



Substance Subgroup Report to Task Force 10 March 2017

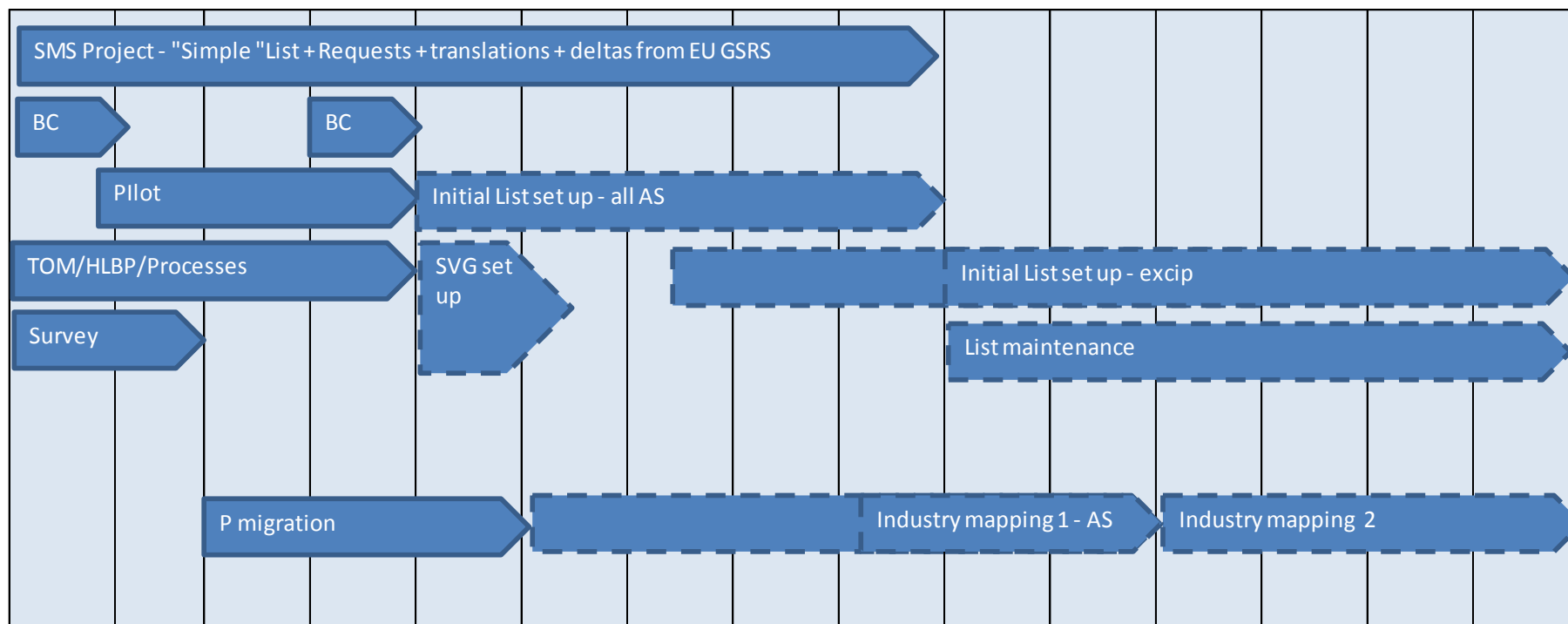


Outline of session

- SMS Project
- Business Cases
- Pilot
- Survey of NCAs
- Target Operating Model
- High Level Business Processes
- Migration
- Product-Subgroup Touchpoint
- Communications



