# Implementation and Maintenance of XEVMPD (eXtended EudraVigilance Medicinal Product Dictionary)

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# Outline

- Current status of implementation and guidance
- Challenges of maintenance of data
- Progress on transition to the ISO IDMP standards

# New Pharmacovigilance Legislation

- Proposed by EU Commission on 2008
- Passed by the European Parliament in September 2010
- Published December 2010 (EU 1235/2010)
- Implementing Measure published June 2012 (EU 520/2012)
- Came into force July 2012
  - With a number of transition arrangement

# Pharmacovigilance Processes

- The legislation will bring about many changes to systems and processes
  - Including ones for ICSRs

- Current EU pharmacovigilance processes for ICSRs involve multiple, duplicative, submissions/collation to NCAs and EMA
- Under the new pharmacovigilance legislation verification of ICSRs will be at NCAs but the sole database will be maintained by EMA
  - EMA will provide access to relevant NCA
- In order to support this new role in pharmacovigilance, requirements have also been included in the legislation regarding the provision of information about medicinal products to EMA (Article 57(2))
  - Drove XEVMPD requirements

# Key Announcements of 1 July 2011(1)

- Submission of medicinal product information required for all authorised products in EU (~500,000 products)
  - Regardless of authorisation route
  - Required by 2 July 2012
- The Eudravigilance Medicinal Product Dictionary ((X)EVMPD) is to be populated
- (X)EVPRM is to be the format for submission of the information
- Any existing records would need to be updated (~125,000 records)

# Key Announcements of 1 July 2011(2)

- After 2 July 2012, any changed information would be required within submitted within 15 calendar days
- (X)EVPRM specification was updated to cover more information
  - Guidance was provided but was known to be incomplete (but it was also of poor quality)
  - More technical guidance, examples and clarification on mandatory/optional nature of elements was to be provided by 1 September 2011
  - Significant reduction in scope and revised guidance and FAQs issued 5 March 2012
- (X)EVPRM is an interim format until 2015 when the ISO Identification of Medicinal Product (IDMP) standards would be implemented

# But…..

- ‘Further Q&A documents issued after 2 July 2012
  - V2 = 31 July 2012
  - V3 = 12 February 2013
- ‘Maintenance’ put on hold in announcement of 4 July 2012
  - And remains on hold
- ISO IDMP to be mandated as part of Pharmacovigilance Implementing Measures – from 1 July 2016
  - In conjunction with new version of ICSR (ISO27593-2)

# Statistics (1)

- Organisations
  - End 2012
    - 3324 MAHs
    - 1255 Headquarters
    - 1608 QPPVs
- Products
  - September 2012
    - 236,827 Products  submitted (47% of estimated number)
  - May 2013
    - 423,735 Products (EV Codes)
      - (85% of estimated number to be submitted)
    - 303,392 Unique MA Numbers
      - (Thus ~120,000 additional presentations within the same MAs)
    - Of which
      - 219,726 Generic products – with 140,268 unique MA numbers

# Statistics (2)

- Substances
  - March 2012 ~ 18,000 substances in the Controlled Vocabulary
  - Mid-September 2012 - additions
    - 10,989 new substances
    - 27,563 translations
    - 455 new synonyms
  - May 2013
    - ~ 32,000 substances in the Controlled CV
      - But there are additional ones that are no longer in the CV!
    - ~120,000 substance names unchecked
      - Includes translations and synonyms

# Technology Options for July 2012

- Extension of current Tracking/RIM system
  - Vendor tool
  - In-house tool
- Stand-alone XEVMPD tool
  - Vendor
  - In-house
- Gateway or EV_Post
- EV Web

# Process options for July 2012

- In-house or outsourced
  - Service provider
    - In-house assistance
    - Out-sourcing
- Headquarters or affiliate responsibility
- Regulatory or Pharmacovigilance

- For initial loading and/or for maintenance

# Challenges (1)

- Time
- Budget
- Process/technology option selection process
  - Interim or permanent
  - Maintenance process requirements uncertain
- Incomplete/evolving guidance from EMA
  - Lack of regular publication of FAQs
- Registration process
- Training
- Constantly changing Substance CV
  - No ownership of records
  - Inconsistent content/presentation

