BAH Meeting, 09. December 2011, Bonn, Germany

Requirements of Article 57(2) of Regulation (EC) 726/2004 as amended – Impact on the Industry

Exalon

LEGISLATION

New Pharmacovigilance Legislation EU

New PV Legislation

Regulation (EU) No 1235/2010

Directive 2010/84/EU

EU Drug Law

Regulation (EC) No 726/2004 (30.04.2004)

Regulation (EC) No 1394/2007 (10.12.2007)

Directive 2001/83/EC (28.11.2001)

Significance

- “The legislation is the **biggest change to the regulation of human medicines in the European Union (EU) since 1995**. It has significant implications for applicants and holders of European Union marketing authorisations.“

  “The EMA is responsible for implementing much of the new legislation and is developing a framework for compliance and delivery of key requirements. The legislation is effective from July 2012”

Quotations from EMA website

THE OBLIGATIONS

Legal Provisions

- Article 57(2) of Regulation (EC) No 726/2004:
  - Newly introduced second subparagraph through Regulation (EU) No 1235/2010:

"*For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union*. To this effect the following measures shall be taken*:"

- see next slide

* Refers to the EEA

Legal Provisions /2

a) *"the Agency shall, by **2 July 2011** at the latest, make public a format for the electronic submission of information on medicinal products for human use"*

b) *"marketing authorisation holders shall, by **2 July 2012** at the latest, electronically submit to the Agency information on all medicinal products for human use authorised or registered in the Union, using the format referred to in point a)"*

c) *"from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a)."*

THE DATABASE

EMA XEVMPD Database

- EVMPD (EudraVigilance Medicinal Product Dictionary) established since 2004:
  - Data on Development (or Investigational) Medicinal Products
  - In scope of the EU Clinical Trial Directive 2001/20/EC
  - Authorized products on voluntary basis
- Major revision to be compliant to the future message standard for authorized products

EVMPD ⇨XEVMPD

Extended EudraVigilance Medicinal Product Dictionary

THE FORMAT

Electronic Submission Format

- On July 01, 2011 EMA announced the first version of the electronic submission format together with the "*Legal notice on the implementation of Article 57(2), second subparagraph of Regulation (EC) No. 726/2004*"
  - Surprisingly complex, very difficult to read, many gaps and errors
  - No schema files and/or vocabularies at that point

Electronic Submission Format - 2

- On September 01, 2011 updated specification documents were published by EMA incl. schema files and detailed description
  - Still difficult to read, more information, structured into six individual chapters, total 640 pages
  - Still some gaps and inconsistencies
- Version 3 announced for October, currently delayed (expected for December)
- FAQs, example files, further vocabularies still outstanding

Electronic submission format - 3

XEVPRM

Ex**E**udra**V**igilance **P**roduct **R**eport **M**essage

An interim format!

XEVPRM
The very Basics

- XML based
  - One overall message (XEVPRM) – *Chapter 3*
  - 0 - n XML messages referenced for SSI (authorized and development substances, excipients, adjuvants) – *Chapter 4*
  - Attachments!
  - In total ~ 460 individual data fields, ~ 250 belonging to SSI
  - Multiple elements, dependencies, optional & mandatory data (technical & business rules)

XEVPRM Summary of Information

- Description of the invented name
- Description of the therapeutic area(s)
- Designation of additional monitoring for biologicals and applicable products
- Details of the MAH
- Clinical particulars, therapeutic indication
- Details of the marketing authorisation and marketing status (MA procedure, country, MA number, MA date and status, procedure number (MRP/DCP), orphan drug designation)