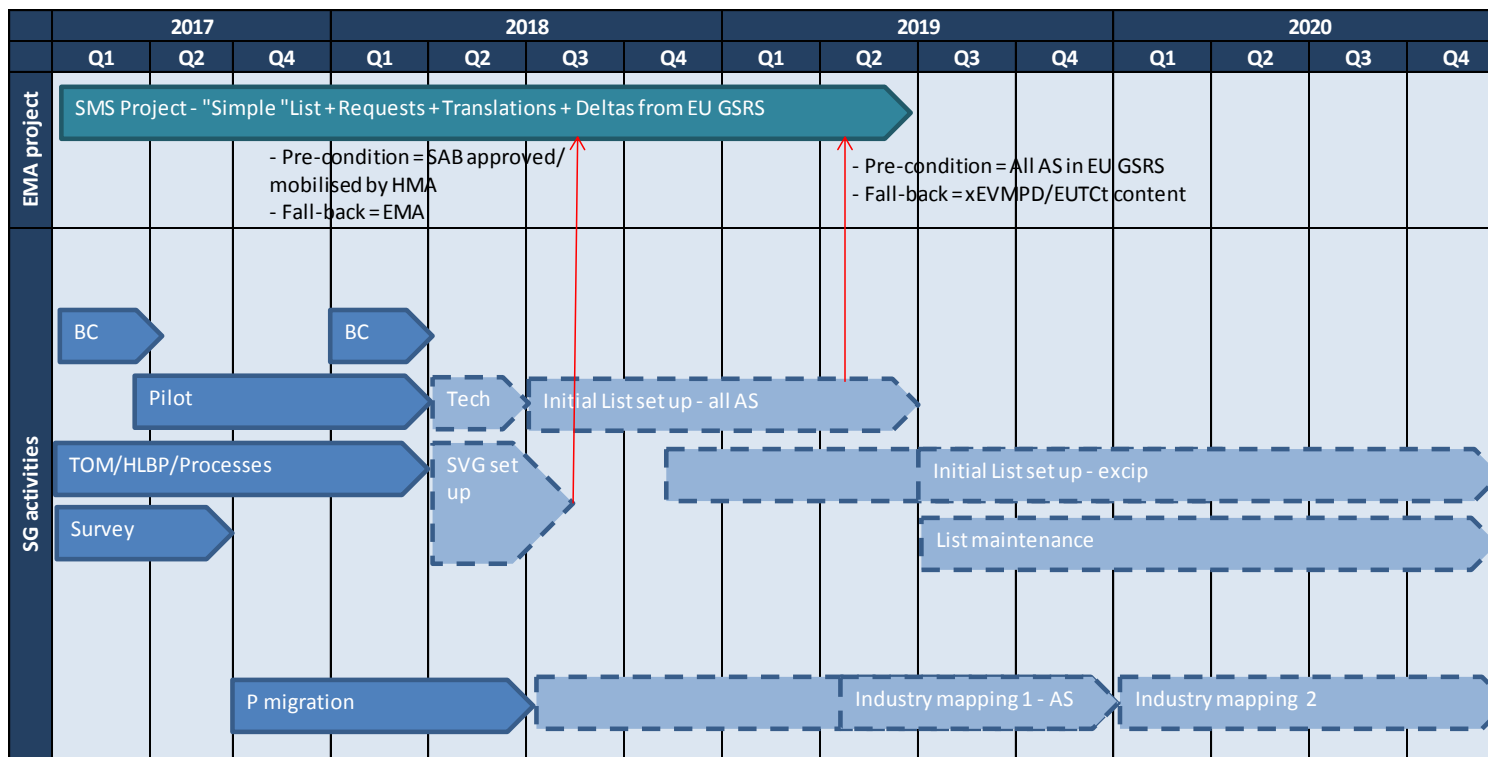
How it "fits" together



Not a "plan" only identification of logical building blocks



How it "fits" together – NEW (from flipchart)



- Not a "plan" only identification of logical building blocks
- Identification of scope and dependencies

- Ideally all AS + Excipients to be available by Q2 2019
- The diagram reflects the MVP with only AS mapped and therefore expands beyond reflecting a worst case Plan B
- Ideally Mapping 1 & 2 by Q2 2019
- The diagram with only AS mapped and therefore expands beyond reflecting a worst case Plan B



In scope:

“Simple” list to support regulatory process across EU network

- Migrated data from EUTCT Human S, EUTCT Vet S, EV Human, EudraPharm Vet
- A consolidated Human and vet list
- Capabilities to Support substance data management – creation and updates, change requests, translations, subscriptions/notifications, etc
- Capability to get updates (deltas) from external source (e.g. GSRS) – * if updates available the list will be ISO IDMP compatible as IDs/records will be uniquely generated according to ISO 11238 specifications

Out of scope – subject to Pilot:

- SPOR integration with GSRS
- Initial mapping/set up of the EU substance list together with NCAs
- Set up of Target Operating Model with Substance Advisory Board
- *ISO IDMP compliant/compatible**
- EU-US consolidated list