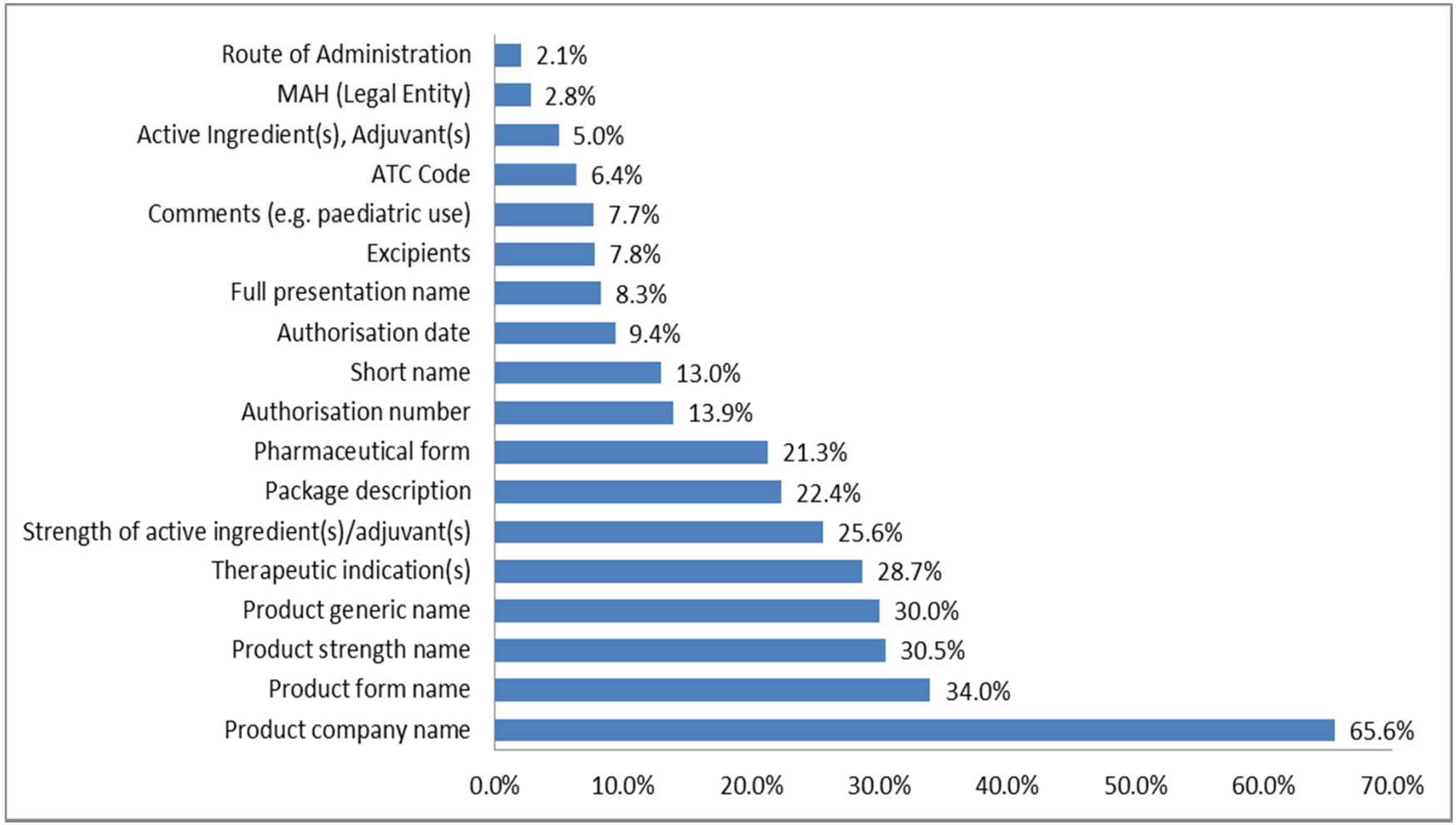
# Challenges (2)

- Access to the data
  - Multiple potential data sources
- Completeness of data
- Quality control
- Initial performance of EV Web
- Initial performance of the Gateway
- Unannounced system down times
- ‘Unconnected’ data instances created
  - Reconciliation with existing databases etc.

# Content validation

- EMA not currently performing content validation
- Undertaken pilot activities
- Phase 1 : 31 products, 108 presentations (random selection)
  - All fields validated (3418 data points)
  - 14.2% error rate
  - Tendency towards higher error rates for organisations with large portfolios
  - 5% duplicates identified