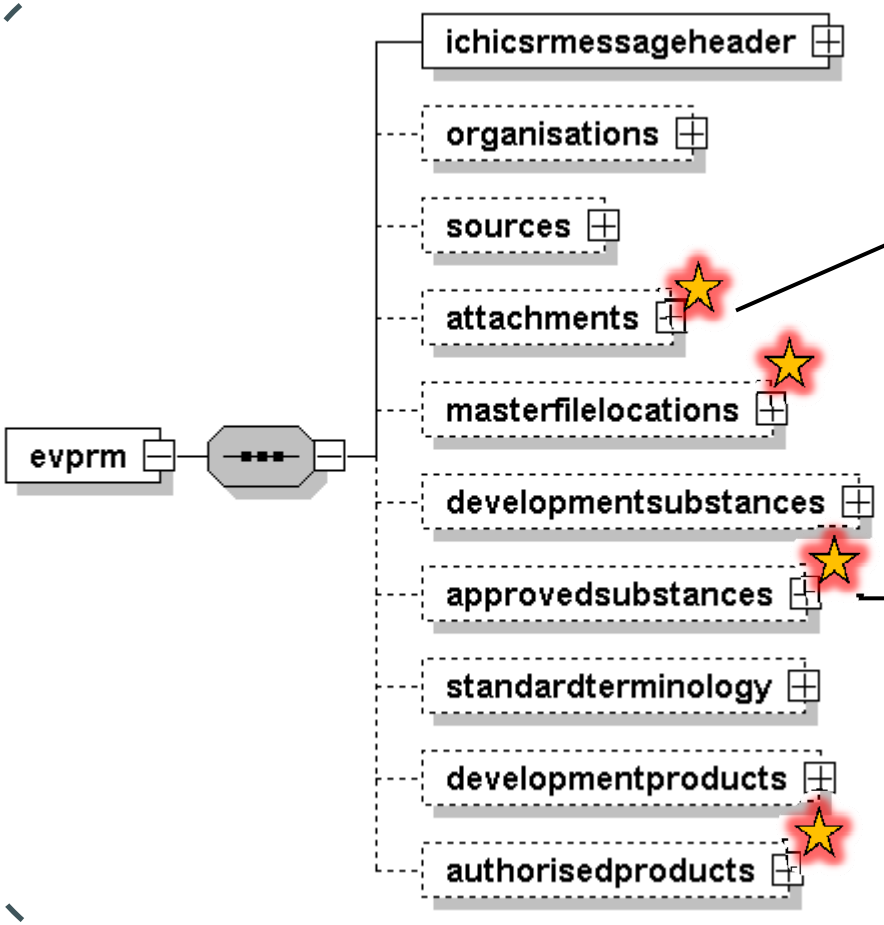
XEVPRM Summary of Information - 2

- Details of the **active substance(s)**, **excipient(s)**, **adjuvant(s)** and their specific characteristics

SSI

- Strength of the API
- Information about the medical device as applicable (acc. to ATMP Regulation 1394/2007)
- Pharmaceutical dose forms
- Route of administration
- Packaging information

XEVPRM
Top-level Structure



XEVPRM
Attachments

- Formats allowed (technically):
  - PDF, DOC(X), XLS(X)
- Printed Product Information:
  - SPC, Labeling, PIL, Annexes IIA + IIB (for CAPs)
  - Merged as single PDF!
- Printed Substance Information (PSI) optional
- Complete XEVPRM < 60 MB, single file < 25 MB

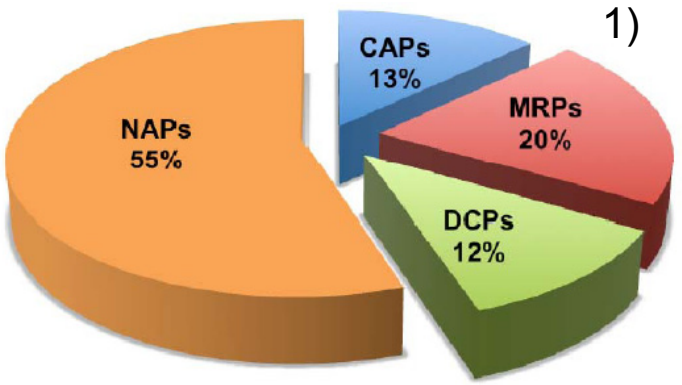
XEVPRM
Interim Format

- In parallel finalization of five ISO IDMP standards:
  - ISO prEN 11615: Medicinal Product Info
  - ISO prEN 11616: Pharmaceutical Product Info
  - ISO prEN 11238: Substances
  - ISO prEN 11239: Pharmaceutical dose forms, units of presentation and routes of administration
  - ISO prEN 11240: Units of measurement
- ISO standards to be finalized by end 2012. To be applied for new and changed records beginning 2015
- By end 2015 all data to be maintained in ISO format

