Feedback to EUNDB on EU-SRS Business Case presentation at HMA II, Sofia

EUNDB, 21st June 2018

Joris Kampmeijer, Frits Stulp (CBG/MEB)

Feedback to SPOR Task Force on EU-SRS Business Case presentation at HMA II, Sofia

SPOR TF, 22nd June 2018

Joris Kampmeijer, Frits Stulp (CBG/MEB)

General

The business case of EU-SRS implementation was presented at the HMA II in Sofia, Bulgaria on June 20th, 2018

Materials provided:

- Cover note – Describing (in Q&A style) contents of business case and all major discussion points
- Presentation deck – Summarizing the business case and requesting decision (including back-up materials)
- Supporting document – More extensive documentation on the work done on the business case

Many pre-discussions had taken place over the past weeks to allow discussion at HMA

Outcomes

- Based on the following request to the HMA:
  - Request to HMA*:
    - Endorsement of strategic direction (as part of Telematics strategy Concept Paper)
    - Endorsement of Substance Validation Group – phased commitment of NCAs to participate with experts on this European Group
    - Endorsement of decision to use and adapt G-SRS (system developed by FDA in collaboration with several European experts) as a basis and adapt to European requirements (EU-SRS)
- **Endorsement** was reached on the strategic direction for EU-SRS to support the SPOR landscape in Europe from substance perspective
- **Endorsement** was reached on the strategic role of the Substance Validation Group – phased participation will be agreed individually and confirmed at HMA II Vienna in November
- Funding, details of investment to be confirmed at HMA II in November

Details of the endorsement

- Scope is agreed as described in Option 4:
  - Minimal fields (signature fields) for Human and Veterinary (with Veterinary being addressed by combined agencies initially)
  - Focus of EU-SRS is on Structurally Diverse substances
- Using experience in Europe (DE, et al)
- Hand-over of system to be done to EMA at suitable moment
- Funding, overall resource commitments to be agreed (preparing for HMA II November 2018)

Summary

We agree on the role of EU-SRS to support ISO IDMP suitable management of substances with focus on structurally diverse substances to complement SMS functionality and thereby ensure this key component of SPOR,

Substances in products for human use and veterinary use are in scope, although those for veterinary use will have a lighter set of requirements and will be handled accordingly in the approach,

SMS is the broker of substances information within SPOR, but will also play a key role in management of Chemicals (as SMS functionality in this area may suffice for initial management),

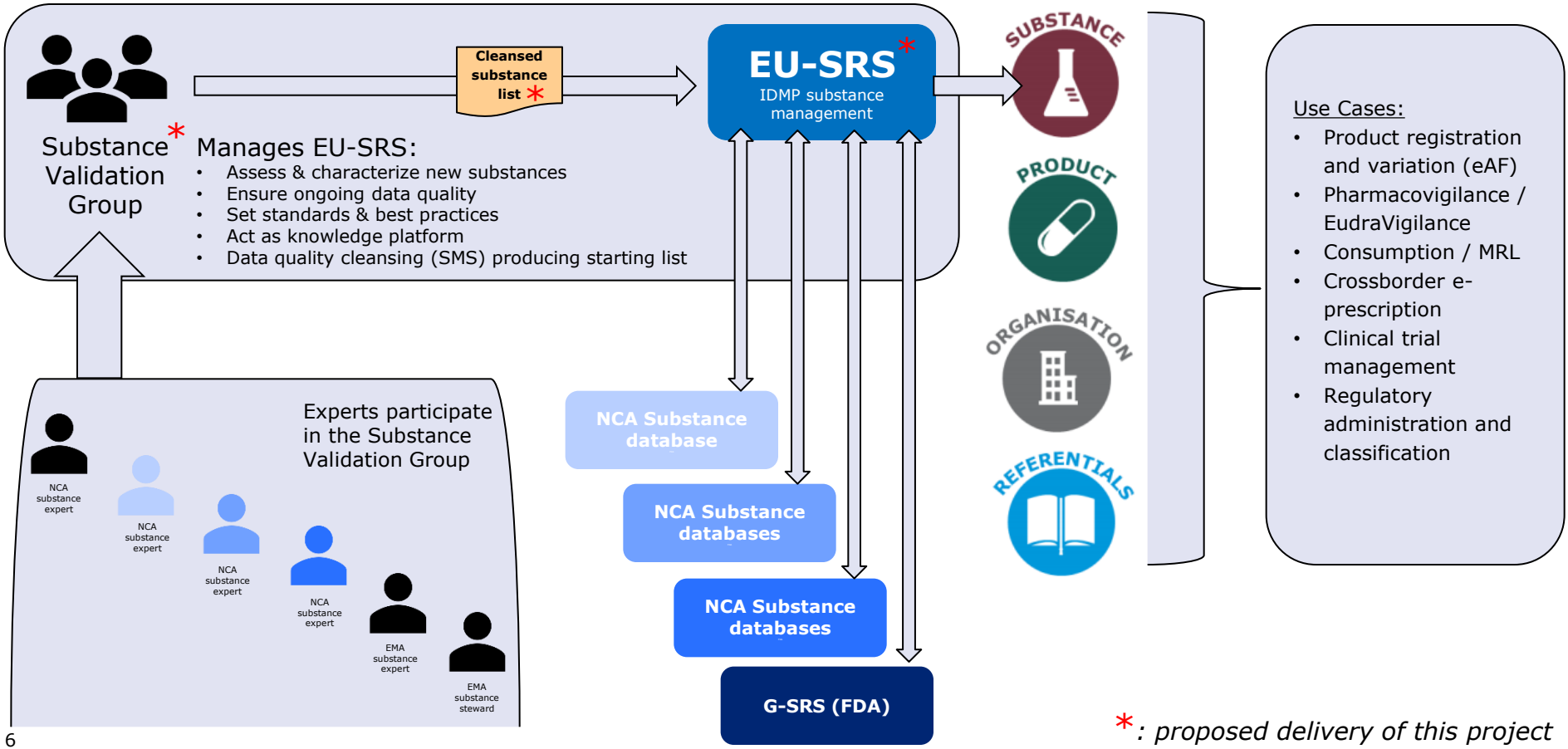
The complexity level of the first release of EU-SRS is minimized to a subset of required fields (known as “signature fields”, maintaining integrity of the ISO IDMP data model) thereby ensuring a feasible level of ambition,