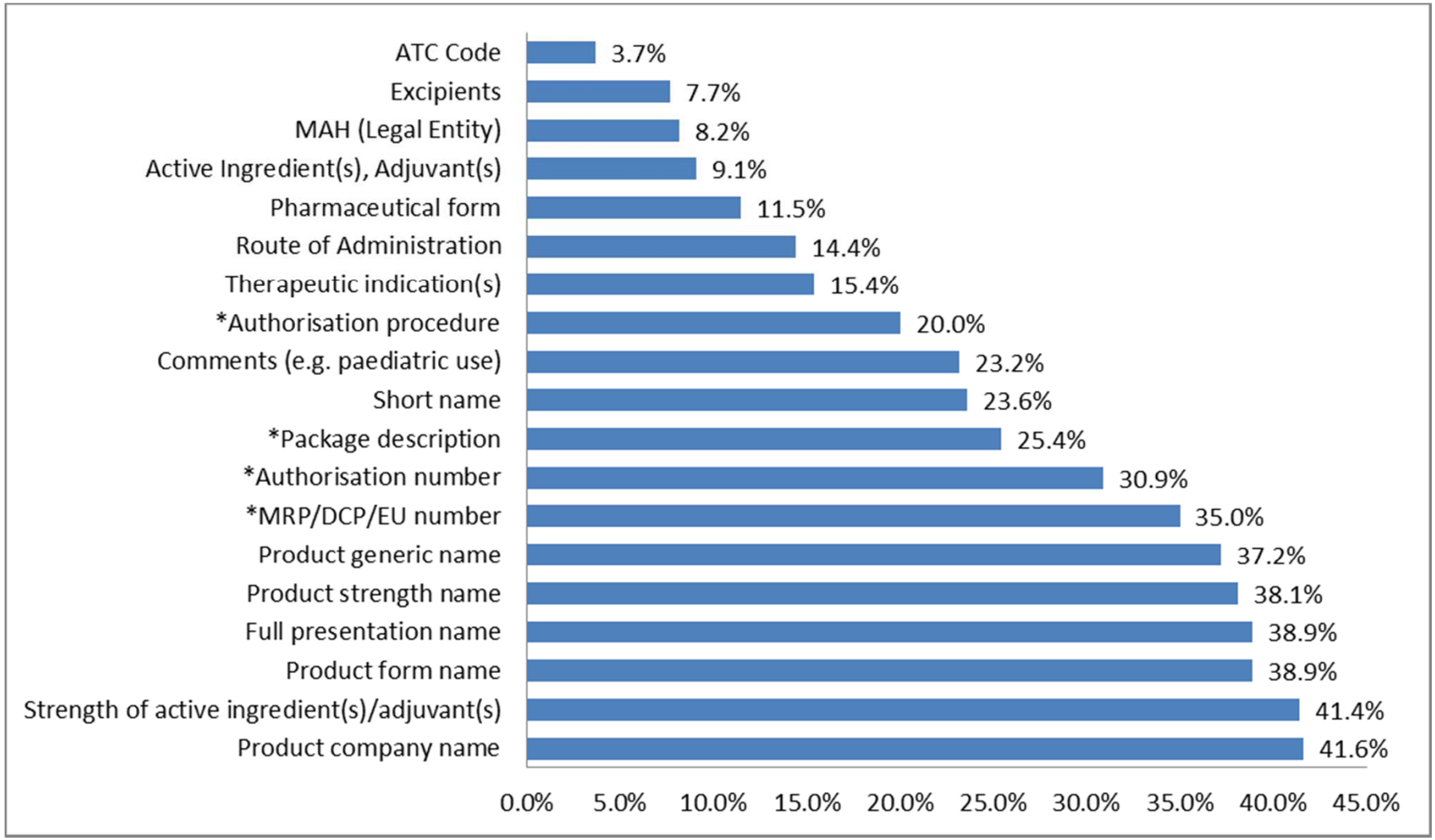
# Phase 1 pilot error rate



# Content validation

- Phase 2 : 85 products, 365 presentations
  - All fields validated (8,695 data points)
  - EV Gateway users (1 experienced, 2 new)
  - EV Web users (5 SMEs CAPs, 3 SMEs non-CAPs, 1 Organisation non-CAP biologics)
  - Overall 18.5% error rate
  - EV Gateway users – above average error rate (25.3%)
  - EV Web users – below average error rate (10.8%)
  - Experienced organisation – below average error rate (11.2%)
  - Gateway inexperienced – above average error rate (31.4%)
  - 84% of products with errors – will affect business processes that have to utilise the data

# Phase 2 pilot error rate



# Fields of interest

- Authorised medicinal product name not specified correctly
  - Medicinal product name parts wrongly defined
- Strength of active ingredients/adjuvant(s) not specified correctly
- Therapeutic indication(s) not coded correctly
- Authorised pharmaceutical form and routes of administration not specified correctly
- Excipient(s) incomplete
- Regulatory information not specified correctly
  - Authorisation procedure
  - Authorisation numbers
  - MRP/DCP/EU number
- MAH legal entity not specified correctly
- ATC code not specified correctly

# Evaluation of Errors

- EMA acknowledges that the sample number is small
- Criteria used have not been informed to industry
  - Hyphen not slash in numbers might be an error
  - Inclusion of 'Not Applicable' is an error
- Expect Gateway user error rate to be higher than EV Web
  - Larger number of products, more pressure
  - Internal assignment of terms versus picklist in EV Web
  - Batch submission versus one-by-one in EV Web
  - EV Web provided opportunity to build on old EVMPD record
    - E.g. all CAPs already entered in by EMA
- Expect higher error rate from inexperienced companies
  - And there were a lot of these

# Maintenance Status (1)

- EMA to clean up substance data first
  - 120,000 substances names are not checked
  - Internal resources to be used to clean-up.
  - Estimate to be done by Q4 2013

- EMA needs to receive updated information for data errors.
  - Before this can be done:
    - De-duplication finished
    - Uploading undertaken
    - Additional functionalities implemented

# Maintenance Status (2)

- Industry proposal to already use maintenance and update information
- EMA proposal: make business rules and finalize document. As soon as that is agreed, send out to company and please apply this.
  - Q1 2014 to aim to submit updated data
  - Industry will have concerns about transition period (wants 9-12 months before being maintenance is made mandatory)
- Upcoming meetings
  - Next meeting of Art 57 Implementation Working Group – 21 June 2013
    - Agenda to include areas of guidance still to be agreed
      - MA-transfer, withdrawal etc
  - September 2013 higher level meeting to discuss ‘roadmap’
    - No specific date set yet for issuing the guidance

# New authorisations

- XEVMPD submissions must be made within 15 calendar days of:
  - Receipt of notification of approval from regulatory agency
  - Availability of the approved SmPC
    - English language agreed text for DCP

# Maintenance classifications

- Two speed system will be adopted
  - Expedited
    - EMA proposing 30 calendar days after notification of approval
      - Or a waiting period if relevant
      - Covers most types of variations
    - Suspensions, revocations and withdrawals would also be 30 calendar days
  - Routine
    - EMA suggesting Annual Report
    - Industry wants flexibility – within 12 months
    - EMA concerned about technical and budgetary implications

# Impact/Action

- No Variations to be submitted until revised guidance is issued and transition arrangements informed
- No Updates to Authorised Products to be submitted either except:
  - MAH can submit Updates to correct errors in data
  - Nullifications of duplicate products can be submitted
- Be registering your PSMF locations
- MAHs should be keeping track of changes that are occurring and be ready to submit them when the guidance is published
    - Variations
    - Updates (apart from corrections that can be submitted now)
    - Withdrawals
    - Transfers
  - Anticipate making a single update for all changes

# Article 57(2) IWG key activities in 2013

- Review and update of Questions and Answers document ✓
- Discussion of Article 57(2) data maintenance based on regulatory processes and potential technical implications with main focus on notifications of:
  - Extensions of marketing authorisations
  - Variations with biggest impact on safety monitoring (requiring updates of core data elements )
  - Changes to QPPV
  - PSMF location
  - Transfers of marketing authorisations
  - Changes of the marketing authorisation status
  - Contact information for pharmacovigilance enquiries
- Discussion of quality review of substance CV and organisation CV
- Development of a detailed Roadmap for XEVMPD implementation and IDMP planning

# Challenges

- Lack of maintenance guidance
  - What/when/how?
- Data quality
  - EMA
  - MAH
- Processes
  - Clean-up
  - Validation
  - Maintenance
- Systems
- Duration before IDMP
- Etc …..

