726/2004

Agreed way forward and next steps

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Overview

- Introduction
- Background
  - Guiding Principles
  - Agency's phased implementation approach
- Main concerns raised by pharmaceutical industry
- Summary of agreed way forward and implications
- Current status and publication documents
- Next steps

Background

- Implementation of the electronic submission of information on medicines - first deliverable of new PV legislation
- Article 57(2), second subparagraph of Regulation (EC) No. 726/2004 requires:
  - The Agency to make public a format for the electronic submission of information on medicinal products for human use by 2 July 2011
  - Marketing authorisation holders (MAHs) to submit information to the Agency electronically on all medicinal products for human use authorised in the European Union by 2 July 2012, using this format
  - MAHs to inform the Agency of any new or varied marketing authorisations granted in the EU as of 2 July 2012, using this format
- Details on the legal provisions and requirements can be found in the Legal notice (updated 05/03/2012)

Background

This information will help the Agency to:

- Create a list of all medicinal products authorised in the EU including medicines authorised centrally via the Agency and medicines authorised by regulatory authorities in EU Member States
- Coordinate the regulation safety-monitoring and pharmacovigilance activities of medicines across the EU

This information will help stakeholders and the Agency to:

- Identify medicines accurately, especially medicines included in reports of suspected adverse reactions
- Facilitate the international harmonisation activities (ICH E2B and ICH M5)

Background

The Agency adopted a phased approach:

Phase one:	Notification of the electronic submission format (deadline of 1 July met)
Phase two:	Electronic submission by marketing authorisation holders
Phase three:	Processing (as of February 2012) Validation of the submitted information (as of release of data validation tool by ICT Unit)
Phase four:	ISO IDMP/ICSR standards implementation (initially scheduled for end 2014 as per agreement with EMA MB in March 2011)

Background - Guiding Principles

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As per EMA Management Board outcome of discussion in March 2011

- To plan for the implementation of the ISO ICSR and IDMP standards – EudraVigilance Audit
  - ISO/HL7 IDMP standards expected to be finalised mid 2012
- To strive for a timely implementation of the new legislative provisions to meet the objectives of the reform of the pharmacovigilance legislation
- To ensure that the EudraVigilance system remains fully operational and to increase transparency on EudraVigilance data in line with the current legal requirements, hereby meeting stakeholders' expectations
  - Adequately identify medicinal products in ICSRs and co-ordinate pharmacovigilance
- To avoid duplication of work
- To be as cost-efficient as possible
  - Use of existing EudraViglance Medicinal Product Dictionary (EVMPD) with minor updates
- To ensure efficient communication on the agreed strategy

Background

Agency delivered on time in accordance with the requirements set out in the new pharmacovigilance legislation

- *(a) Make public a format for the electronic submission of information on medicinal products for human use (by 2 July 2011)*

Taking into account the short time period (12 months) there is a challenge for pharmaceutical industry to comply