The Substance Validation Group is initiated made up of experts from NCAs and EMA to cleanse the SMS dataset, and maintain the substances scientifically on an ongoing basis,

In the initiation of the project we will seek maximum re-use of experience and technology from US developed GSRS, but also from experience gained in Germany with the similar technology,

Funding, project timing and speed of adoption will be set jointly with HMA/EMA (confirmation at the HMA II meeting in Vienna in November).

Outcomes



*: *proposed delivery of this project*

Consequences

Formally continue in the direction as set!

Next steps:

- Detailing of consequences with stakeholders and partners (Network, EMA, FDA, Industry)
- Discuss funding (direct and in kind)
- Prepare project initiation:
  - Finalize architecture assessment (with EMA)
  - Align with development plans FDA
  - Start installation of Substance Validation Group, including Terms of Reference, call for participation & onboarding – to allow for data cleansing approach
- Formalize all arrangements at HMA II in November

Closing

Thank you for your contributions!

The team will take a slower pace at this moment

Please find the slides used at the HMA attached.

Please contact us in case of any questions!

Item 2.11 Business Case for implementation EU-SRS

HMA II, 20 June 2018 in Sofia

Joris Kampmeijer, Frits Stulp (CBG/MEB)

Version 1.1

eu2018bg.bg

Bulgarian Presidency of the Counsil of the European Union

Why and What?

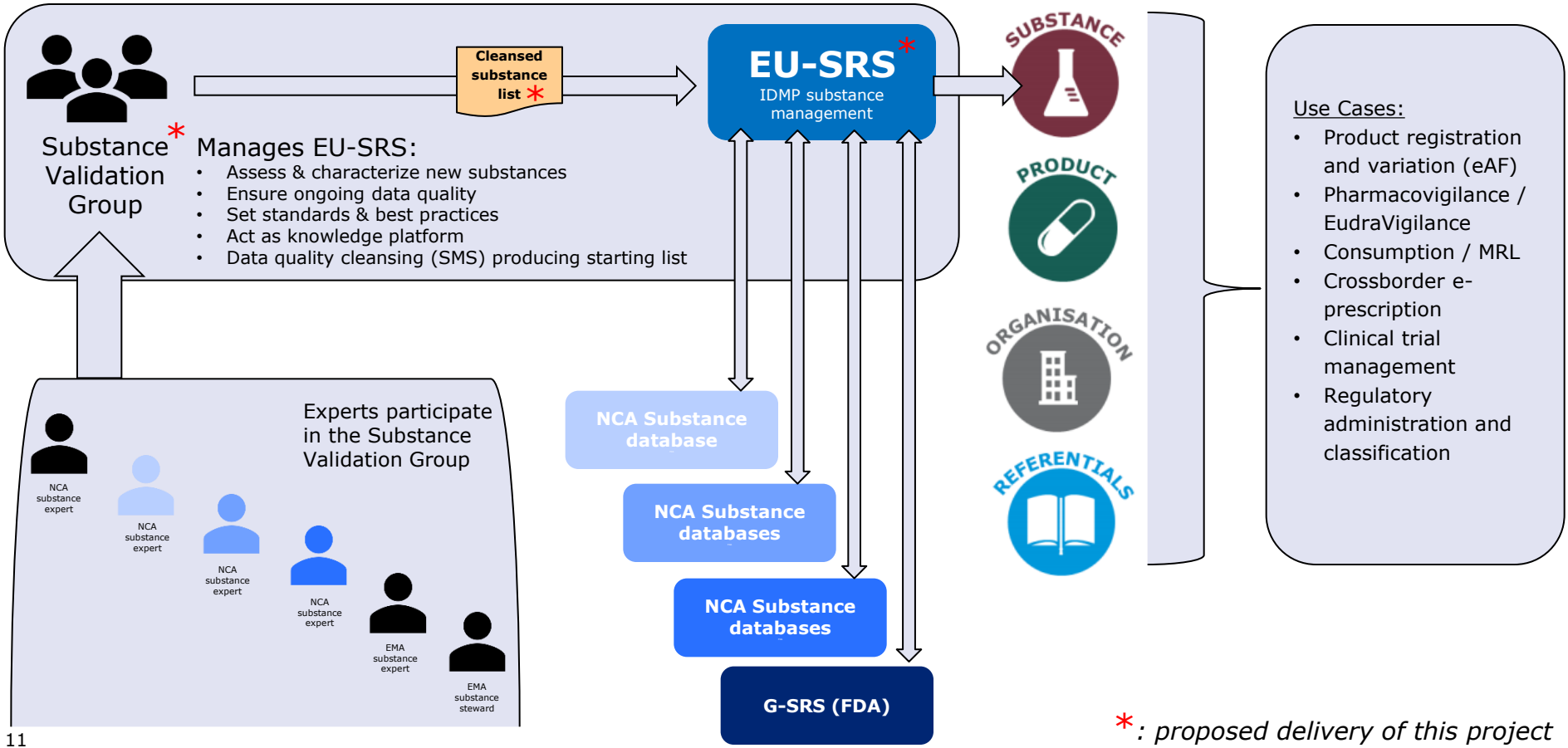
Why?