# IDMP

# Five Standards constituting IDMP - published

- ISO11615:2012 Health Informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated medicinal product information
- ISO11616:2012 Health informatics – Identification of medicinal products - Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information
- ISO11238:2012 Health Informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances
- ISO11239:2012 Health Informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
- ISO11240:2012 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement

# Implementation Needs

- ICH guidance
  - Common agreed data to uniquely identify medicinal products for pharmacovigilance purposes
- Regional guidances
  - Specific additional data and processes to support further pharmacovigilance and other regulatory activities
  - Will also be covering Investigational Medicinal Products
- Messages for exchange
  - Industry/regulator, regulator/regulator, regulator/public
- Maintenance organisation(s)
  - Create and maintain vocabularies

# A Pictorial Representation

Conceptual Level:

ISO International Standards

Implementation Level 1:

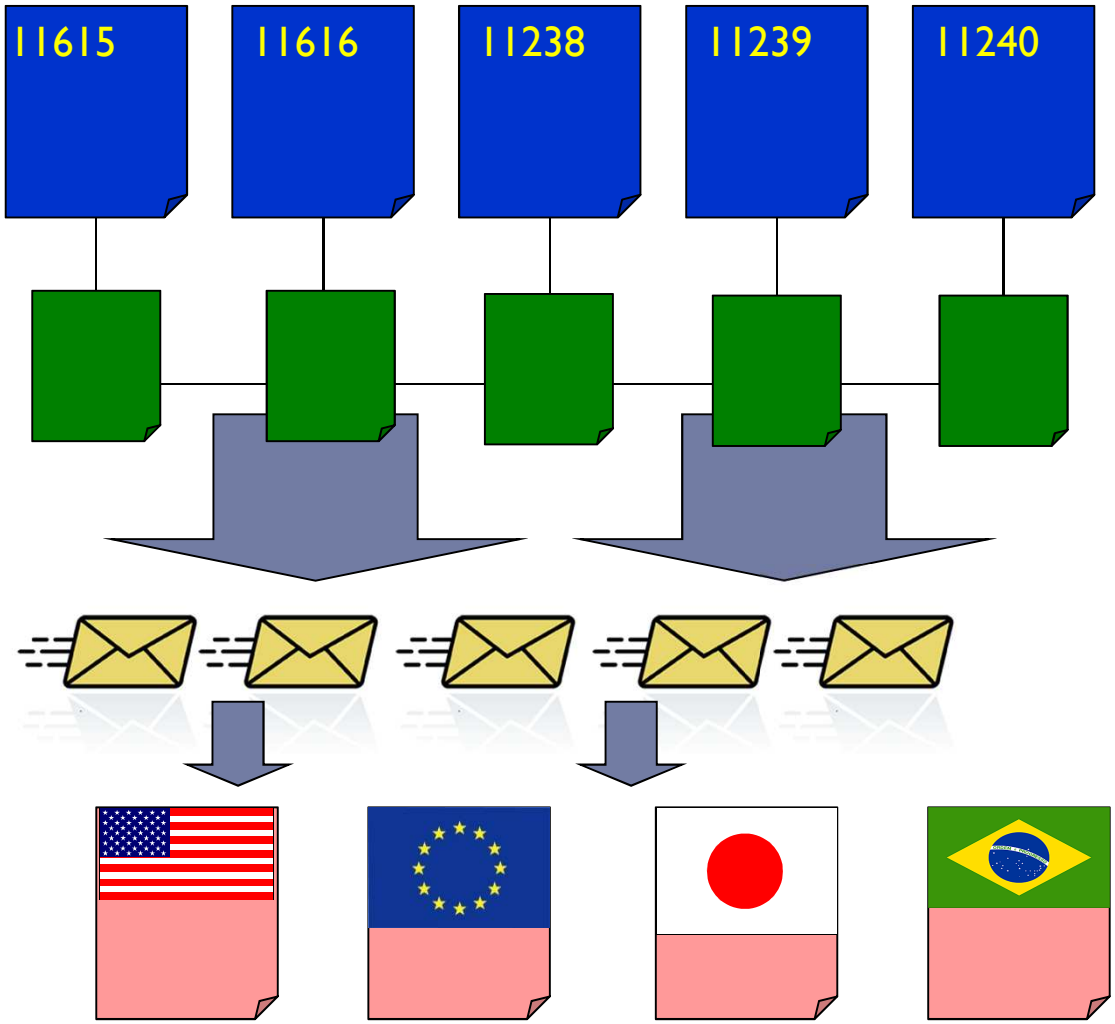
ICH Implementation Guides

Implementation Level 2:

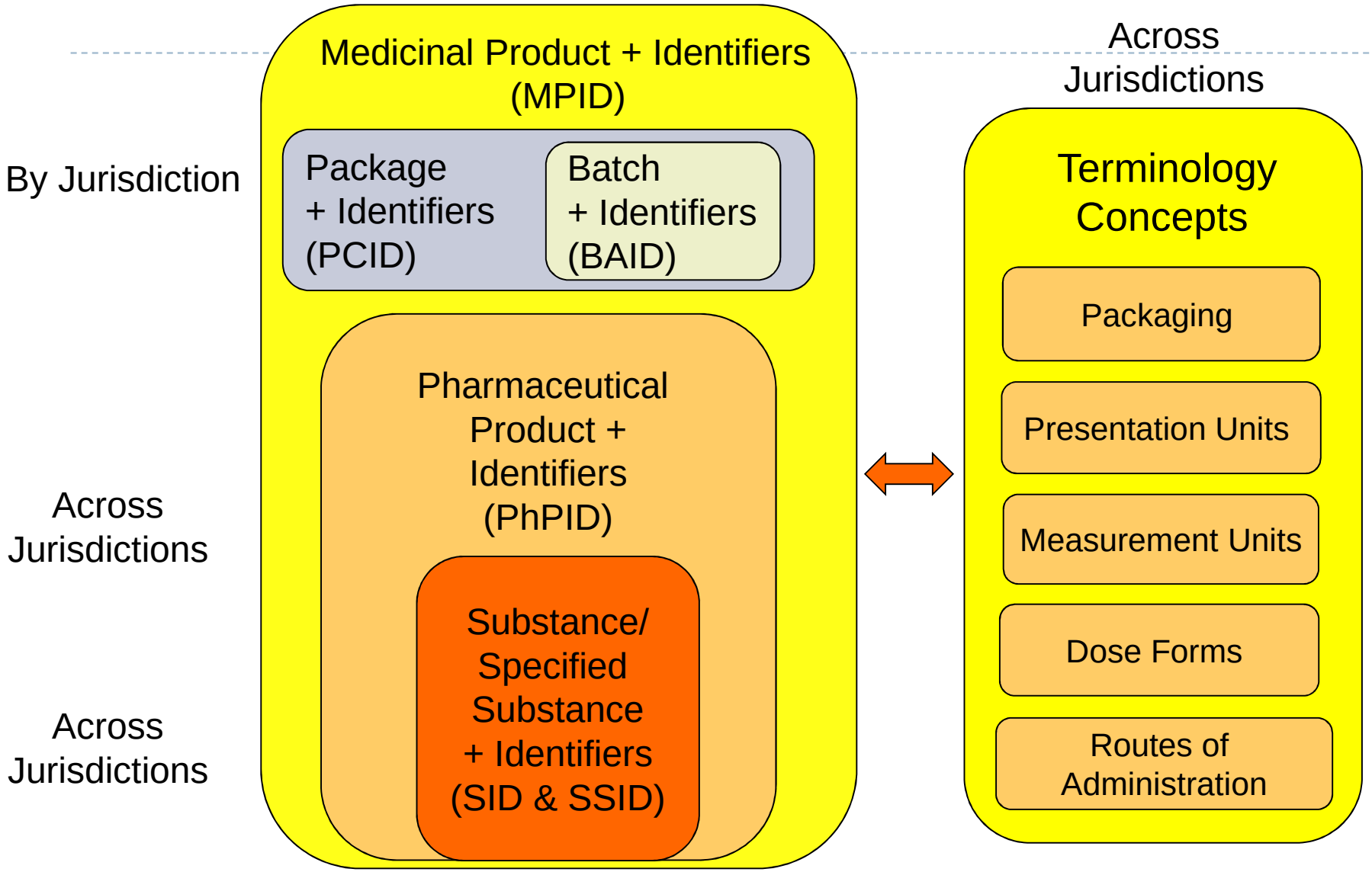
HL7 Messaging Standards

Implementation Level 3:

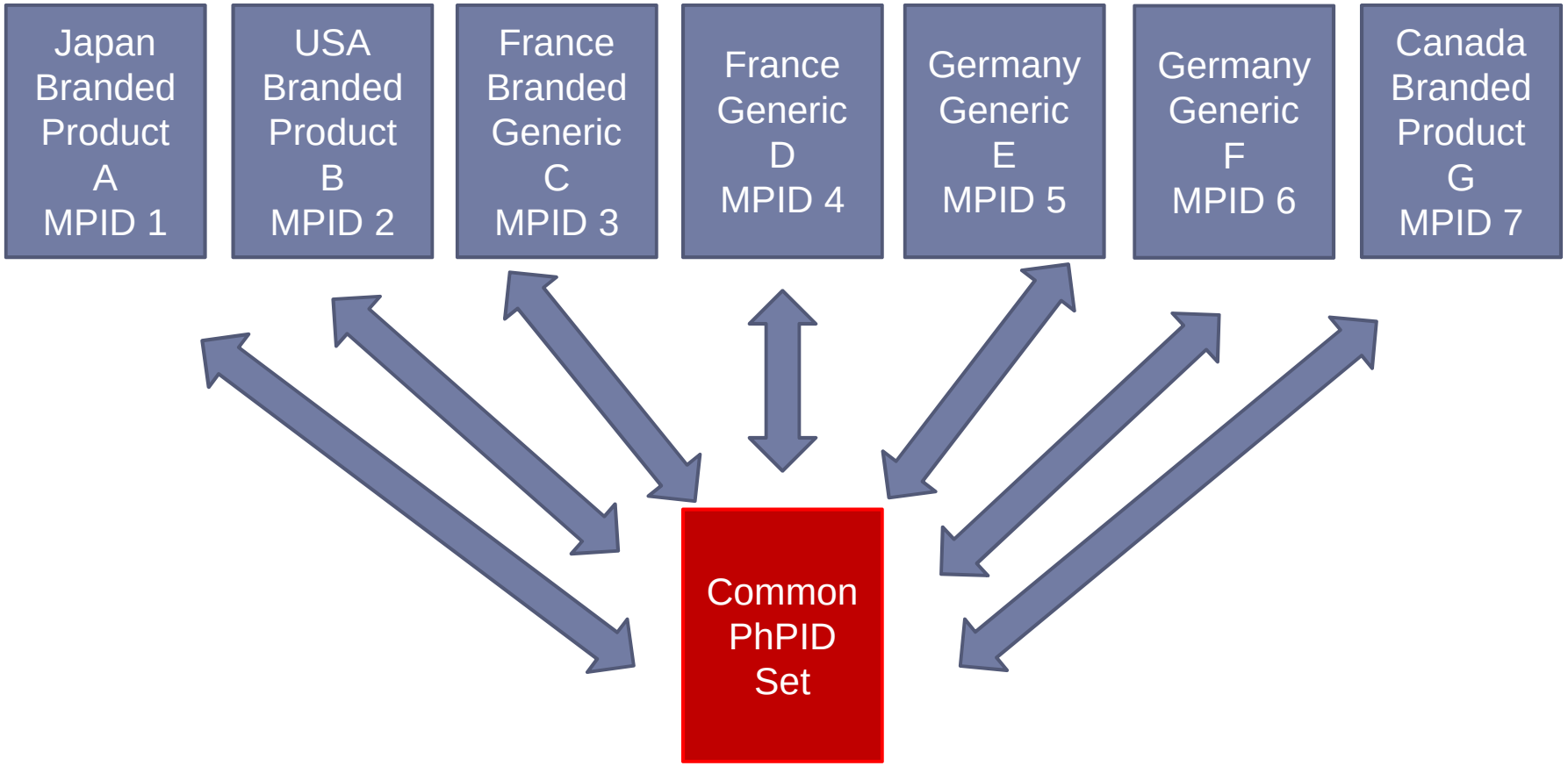
Realm-specific implementation guides



# Identifiers and Terminologies



# MPID - PhPID



# ISO/ICH ICSR

- ICH E2B(R3) standard nearing completion
- ISO Standards issued
  - ISO/HL7 27953-1 – framework for adverse event reporting
  - ISO/HL7 27953-2 – specifics for human pharmaceutical reporting for ICSR
- ICH Step 4 (Regulator sign-off) achieved November 2012
  - Not yet published – revisions occurring at ICH – June 2013
  - Regional implementation guides should be available for EU consultation process some time after (TBD)
- EU to implement in July 2016 – stated in the Pharmacovigilance Legislation implementing measures
- IDMP Identifiers and Terminologies embedded in ICSR

# ICH Implementation Guides

- ICH has preparing Implementation Guides for each of the five standards (plus an introduction)
- They are to address all of the standards, not just those specific to identification to support pharmacovigilance activities
  - But this does not mean that all regions will implement all parts but provides a basis for commonality when used
- Target for ICH Step 2 (all party agreement of draft for consultation) **was** March 2013 but….
  - MHLW has decided that it no longer wishes to continue with ICH M5 and so the ICH Steering Committee concluded on 6 June 2013 that ICH M5 would stop
- FDA and EMA plus Health Canada and Swissmedic will continue to collaborate on the development of guidance and support for implementation
  - Challenge will be how collectively the guidance can be agreed and maintained and what will be the impact upon timelines