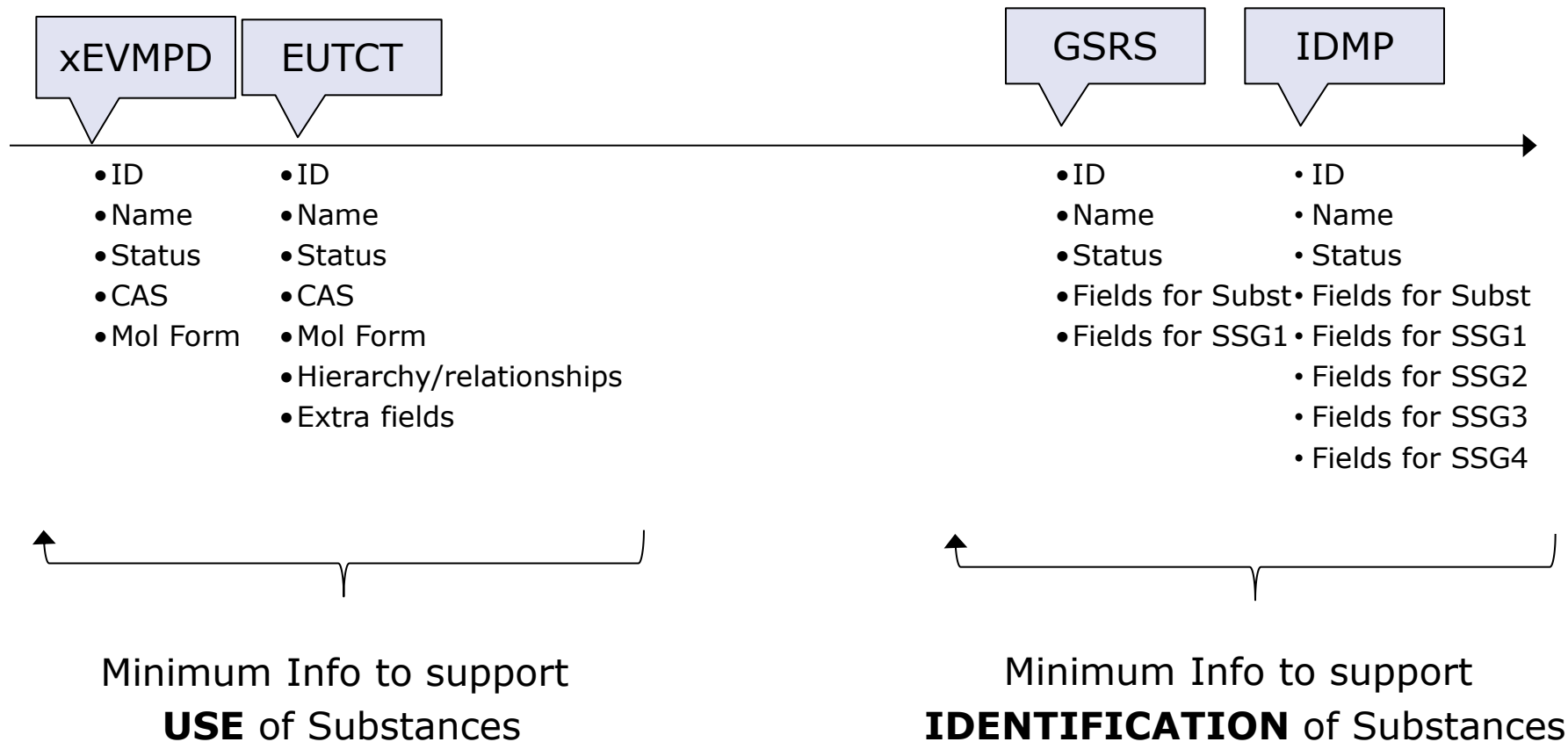


Scope clarifications - NEW

	SMS if EU GSRS not in time	EU GSRS Pilot	SMS if EU GSRS & SAB in time
Description	<ul style="list-style-type: none"> • Minimum Viable Solution delivered 		<ul style="list-style-type: none"> • Solution delivered if: <ul style="list-style-type: none"> • Initial list of all AS (& excipient?) is available in EU GSRS by 2019 • SAB approved by HMA and mobilised by 2019
Data content	<ul style="list-style-type: none"> • xEVMPD/EUTCT V content <ul style="list-style-type: none"> • Auth Substances • Dev Substances • H&V 	<ul style="list-style-type: none"> • xEVMPD/EUTCT V/NCAs/GSRS content <ul style="list-style-type: none"> • Auth Substances • H&V 	<ul style="list-style-type: none"> • IDMP compatible content <ul style="list-style-type: none"> • Auth Substances • H&V • Other content <ul style="list-style-type: none"> • Dev Substances • Legacy Substances
Data structure	<ul style="list-style-type: none"> • EUTCT structure <ul style="list-style-type: none"> • ID + name + relationships + extras • No new fields <ul style="list-style-type: none"> • To be confirmed if use feasible with existing fields alone • Any additional fields by Sep 17 	<ul style="list-style-type: none"> • IDMP compatible structure <ul style="list-style-type: none"> • ID + name + min fields 	<ul style="list-style-type: none"> • EUTCT structure <ul style="list-style-type: none"> • ID + name + relationships + extras • No new fields (content would be updated but not structure) • Issue – what would distinguish two similar Subst/SS? <ul style="list-style-type: none"> • To be confirmed if use feasible with existing fields alone • Any additional fields by Sep 17
People/ Process	<ul style="list-style-type: none"> • EMA only • Validation based on SmPC 	<ul style="list-style-type: none"> • Volunteers from EMA/NCAs/Industry • Validation based on Mod 3/Part II 	<ul style="list-style-type: none"> • EMA & SAB • Validation based on Mod 3/Part II
Technology	<ul style="list-style-type: none"> • SMS Portal/DB 	<ul style="list-style-type: none"> • Excel 	<ul style="list-style-type: none"> • SMS Portal/DB • feeding from EU GSRS