There is no EU wide list of substances of adequate quality for use in regulatory use cases, leading to errors in submissions, rework by assessors and duplication of substance expert work across the network.

What?

This project proposes to install an EU Network wide substances database (based on IDMP standards), governed by a group of NCA substance experts (=Substance Validation Group), who ensure data quality is fit for use.

Outcomes



*: *proposed delivery of this project*

Objectives of EU-SRS implementation

- Implement IDMP compliant solution for management of substances in medicinal products (actives and excipients) - Human and veterinary*
- Support the IDMP Legal Remit (EMA) – by complementing required functionality of SMS (substance management service in SPOR)
- Ensure contents of EU-SRS is managed by suitable level of experts (Substance Validation Group) ensuring data quality and scientific correctness
- Execute cleansing of substances content for use in SMS (2018)
- Maximize re-use of existing FDA system to allow for efficient implementation in Europe

The EU-SRS implementation is aligned to Telematics strategy to ensure high quality master data via SPOR for use in efficiency improvements in the EU Network

* Different requirements exist for Veterinary – see note

Benefits – Efficiency Increases

- IDMP based substance repository maintained by European experts (SVG)
  - Acting as future proof knowledge platform for all substance experts in the network
  - Increasing the cumulative substances knowledge for all agencies in the network – reducing duplicate efforts
- Supplies high quality substance data for SPOR (and other) use cases, e.g.
  - Reliable master data (substances) allows optimization and automation of processes and (semantic) interoperability (Telematics strategy, e.g. variations)
  - Selection of substance / declaration of strength for product composition (in eAF) strongly improved, reducing rework
  - Pharmacovigilance signal management – using high quality substance identifiers and hierarchy will improve side effect reporting and analysis capabilities
  - Cross-border ingredient management – facilitating generic e-prescription
  - European (and global) product supply chain traceability – control over ingredients in case of issues, Falsified Medicines
- Project will execute substance data cleansing (EV/EUTCT) for use in SMS and SPOR
- Leverages the investment done into IDMP database by FDA with strong input from several EU Network experts

Benefits – Legal compliance

- Implementation of ISO 11238 standard (ISO IDMP) in accordance with Pharmacovigilance Implementing Regulation 520/2012
  - Requirements to signal management and the use of ISO IDMP standards increasing interoperability and quality of analysis
- Implementation of Article 81 as part of Regulation 536/2014
  - Identification of products and substances in Investigational Medicinal Products in accordance with ISO IDMP standards
- Compliance to veterinary legislation - Directive 2001/82/EU (as amended), Guidance Volume 9B &upcoming Veterinary Regulation (in process):
  - Reduced requirements in comparison to substance management in medicinal products for human use, so a lighter version would be applied and maximum re-use of the data of substances for human use products is proposed

Substance Validation Group estimation

Class	Estimate of number on European market	Number of experts needed (headcount)	Minimal capacity for migration (FTE)*	Minimal capacity for maintenance (FTE)
Chemicals	30.000	4	2	2
Proteins	2.000	2	1,5	1
Polymers	2.000	2	1	0,7
Nucleic acids	50	1	0,1	0,1
Vaccines	800	2	2	1,5
Advanced Therapies	10	1	0,1	0,2
Allergens	1.200	1	0,5	0,3
Homeopathics	3.000	1	0,3	0,2
Plasma Derived	100	1	0,2	0,2
Herbals	2500	2	1,5	1
Veterinary specifics	800	2	1,8	0,8
Excipient specifics*	-	1	0,5	0
Taxonomical expertise*	-	1	0,5	0
Immunologial expertise*	-	1	0,5	0
Herbal / Homeopathic expertise*	-	1	0,5	0
TOTAL:	**42.460**	**19**	**13**	**8**