# Potential Maintenance Responsibilities

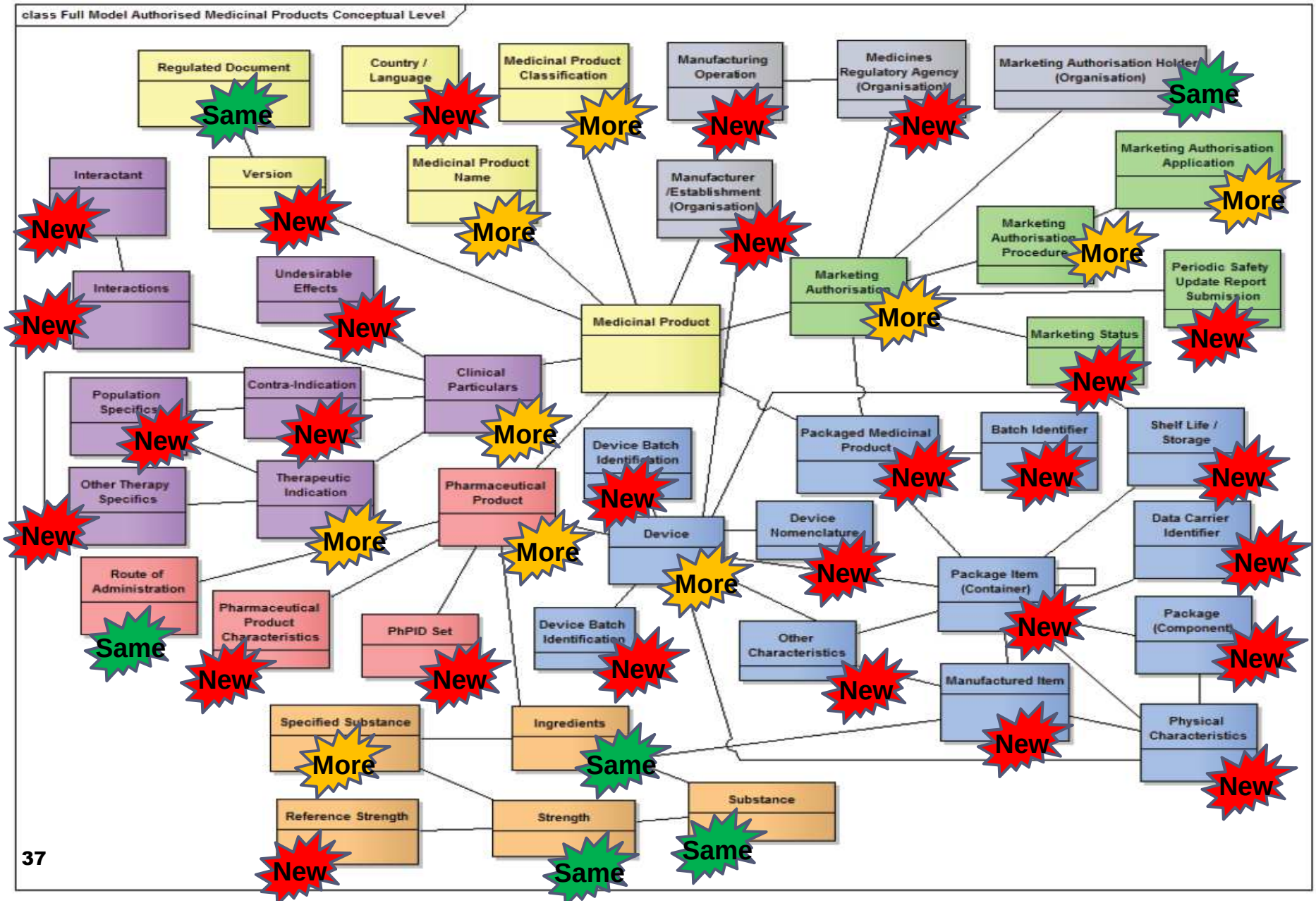
- Terminology where local regulators maintain to accommodate local processes
  - MPID
  - PCID
  - BAID_1 & BAID_2

- Terminology requiring global maintenance for consistency & interchange
  - Substances & Specified Substances (FDA proposed as lead)
  - Pharmaceutical Dose Forms (EDQM proposed as lead)
  - Routes of Administration (EDQM proposed as lead)
  - Packaging (EDQM proposed as lead)
  - Units of Presentation (EDQM proposed as lead)
  - Units of Measurement (UCUM)
  - PhPID (Algorithm)

# Implementation of IDMP

- European implementation defined in PV Implementing Measures
  - 1 July 2016
  - In conjunction with new ICH ICSR (ISO) version
- European Implementation Guides to be drafted
  - Also targeted for June 2014
- Others
  - FDA no date yet but intend to evolve SPL as needed
  - Japan not yet defined(if ever)
  - Canada – will implement but no specifics yet
  - Switzerland – initiating a strategic assessment

# MPID – XEVMPD coverage



# MPID components – relationship to XEVMPD (1)

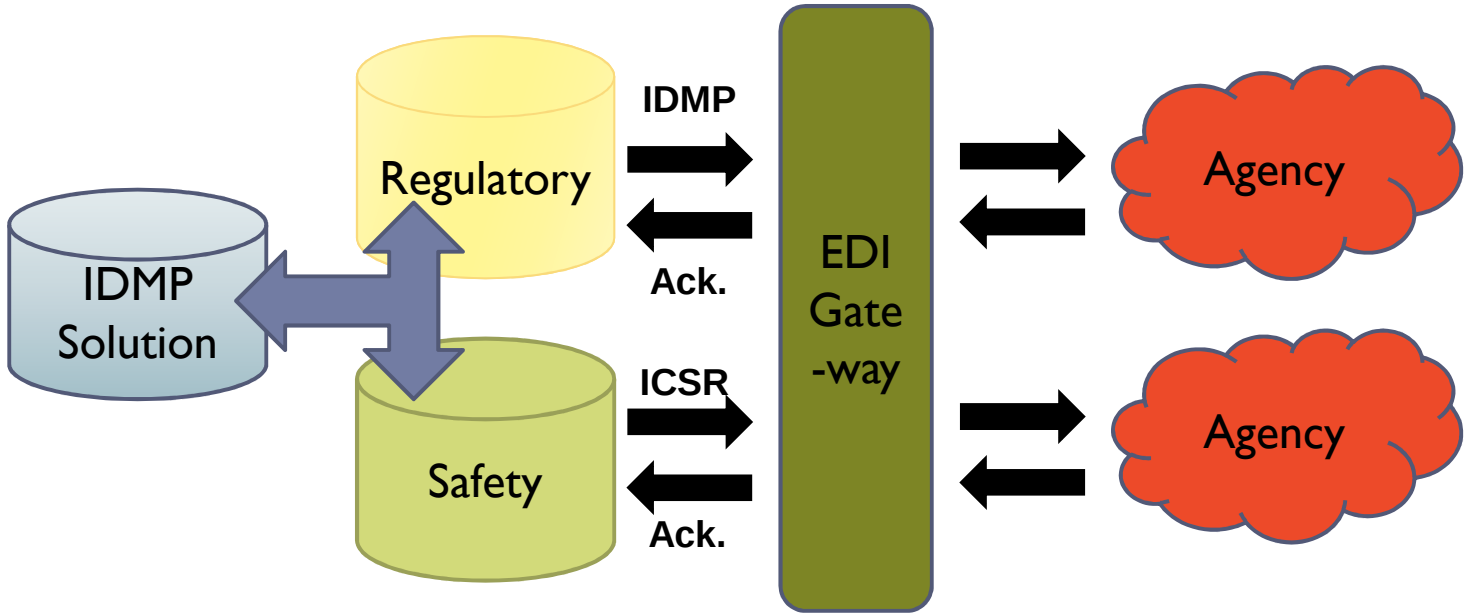
- Medicinal Product
  - Most information included in XEVMPD
- Market Authorisation
  - Most information included in XEVMPD
  - Marketing details not included in XEVMPD
- Organisation (MAH/Regulator)
  - Regulator details not included in XEVMPD
- Manufacturer/Establishment
  - Not included in XEVMPD