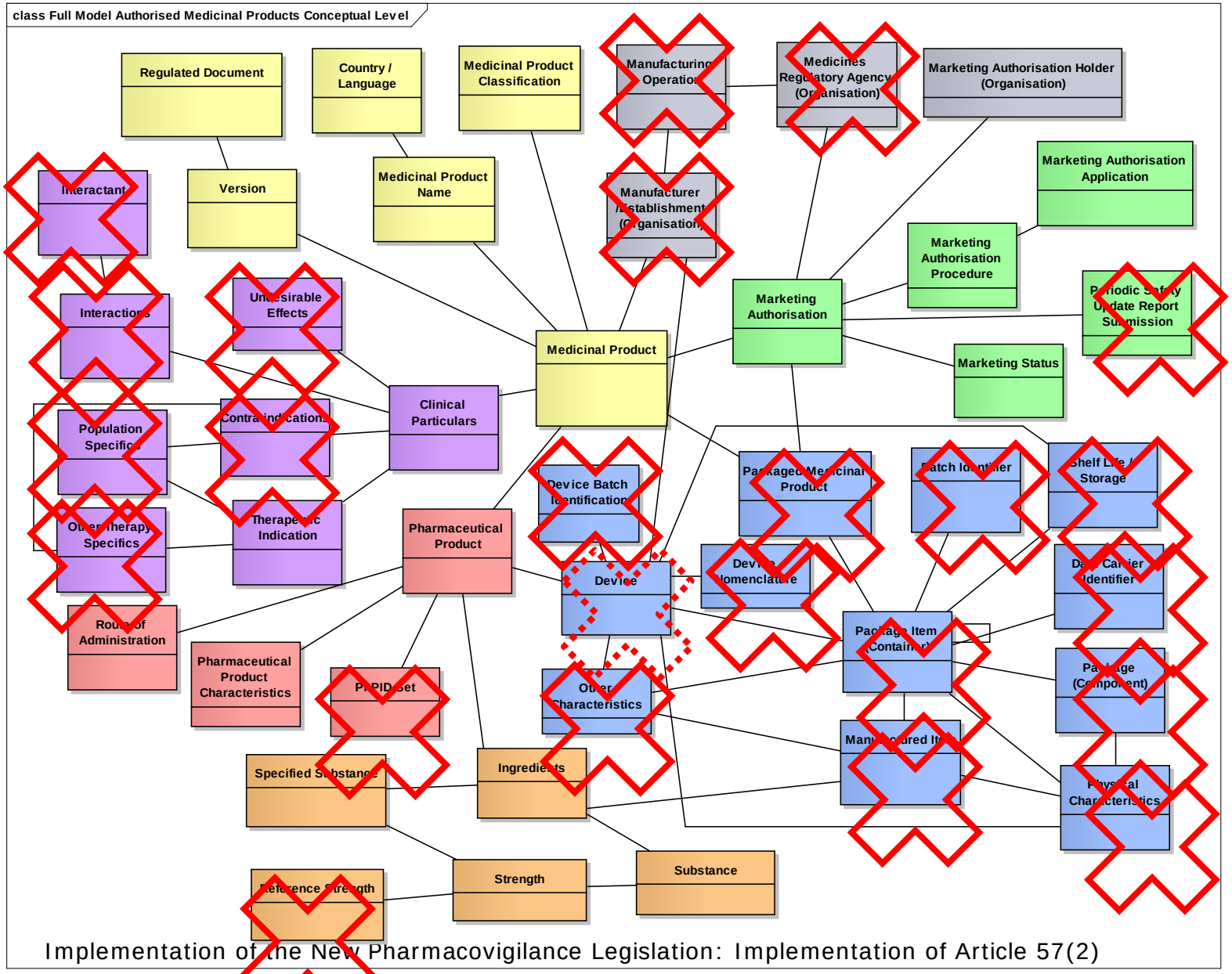
- *b) MAHs shall electronically submit to the Agency information on all medicinal products for human use authorised in the Union, using the format referred to in point (a) (by 2 July 2012 at the latest)*
- *c) MAHs shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a) from the date set out in point (b).*

Background – What the Agency delivered

The Agency delivered on 1 July 2011:

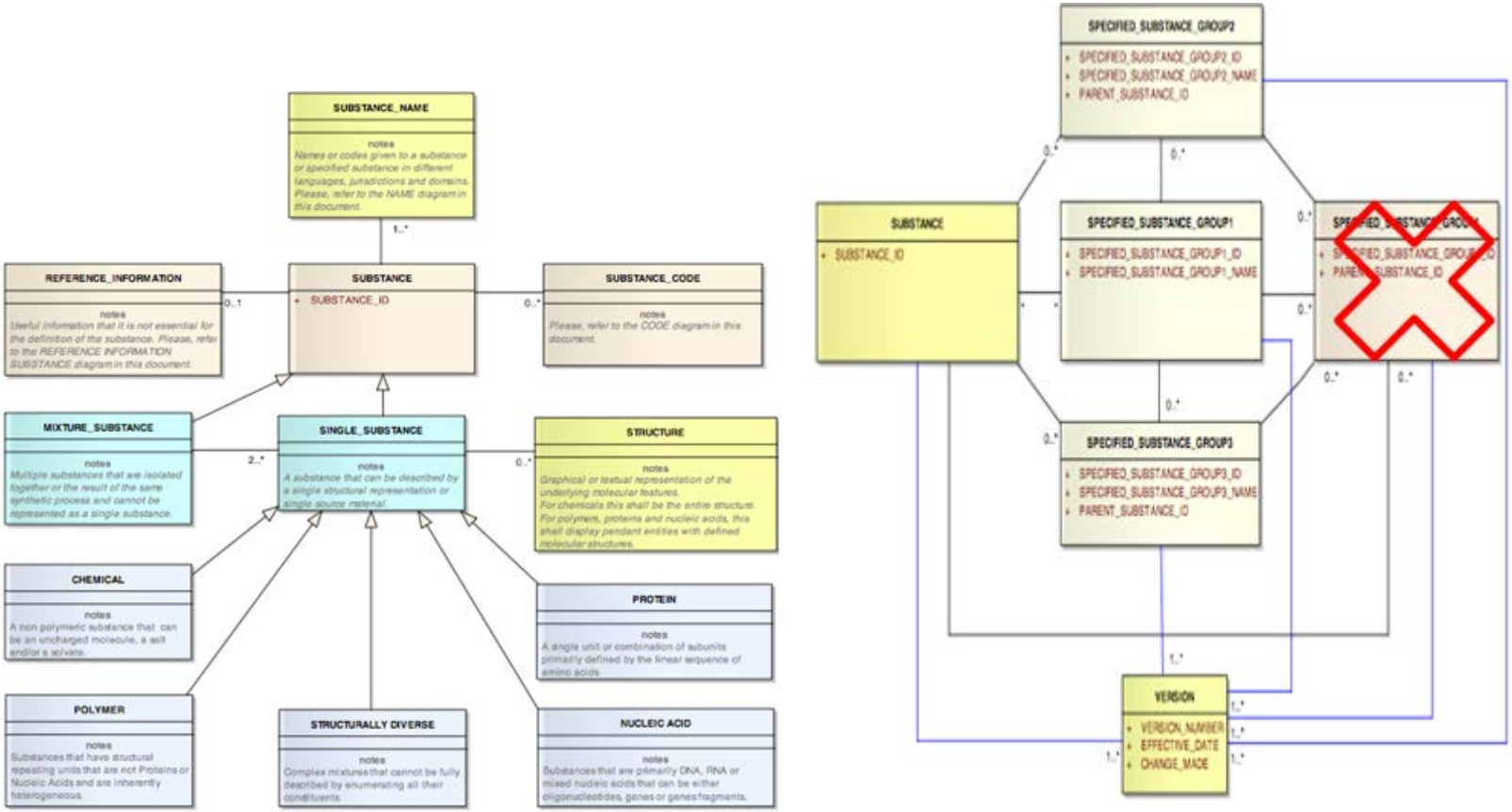
- Legal Notice: defines high level content and phased implementation
- Detailed Guidance: format for electronic submission of medicinal product information (Extended EudraVigilance Medicinal Product Message)
    - Data elements that characterise a medicinal product
        - 30% of ISO IDMP standard (FDIS 11615) chosen for the following reasons:
        - Corresponds to EVMPD data set already in use with minor modifications to ensure ISO IDMP compliance (e.g. expression of strength)
        - Further investment in EVMPD was not considered justified in view of EUTCT development
    - Data elements that characterise the substances contained in a medicinal product
        - 90% of ISO IDMP standard (FDIS 11238) chosen for the following reasons:
        - Substance identification is building block for maintaining information on medicinal products
        - Important for the Agency to regulate medicines including support of pharmacovigilance (coding of ICSRs, signal detection, EV Access Policy implementation, PSUR work sharing)
- The XML Schema Definition (XSD) for the individual data elements