Costs

- Initial set-up (estimated at 12 months throughput time):
  - Installation of EU-SRS & G-SRS functional update to EU-SRS
    - Estimated at least 12 months throughput time
  - Data cleansing of substances list* for Europe by SVG using SRS tools
    - Estimated at least 12 months throughput time
- Maintenance:
  - Substance experts (NCA/EMA) participating in Substance Validation Group
  - Hosting, technical and functional maintenance

Cost areas	Direct costs (kEUR/Year)	In kind contribution in SVG (FTE/Year)
EU-SRS Project implementation (system, SVG & data cleansing)	€ 965.466,91	13
EU-SRS maintenance (system & data)	€ 486.269,03	8

- Implementation options have been designed: this estimate is based on a minimal IDMP fields set and substances in both Human and Veterinary products in scope

* Proposed approach on data cleansing is included in the background slides

Implementation options

Several implementation options have been designed (see appendix), main options:

- No action scenario - keep SMS only:
  - Missing substance hierarchy, business logic / governance, not IDMP compliant, not future proof
  - Minimal update can be considered to increase data coverage & functionality (mainly Chemicals)
- Expand SMS to cover EU-SRS functionality:
  - High investment due to low re-use of G-SRS, not aligned to EMA strategy for SMS, not viable
- Minimized EU-SRS-based (Human only, Human/Veterinary):
  - Preferred option, capable of delivering benefits, future-proof with data scope expansions only
- Full EU-SRS
  - Full delivery of IDMP solution, future-proof, high maintenance requirement

More details in slide 21

Requested decision

- Value of EU-SRS lies in:
  - Increased data quality for use in SPOR (and beyond)
  - EU Network platform to optimize substance knowledge and management
  - Legal compliance to IDMP

- Request to HMA*:
  - Endorsement of strategic direction (as part of Telematics strategy Concept Paper)
  - Endorsement of Substance Validation Group – phased commitment of NCAs to participate with experts on this European Group
  - Endorsement of decision to use and adapt G-SRS (system developed by FDA in collaboration with several European experts) as a basis and adapt to European requirements (EU-SRS)

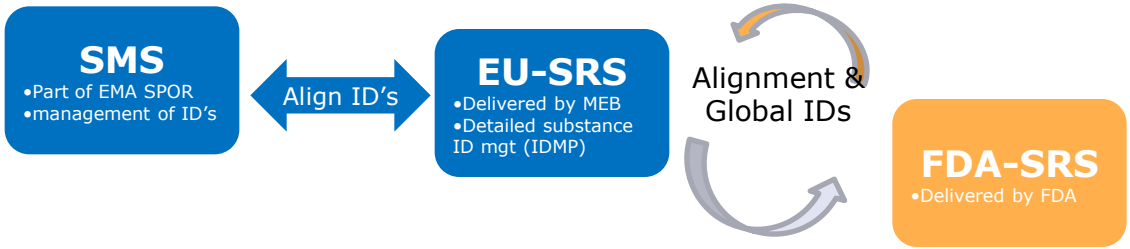
* Proposed next steps upon endorsement are included in the background slides

Questions ?

Background information

What is EU-SRS?

Precise substance identification supports unambigous description of product composition as well as clinical safety and minimized toxicological risk
– as part of the IDMP business case



EU-SRS will focus on:

- Identification of complete chemical, protein, polymer, multi-substance material
- And structurally diverse substances in particular SMS is not equipped to capture the level of detail required for these classes:
  - Vaccines
  - Biologicals (e.g.monoclonal antibodies, plasma-derived substances)
  - Herbals
  - Homeopathics
    Allergens

Project deliverables

- Implementation of a European substances database (EU-SRS):
  - with IDMP business logic for characterization of substances
  - Leading to a higher reliability of the list
  - Functionality to manage the more complex molecules such as biologicals, vaccines and herbals (known as structurally diverse)
- Introduction of the European Substances Validation Group (SVG):
  - European (NCA/EMA) substance experts in virtual group
  - Governs the contents and enable European-wide use of substance information
  - Ensures high data quality and combines knowledge within EU Network
- Cleansing of the current substances list (EUTCT & EV):
  - To level of quality that supports the required processes (in SMS to SPOR, eAF, etc)