The following diagram depicts the currently available data structures (not the available content):



Issue – How to distinguish two similar Subst/SS?



Business Cases

- Work so far
- Interim conclusions
- Work still to do



Substance/Specified Substance Categories (1)

Substances

- Active Ingredient
- Adjuvant
- Non-active Ingredient

SSG1

- Multi-constituent substance - including an active ingredient
- Multi-constituent substance – excipient
- Physical form - Active Ingredient
- Physical form - Inactive Ingredient



Substance/Specified Substance Categories (2)

SSG2

- Manufacturer - Active Ingredient
- Manufacturer and high level manufacturing process - Active Ingredient
- Manufacturer and extended manufacturing process detail - Active Ingredient
- Manufacturer - Inactive Ingredient
- Manufacturer and high level manufacturing process - Inactive Ingredient
- Manufacturer and extended manufacturing process detail - Inactive Ingredient



Substance/Specified Substance Categories (3)

SSG3

- Active Ingredient – Pharmacopoeial
- Active Ingredient - In-house specification (Pharmacopoeial plus)
- Active Ingredient - In-house specification (non-pharmacopoeial)
- Inactive Ingredient – Pharmacopoeial
- Inactive Ingredient - In-house specification (Pharmacopoeial plus)
- Inactive Ingredient - In-house specification (non-pharmacopoeial)



Business Cases (AMPs)

- Business Cases aligned with 'Product'
 - Pharmacovigilance
 - E-Prescription
 - Variations (manufacturer details change)
 - Evaluation of Risk of Shortages
- Business Case aligned with Telematics Project
 - Portal Support
- Additional Business Cases in support of Regulatory Network activities
 - GMDP Inspection Support
 - ASMF Management
 - CEP Management
 - Supply Chain Traceability
 - Batch Recall Support
 - Consumption (Veterinary business case)
 - Substance ID Linking (using Substance ID ubiquitously in e.g. correspondence, reports, systems etc)





Business Case - Pharmacovigilance

High Priority	Medium Priority
Substances – actives SSG1 – multi-constituent including an active SSG2 – manufacturer ID - actives	Substances – adjuvants Substances – excipients SSG1 – physical form – actives SSG2 – manufacturer ID and high level process – actives SSG2 – manufacturer ID and extended level process – actives (certain classes only)
Low Priority	None
SSG1 – multi-constituent – excipients SSG1 – physical form - excipients	SSG2 – excipients SSG3 – excipients

- Highest priority relates to active substances, some of which may be SSG1s
 - The manufacturer ID should be beneficial in determining whether a specific issue could be traced to a manufacturer



Key Iteration 1 business cases require:

Substances

SSG1

Manufacturer ID



Business Cases - Substances

	PV	e-Pres	Variat.	Short.	Portal	GMDP	ASMF	CEP	Supply	Recall	Consum	Linking
Active	H	H	L	N	H	N	N	N	N	N	H	H
Adjuvant	M	H	L	N	H	N	N	N	N	N	L	H
Non-active	M	H	L	N	H	N	N	N	N	N	L	H

- Key business cases are:
 - Pharmacovigilance
 - E-prescription
 - Portal Support
 - Consumption for veterinary products
 - Substance linking



SSG1 – Multi-constituent Substances

	PV	e-Pres	Variat.	Short.	Portal	GMDP	ASMF	CEP	Supply	Recall	Consum	Linking
Incl. Active	H	H/L *	L	N	H	N	N	N	N	N	L	H
Excipient	L	L	L	N	H	N	N	N	N	N	L	H