# MPID components – relationship to XEVMPD (2)

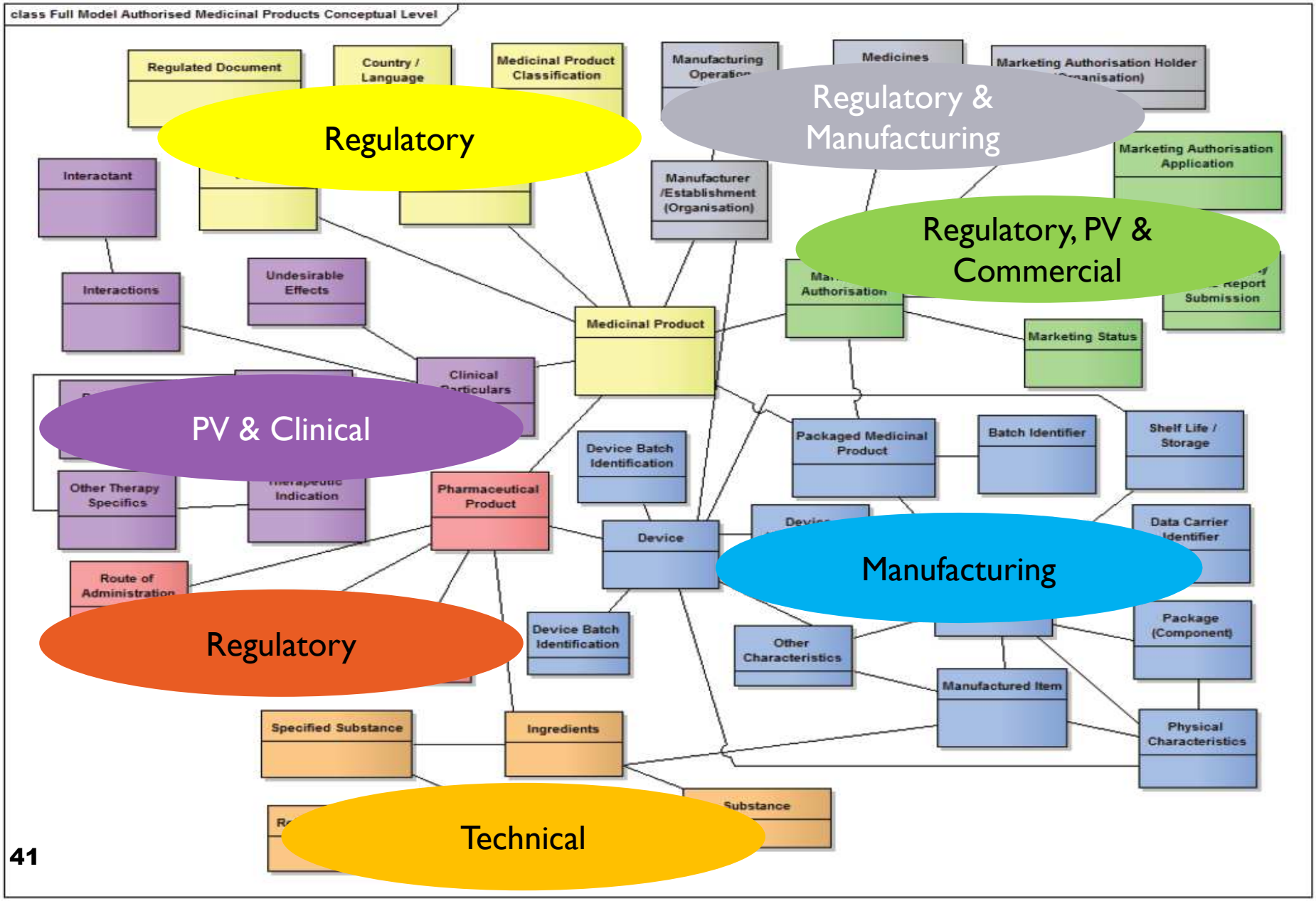
- Packaged Medicinal Product including Manufactured Item and Device
  - Not included in XEVMPD
- Ingredient, Substance and Strength
  - Most information included in XEVMPD
- Pharmaceutical Product and Device
  - Not included in XEVMPD except for very high level info about Device
- Clinical Particulars
  - Only indication included in XEVMPD

# Impact

- Much tighter interaction between Regulatory Information Management System (IDMP data) and PV systems
  - At least share vocabularies



# Potential Responsibilities



# Conclusion

- Initial submission for XEVMPD is nearing completion
- Significant quality issues exist
  - Controlled vocabularies
  - Submitted information
- Validation has not yet started
- Maintenance guidance yet to be issued
- Significant re-submission activity likely for 2014
- IDMP roadmap in EU has not progressed
- Issues at ICH regarding all party involvement
- Process and timing for guidance not clear
- Deadline for implementation of IDMP is in legislation – July 2016

# Q&A

# Contacts

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