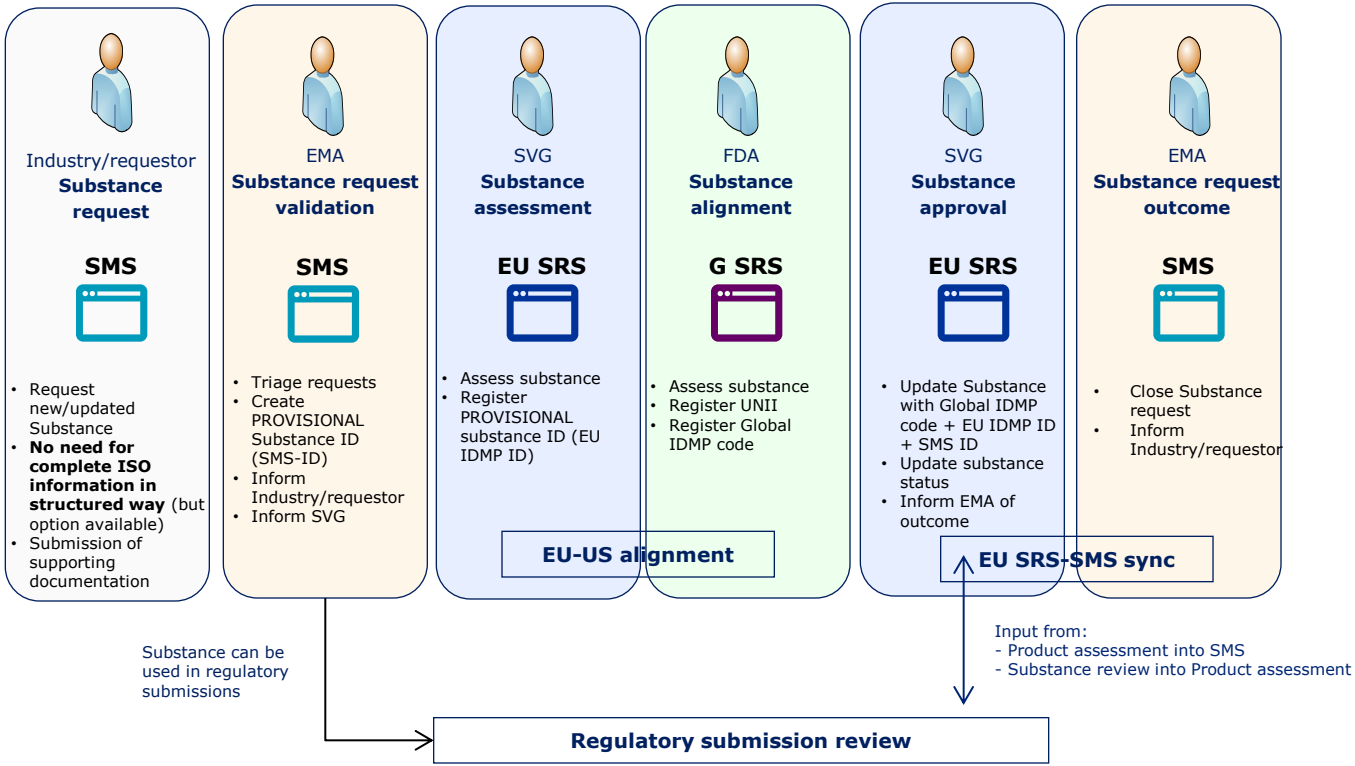
Use cases for substance management

These are already divided into categories based on the initial release

Backwards compatibility	Must	Should	Could	Won't (Read: later release)
Via EUTCT: • Clinical Trials: (EudraCT, new CT) • H Pre-submissions (Orphan, UPI, PedDRA) • H&V MAA & Var Regulatory submission (SIAMED, eAF, CESSP, CTS) • NCAs **Via Art 57:** • Pharmacovigilance: (EV H, PSUR rep.) • Referrals • Fees	• Pharmacovigilance (signal detection, analytics) – legal driver • Product (composition) registration (H&V) – PMS TOM • Consumption (Veterinary business case) – legal driver • MRL (veterinary use case) – legal driver • Cross Border ePrescription – EC/public health	• Evaluation of Risk of Shortages - EC/public health • Variations (manufacturer details change) – ROG • CEP Management – ROG • Toxicology use case (under investigation)	• GMDP Inspection Support	• ASMF Management • Batch Recall Support • Supply Chain Traceability

For Veterinary: although legal requirement for substance management is present, actual detailed requirements will vary. Therefore, consideration to do a more stepwise implementation for veterinary.

Target Operating Model



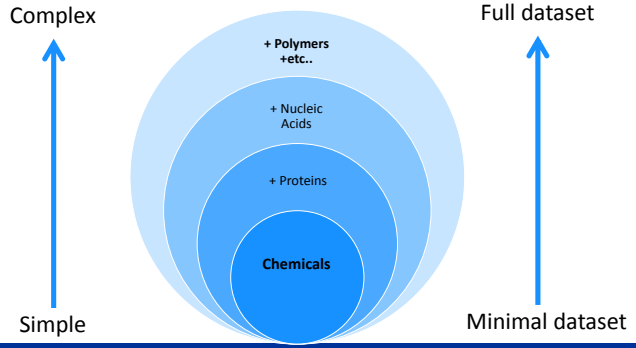
SMS TOM ensures:

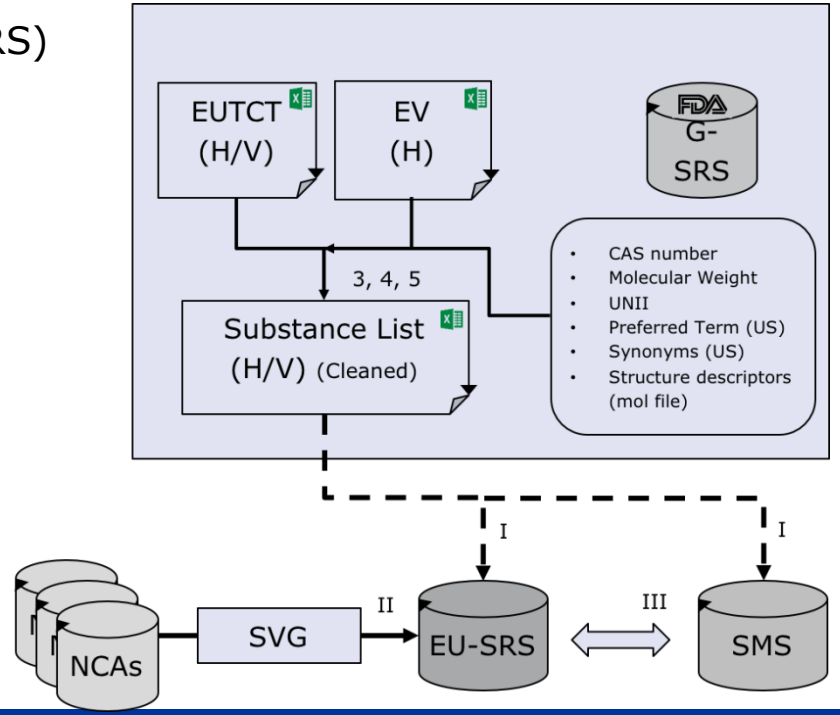
- Regulatory processes can start as soon as substance is Provisionally registered
- EU-US alignment
- Data is approved by SVG before conclusion of regulatory processes i.e **only trusted data is used in regulatory processes**

Data cleansing approach

As agreed in project charter and EU-SRS day, a stepwise data cleansing is proposed:

- Priority on structurally diverse in EU-SRS approach, SMS as initial repository for Chemicals
- Matching of EUTCT/EV contents by SVG
- Using NCA sources (and available FDA data in EU-SRS)
- Include mapping identifiers to allow backwards and national traceability
- Stepwise participation of NCAs in SVG based on substance class priority





EU-SRS Signature fields (1/2)

- Definition:
  - Signature fields describe field values containing Essential Characteristics of a substance or specified substance used for unambiguous description of a substance or specified substance;
  - Signature fields are not used for exhausting definition of the substance giving a 100% unique identified substance, but provide a ‘fingerprint’ of the characteristics covering the overall, but not complete defining identity of a substance;
  - Selection of the Signature fields does NOT replace the ISO 11238 standard or ISO 19844 TS

EU-SRS Signature fields (2/2)

A) General Fields:

- EU-SRS ID; Preferred Name; Official Name;
  Systematic Name; CAS-RN; Codes and Reference Source information

B) Chemical fingerprint fields:

1. Structural Representation/ Isomeric SMILES
2. Molecular formula
3. Molecular formula by Moiety
4. Molecular weight
5. Physical form state/ type (e.g. solid, polymorphic form)
6. Characteristic attribute name (e.g. particle size)
7. Production method type (e.g. extraction, semi-synthetic, fermentation, fractionation, biosynthetic)
8. Pharmaceutical Grade (e.g. Ph. Eur., USP, In-House)

Minimized set of IDMP fields

Class	Minimum fields to identify substance (excl. general fields): *Signature fields*
Chemicals	8
Proteins	14
Polymers	10
Nucleic acids	10
Vaccines	14
Advanced Therapies	10
Allergens	12
Homeopathics	6
Plasma Derived	10
Herbals	12
Mixture	10

Total number of fields to describe fully ISO IDMP is described in ISO 11238 an ISO TS 19844
The General fields and codes are not concluded

Implementation options *(copied slide)*

Several implementation options have been designed (see appendix), main options:

- No action scenario - keep SMS only:
  - Missing substance hierarchy, business logic / governance, not IDMP compliant, not future proof
  - Minimal update can be considered to increase data coverage & functionality (mainly Chemicals)
- Expand SMS to cover EU-SRS functionality:
  - High investment due to low re-use of G-SRS, not aligned to EMA strategy for SMS, not viable
- Minimized EU-SRS-based (Human only, Human/Veterinary):
  - Preferred option, capable of delivering benefits, future-proof with data scope expansions only
- Full EU-SRS
  - Full delivery of IDMP solution, future-proof, high maintenance requirement