STATUS QUO

Status Quo

- EMA estimates about 500.000 authorized products across the EU
- Currently, the EVMPD holds about 128.000 records (authorized)
- Current records must be updated to comply with XEVPRM standard
- Records for CAPs also to be maintained by MAHs



1)

⇨ About 400.000 records to be entered by July 02, 2012 and to be maintained afterwards

[1] A. Cochino (EMA): Medicinal Product Information management from an EMA perspective, EMA Information Days, September 23, 2011, London

THE CHALLENGES

Challenge 1: Timelines

- Usable Specification available only since Sep 01, 2011
  - Further guidance still outstanding
  - Example messages still outstanding
  - Vocabularies outstanding
  - Gateway not yet ready
  - EVWEB not yet ready

⇨The clock is ticking!

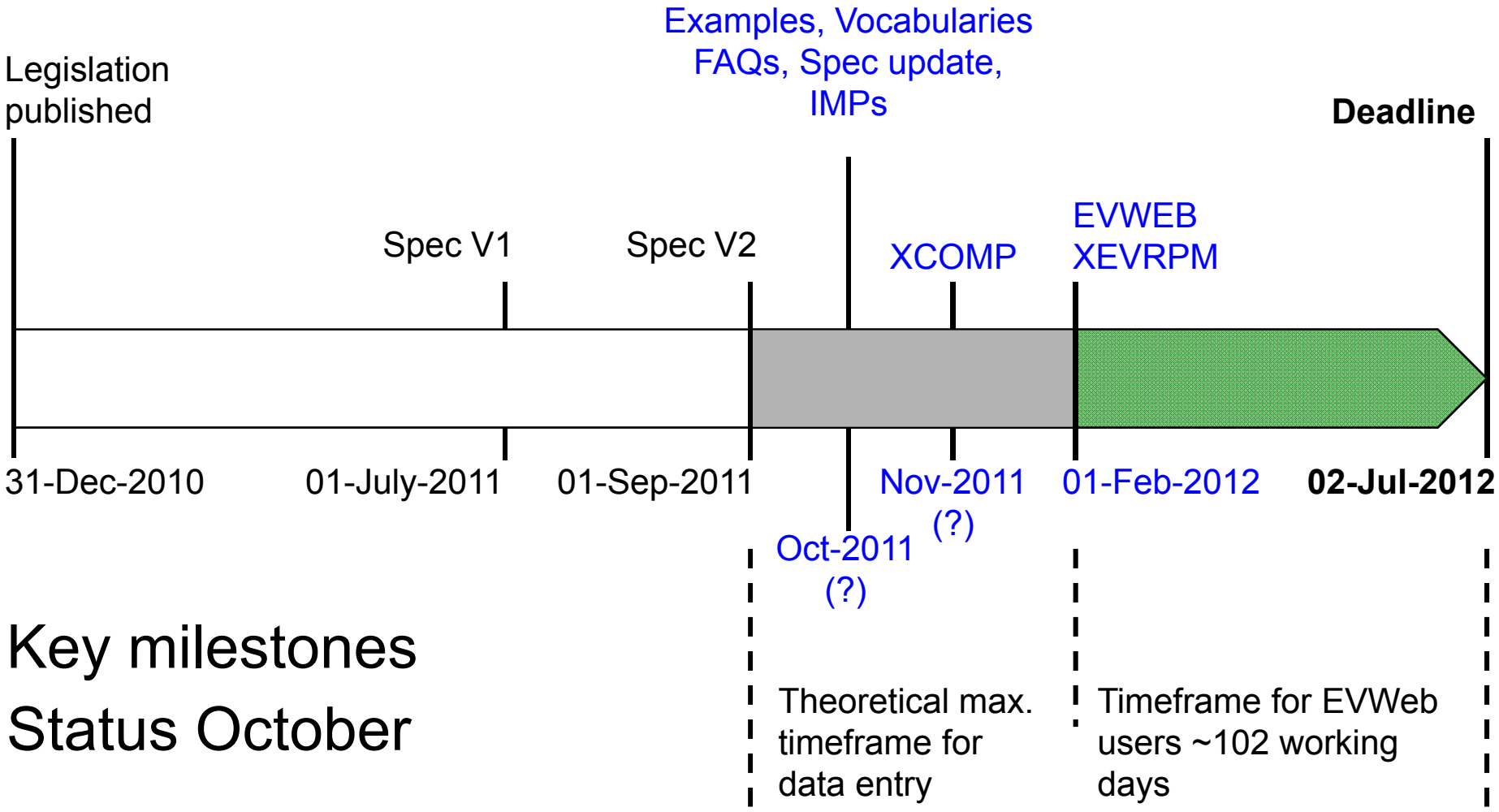
Challenge 1: Timelines

- Push-back from Industry on EMA to postpone deadlines:

  "Whilst the Agency understands and acknowledges the efforts required by pharmaceutical industry to implement the provisions of Article 57 paragraph 2, second subparagraph, the ***obligations remain with the marketing authorisation holder and the deadlines as defined by legislation cannot be extended"*** [1)]

[1)] S. Brosch, I. Del Seppia, P. Oliveira (EMA): The New XEVPRM Questions & Answers Session, EMA Information Days, September 23, 2011, London

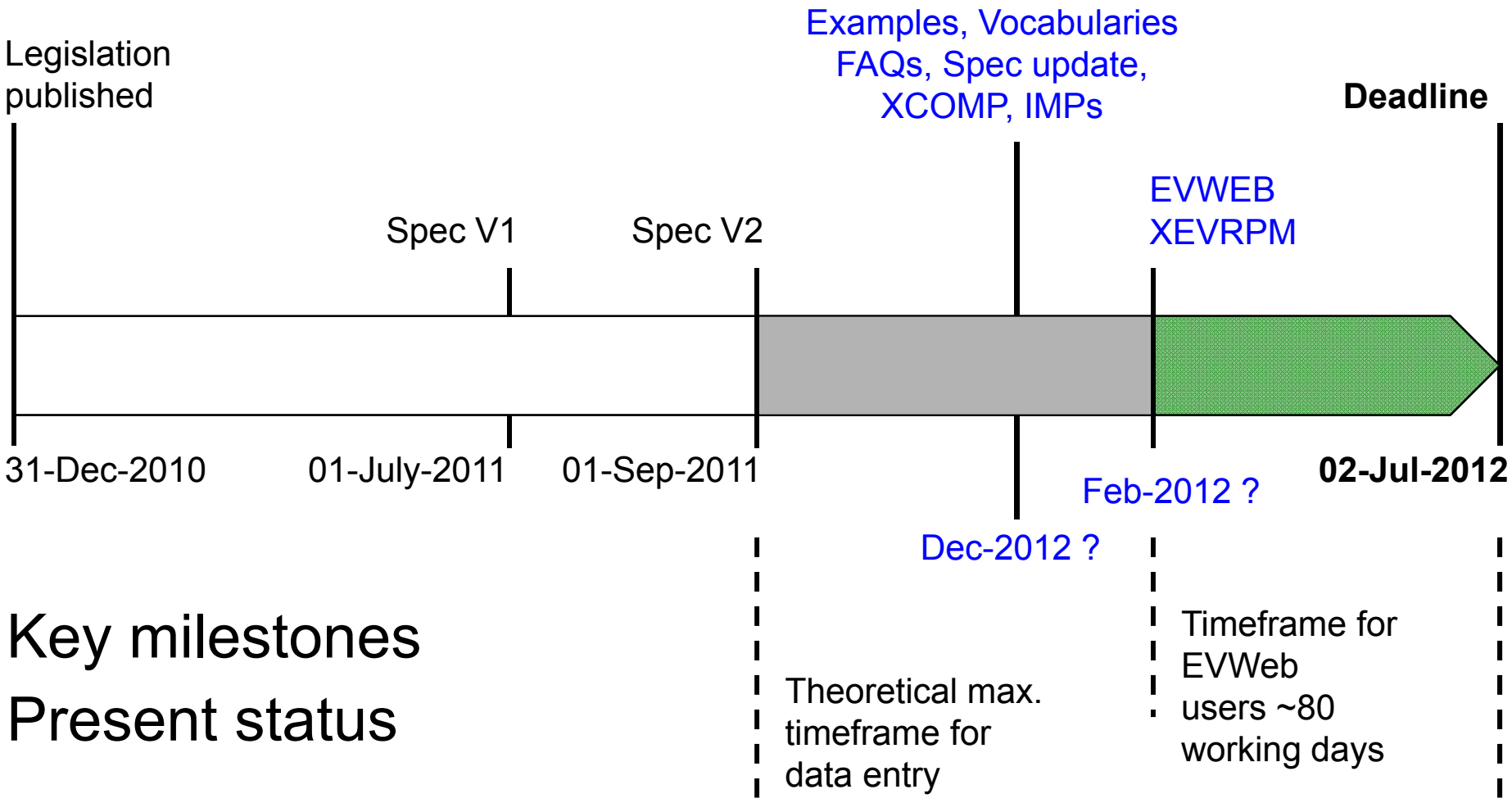
Challenge 1: Timelines



Key milestones Status October

exalon

Challenge 1: Timelines



Key milestones

Present status

Theoretical max. timeframe for data entry

Timeframe for EVWeb users ~80 working days

exalon

Challenge 2: Data

- Company databases, spreadsheets incomplete in terms of
  - Required data fields
  - Countries covered
  - Product portfolio covered
- Data distributed between systems
- Information partly only available in documents

⇨ How to bring the data together ?
⇨ How to fill-in the gaps ?

Challenge 3: Redundancy

- Cross-referencing to existing SSI from other MAHs not supported
- EMA not in the position to validate SSI data and publish corresponding EV codes
- Multiple entries in XEVMPD for many substances used identically in different medicinal products by different MAHs

⇨ How to benefit from synergies?
⇨ How to do reliable signal detection with many redundant (and most likely differing) records?

Challenge 4: Specification

- Specification significantly more complex
  - Many new data fields, especially for substances
  - Little information is truly optional (business rules)
  - Concerns about level of details, confidentiality
  - Questions regarding language of the data
- Currently no validation tool available
- ISO IDMP already at the gates!

⇨ Call for interim solutions ?
⇨ Will it happen or is it going the “PIM route”?

Challenge 5:
Resource Constraints

- Human
  - Only limited experience available
  - Trainings just about to commence
- IT
  - Software tools currently not compliant
  - XCOMP testing still not available
  - EVWEB not until February 2012 (?)
- Budget (?)

⇨ How to start without tools, no people and only little draft guidance?