Detailed Guidance published in – July 2011



1 1 6 1 5 ISO INFORMATION MODEL

Detailed Guidance published in – July 2011



ISO FDIS 11238 Structured Substance Information Model

Background – What the Agency delivered

The Agency delivered on 1 September 2011:

- Update to the Detailed Guidance
- Update to the XML Schema Definition (XSD) for the individual data elements
- Controlled Vocabularies
- XSD schema files and naming conventions for substances

The Agency delivered until January 2012:

- 2 ISO IDMP Information Days
- 1 Article 57 Information Day
- 5 meetings with interested stakeholders
- 7 Training courses
- 409 responses to Help Desk requests

Pharmaceutical industry's concerns

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Timelines

- Short timeline to comply with e-submission requirements
  - High workload
  - Lack of/late availability of IT tools for industry (EMA data entry tool and private initiatives)

Content (not always harmonised view by all Pharmaceutical Industry Associations)

- Structured information contested vs. non-structured information (SPC, PIL, Label)
- Duplication of efforts for generic substances
- SPC, PIL, Label - which documents to be submitted and in which language?
- Manufacturing information for non-biologicals (extension of deadline)
- Excipients (extension of deadline)
- Extension of timelines for notifying variations

Pharmaceutical industry's concerns

- Agency listened carefully to all stakeholders since the initial publication of the requirements in July 2011
- Agency held a workshop with European pharmaceutical industry associations in January 2012 to discuss feedback on the requirements
  - Stakeholders were supportive of the Agency's proposal to considerably reduce the mandatory data fields initially required in the format published on 2 July 2011
  - Key objectives to maintain public-health goals of the legislation and patient safety were not compromised
  - Significantly reduces the administrative burden and helps marketing authorisation holders to meet their legal deadline of 2 July 2012

Proposed solutions to address the concerns

The following aspects were taken into account

- The legal deadline cannot be extended
- A stepwise approach to move towards ISO IDMP implementation as ultimate and longer term objective
- Guiding principle that focuses on the submission of information necessary to support pharmacovigilance
- Substantial reduction of the mandatory data set for July 2012
    - Optional data elements are still supported for use by industry
- To maintain a core set of ISO IDMP data elements to support pharmacovigilance activities
- Three options to progress
    - These options reduce mandatory data elements for July 2012
        - Overall between 40-10% ISO IDMP compliance

NOTE:

- Full ISO IDMP implementation = 100% compliance
- Agency's July 2011 proposal = overall 60% ISO IDMP compliance (30% medicinal products and 90% substances)

Proposed solutions to address concerns

- The submission of SPC only for validation purpose
- Clarification of the language requirements depending on the authorisation procedure
- Reduction of the mandatory data set for medicinal products compared to July 2011
- One of the following options related to the description of structured substances:
    1. Further reduce the mandatory data set for structured substances (in accordance with ISO IDMP standards)
    2. As point 1 but restricted to biological medicinal products only
    3. Not to request any mandatory data set for structured substances (in accordance with ISO IDMP standards)

Agreed solution to address concerns

Preferred Option to meet legal deadline of 2 July 2012 Option 3 that implies:

- The submission of SPC only for validation purpose
- Clarification of the language requirements depending on the authorisation procedure (see next slide)
- Reduction of the mandatory data set for medicinal products compared to July 2011 i.e. the Agency will NOT ask the following mandatory data elements/set for medicinal products by July 2012:
  - Additional Monitoring
  - Location of the Pharmacovigilance System Master File
  - Description of packaging information
  - Regulated documents
    - » Condition of marketing authorisation
    - » Labeling
    - » Package Leaflet
- Structured Substance Information optional