More details in slide 21

Options for implementation

The following options have been prepared for decision-making

Nr	Scenario	Implementation effort	Maintenance effort	ISO IDMP compliance (Interoperability)	Value to use cases	Future-proof
1	**SMS only, no EU-SRS, no SVG** Limited fields in SMS, no business logic	Includes initial (technical) data cleansing by EMA	EMA stewards only - minimal fields	ISO IDMP Compatible, assuming data mapping and adherence to SPOR API	Adequate for some, limited for other use cases due to limited information and data quality issues	Likely to be subject to massive changes
2	**Expanded SMS, no EU-SRS, no SVG** Comparable EU-SRS functionality built into SMS	High investment needed to (re-)build SRS-like IDMP functionality	Comparable to scenario 3 & 4, but dependent upon availabilty of SVG in this scenario.	ISO IDMP Compatible, assuming data mapping and adherence to SPOR API	Higher value to use cases due to extended dataset - concern on governance	May need further expansion later - strongly dependent upon quality of solution developed
3	**Signature EU-SRS (H only) & SVG** More fields in SMS & EU SRS, business logic managed by EU-SRS, SMS-EU-RSR sync (H only)	HMA approval required, as well as NCA resources for SVG and technical update	HMA approval required for NCA resources in SVG	Fully ISO IDMP compliant, although not all data is used yet	Suitable for all use cases and first expansions	ISO IDMP model available, expansion of data requires attention
4	**Signature EU-SRS (H/V) & SVG** More fields in SMS & EU SRS, business logic managed by EU-SRS SMS-EU-RSR sync (H/V)	HMA approval required, as well as NCA resources for SVG and technical update	HMA approval required for NCA resources in SVG	Fully ISO IDMP compliant, although not all data is used yet	Suitable for all use cases and first expansions	ISO IDMP model available, expansion of data requires attention
5	**Full ISO IDMP EU-SRS (H/V) & SVG** All ISO fields in EU-SRS, limited fields in SMS, business logic managed by EU-SRS SMS-EU-RSR sync (H/V)	Technically comparable to scenario 3 & 4, but high capacity required for data completion	High maintenance due to extensive dataset.	Full ISO compliance	Optimal value to use cases, but possibly overshooting	Optimal design for future expansion

Funding – under discussion

Type of costs	Implementation	Maintenance

Substance experts (SVG)	• NCA in kind contribution:
	  • Substance experts
	• EMA in kind contribution:
	  • SVG Stewards
	  • Data cleansing outsourcing support (under discussion)
		• NCA in kind contribution:
		  • Substance experts
		• EMA in kind contribution:
		  • SVG Stewards
		  • Data cleansing outsourcing support (under discussion)
		• Formalised as EMA sponsored group (location, etc)

System (EU-SRS)	• EMA project budget
	  • Under discussion
	  • Run under EMA conditions
	• Contribution in kind by NCAs willing & able, e.g.:
	  • MEB – Scientific Lead & Project Manager
	• Other funding (under discussion)
		• To be included in RUN budget of EMA starting 2019
		• Maintenance fee for use of EU-SRS to be determined

Draft

EU-SRS Preview

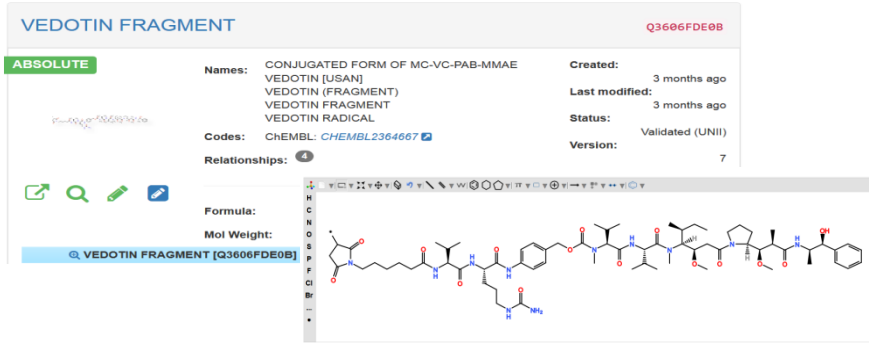
List of substances

Formula: C13H18O2

Mol Weight: 206.28

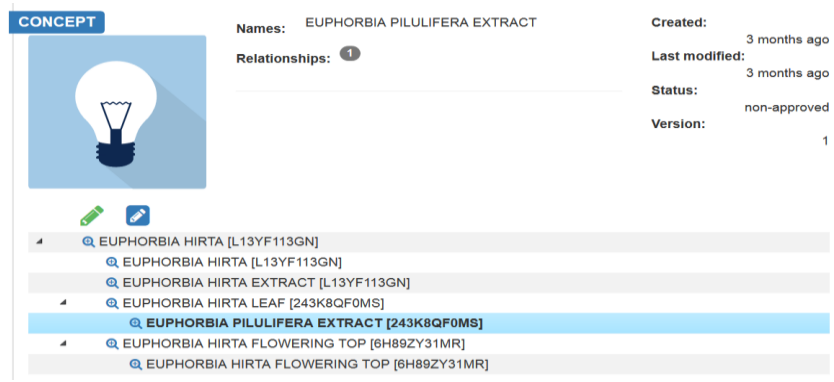
- **IBUPROFEN [WK2XYI10QM]**
  - **IBUPROFEN [WK2XYI10QM]**
  - IBUPROFEN MEGLUMINE [56SFW97YYQ]
  - IBUPROFEN POTASSIUM [48304089JJ]
  - IBUPROFEN LYSINE [N01ORX9D6S]
  - IBUPROFEN SODIUM [RM1CE97Z4N]
  - IBUPROFEN PICONOL [B0F91K5U4N]
  - IBUPROFEN ALUMINUM [D0YGZ1VO1B]
  - IBUPROFEN SODIUM ANHYDROUS [O0PJ4UZ01U]