Challenge 6: EMA Policy

- Due to “Policy Reasons”, access to XEVMPD is restricted to
  - MAHs
  - Sponsors
- Vendors and Consultants to liaise with MAHs, Sponsors
  - Slows down the development of software solutions, services, and trainings

⇨ How to develop and test software tools with no support from EMA?

Challenge 7:
Printed Product Information

- SPC, Labeling, PIL and Annexes (for CAPs)
  - Within 15 days after initial approval
  - Updated within 15 days after variation approval
    - Guideline addressing variations / lifecycle outstanding
    - Plans to soften timelines for variations not significant to public health
  - Required in all applicable local languages!
  - Additional formal requirements

⇨Timeline “approval” of Labeling in an MRP/DCP variation?
⇨Optimal process for Printed Product Information?

Challenge 7:
Printed Product Information

- Change from “data only” to “data and documents”
- Data maintained in registration databases, spreadsheets , whereas SPC, PIL, Annexes maintained in DMS, publishing systems, file systems
- Centralized EVMPD process ↔ Decentralized process for Product Information translation

⇨How to link databases with DMS records for PPI?
⇨Impact on critical regulatory processes for PPI:
Central → Local → Central(?)

Challenge 8: Inspections

- The obligations within context of PharmacoVigilance legislation: potential impact on patient safety!
  - Question: can IT systems related to the submission of XEVMPD data be addressed in a PharmacoVigilance inspection?
  - Most likely answer – ***YES, they can!***

⇨ Validated and controlled systems and well-documented processes required

CONCLUSIONS

Conclusions

- Technical and regulatory requirements not fixed!
- Guidance, examples, software tools still missing!
- Complex standard with excessive data requirements!
- High maintenance efforts expected!
- Impact on DRA business processes!
- EMA not yet ready!
- MAHs not yet ready!
- Vendors not yet ready!
- Only 205 days left!

Conclusions

⇨Anything else planned for 2012?

THANK YOU!

Dr. Michael Braun
Exalon GmbH
michael.braun@exalon.com
www.exalon.com
Office +49(0)7732.939.1650