Summary

Option 3 includes language requirements depending on the authorisation procedure

Language Requirements for Information on Medicinal Products

Type of medicinal product (by procedure)	Medicinal Product Data Elements	Substance Name	Structured Substance Information (SSI)	SPC only
Centralised Procedure (CAP)	English	All Official EEA languages	English	English (Other languages available at the Agency)
Mutual Recognition Procedure (MRP)	National language(s) of the country of authorisation	National language(s) of the country of authorisation plus English translation	English	Common approved English text
Decentralised Procedure (DCP)	National language(s) of the country of authorisation	National language(s) of the country of authorisation plus English translation	English	Common approved English text
National Procedure (NAP)	National language(s) of the country of authorisation	National language(s) of the country of authorisation plus English translation	English	National language(s) of the country of authorisation
Registration Procedure (RP)	National language(s) of the country of registration	National language(s) of the country of authorisation plus English translation	English	National language(s) of the country of authorisation

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Option 3 – Pros and Cons

Pros	Cons	Risks
• Significant reduced burden for MAHs making it most likely to meet the legal deadline • Allows the Agency to establish a complete list of medicinal products authorized and registered in the EU	• Substance data set not compliant with ISO IDMP standard – will require duplication of efforts by MAHs (data entry and re-linking of substances and products) and the Agency (validation) at time of ISO IDMP implementation • Agency cannot establish comprehensive substance registration system • Delay of the release of the EMA data entry tool/DB for MAHs due to necessary adaptation (15 April 2012 at the latest) • Delays for vendors and MAHs to further adapt and test their IT systems based on proposed solution • Requires updates to the Legal Notice, Detailed Guidance and schema	• No improvement of current deficiencies in signal detection for the Agency and the EU Regulatory Network • Complaints from IT vendors and MAHs that already invested in IT tools and resources to comply with format published on 1 July 2011 • Collaboration/harmonisation with FDA on substance maintenance at risk due to lack of data in the EU

Option 3 (20% medicinal products and 0% substance ISO IDMP compliance)

Summary

- From an Agency's perspective option 3 implies:
  - For CAPs – status quo of current situation
  - For non-CAPs:
    - To obtain SPCs for non-CAPs (validation purposes)
    - The establishment of a "complete" list of medicinal products authorised in the EU by 2 July 2012 linked to substance names only, as reflected in the SPC
    - No real improvement of current deficiencies in signal detection for the Agency and the EU Regulatory Network
  - The Agency will have less information, specifically structured substance information
    - Agency should be able to obtain such information at the time of the ISO IDMP implementation

Summary

- From a Pharmaceutical Industry perspective option 3 implies:
  - Significant reduced burden for MAHs short term hence facilitating compliance with legal deadline
  - Substance data set not compliant with ISO IDMP standard – will require duplication of efforts by MAHs long term (data entry and re-linking of substances and products) at time of ISO IDMP implementation
  - Adaptation and testing of IT systems
    - Release of data entry tool by the Agency 15 April 2012 at the latest

Current status

The following documents were published on 5th March on EMA website:

- Background info: Press release, Article 57 webpage, summary of EMA workshop with EU Pharmaceutical Industry Associations (New)
- Revised Legal Notice
- Revised Detailed Guidance
  - Including chapter 3.I: Revised technical specs
  - Including chapter 3.II: Business guidance (New)
  - Including chapter 3.III: XEVPRM examples (New)
- Questions & Answers (New)
- XEVPRM Terminologies and Controlled Vocabularies (New)
- Revised XEVPRM schema
- Additional WebPages: Training, Registration (New)

The XEVMPD web application (new EVWEB) deployed in production on 5th March

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000336.jsp&mid=WC0b01ac05804d8b2b

Next Steps

The Agency will work with stakeholders throughout 2012 on:

- Further defining requirements for data maintenance (e.g. variations)
- Submission of structured substance information
- Develop a road map to progress from 2 July 2012 towards ISO IDMP standards implementation

Next Steps

The Agency continue assist MAHs for the electronic submission of information on medicinal products:

- Article 57 Info Days
- Release of the new XEVMPD training

- Helpdesk dedicated contacts:
  - art57@ema.europa.eu
  - Telephone: +44 (0)20 7523 7010

Questions