Details available



Links to sources and other codes

Hierarchy to related substances



EU-SRS preview:

Use of hierarchy for selection/ Parent Child relationship

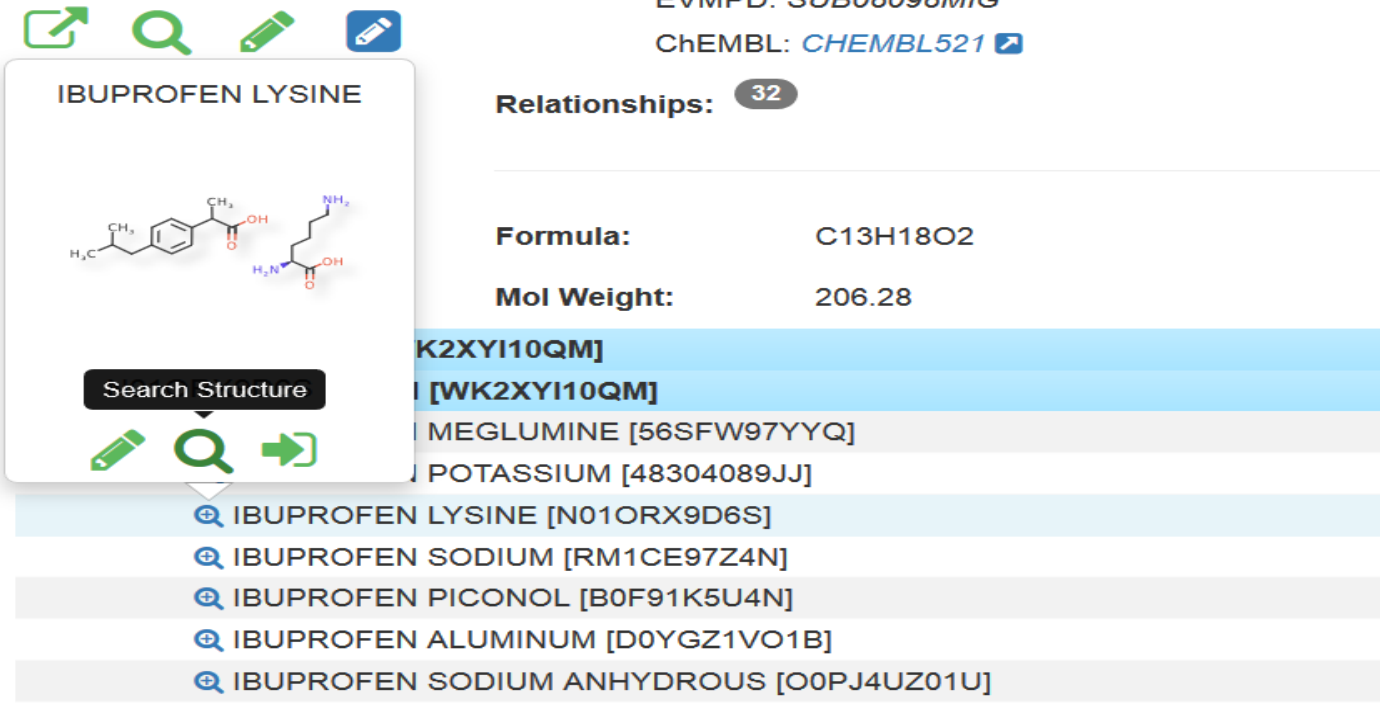
Formula: C13H18O2

Mol Weight: 206.28

- **IBUPROFEN [WK2XYI10QM]**
  - **IBUPROFEN [WK2XYI10QM]**
  - IBUPROFEN MEGLUMINE [56SFW97YYQ]
  - IBUPROFEN POTASSIUM [48304089JJ]
  - IBUPROFEN LYSINE [N01ORX9D6S]
  - IBUPROFEN SODIUM [RM1CE97Z4N]
  - IBUPROFEN PICONOL [B0F91K5U4N]
  - IBUPROFEN ALUMINUM [D0YGZ1VO1B]
  - IBUPROFEN SODIUM ANHYDROUS [O0PJ4UZ01U]

EU-SRS preview:

Select the correct Preferred term by direct name/ID and Structure display



Next steps upon approval of the business case?

- The EU-SRS business case has been developed to the best of our abilities and available information and invites to make a principle decision for EU-SRS as a strong backbone to SPOR for the future-proof management of substances. Approval of this principle will lead to:
  - Finalization of project funding (in discussion with HMA / EMA),
  - Project initiation, including detailed project plan, timeline and budget,
  - Installation of the Substance Validation Group,
  - Start of the substance data cleansing project work,
  - Report back to allow kick-off of the project.

Questions

Thank you