*High for Herbals

Key business cases are

- Pharmacovigilance (higher for actives)
- E-prescriptions (higher for actives)
- Portal support
- Substance linking



SSG2 – Manufacturer ID only

	PV	e-Pres	Variat.	Short.	Portal	GMDP	ASMF	CEP	Supply	Recall	Consum	Linking
Active	H	N	H/N*	H	H	H	H	H/N**	H	H	H	H
Inactive	N	N	N	L	N	N	N	N	N	N	N	N

*High for address change; None for manufacturer change

**High if CEP owners allowed to manage their own Org ID

Note: Manufacturer ID only could be implemented without SSG2 – just as an attribute in the Product/Ingredient

Strong business case for Manufacturer ID for actives

- No business case for excipients



Business Cases

- Work still to do
 - Confirm MRL business case
 - Pilot will indicate whether additional identified business cases can be supported
 - Data availability from pilot can form the basis for further business case identification



Pilot Objectives and Scope

- Objectives
 - Establish the nature of the data we have
 - Establish the 'right' granularity to support going forward
 - Quantification of effort/resource skills required for the initial set up of the list
 - Identify needs/steps for implementation and maintenance of EU-GSRS software
- Scope
 - AMPs – Human and Veterinary
 - In scope (see next slide)
 - Focus on Substances and SSG1 initially – and report on these
 - SSG2 and SSG3 will be as a follow-on
 - Number of products to be determined (number of NCAs?/ number of products per NCA) – to lead to 'sufficient' substance coverage
 - No active piloting of IMPs – will consider what it mean to manage current processes



Scope

- Authorised substances and related specified substances used in Human and Veterinary Authorised Medicinal Products (AMPs)
 - Actives
 - Excipients/Adjuvants
 - **Substances and SSG1** – Higher priority
 - **SSG2 & SSG4** - Lower priority, only to be completed in all of above is done ahead of time
- All substance types
 - Chemicals
 - Proteins
 - Nucleic Acids
 - Polymers
 - Herbals
 - Homeopathics
 - Plasma-derived
 - Allergens
 - Vaccines (note: no 19844 annex yet available)
 - Advanced Therapies (note: no 19844 annex yet available)



Need to define a **comprehensive sample** considering:

- Participants
 - Products will be representative of participating NCAs and Companies such that workload is doable in the period available
- Product characteristics
 - Recent vs Older products
 - Inovators vs Generics
- Substance characteristics
 - All ingredients (actives and excipients) of the selected products will be reviewed
 - Simple/Complex molecules
 - Multi-constituent ingredients
 - In-house/full composition available
 - Out-of-house/full composition not available
 - contained in products produced by third party manufacturers
 - Good/medium/poor data availability in G-SRS ?
 - Substances obtained from food industry

Regulator Activities (1)

Create list of EU substances – starting point XEVMPD and EUTCT veterinary substances

- Substances and SSG1s

Populate data from FDA and NCAs

Classify

- Substances with good data (Category A)
- Substances with data that needs improved data (Category B)
- Substances with no data (Category C)
- **Ambiguous/incorrect substances (Category D)**
 - **Not dealt with by the pilot**



Need to be migrated as deprecated records anyway



Regulator Activities (2)

Selection of products made which will cover matrix of substances with data deficiencies **i.e. sampling or substance selection criteria**

- **Will use Category B and C substances**

Regulators will try to source missing data from dossiers

Determine effort, resources, skills, issues etc.

Remaining missing data will be requested from participating companies



Industry Activities

Confirm Regulator substance and **Product** composition data versus company interpretation

Identify and complete any missing substance/SSG1 data

Determine effort, resources, skills, issues etc.

- The report should focus on effort to complete substance data but we are also looking into composition...
 - Should we determine issues with composition such as different granularity; different mapping rules – this would feed into P data validation
 - Or is it out of scope?
- **See Mettes notes in notes below**
- Propose not to change slide and to keep notes separate – could be used in working instructions



Deliverables

- Spreadsheet of EU substances
 - Based upon Art 57 and EUTCT vet
 - Additions e.g. More granularity
 - Deprecations
 - Enriched from FDA/NCA databases
- Interim report – Quantification of Category A,B Cs by substance class(es)
- Quantification of effort taken & extrapolation for the 'simple' list (GSRS-light) and 'full GSRS'
- Identification of GSRS enhancements are needed

- **Out of scope:**
 - **Substance (legacy) Implementation plan**
 - **Solution implementation**



Not to be delivered by the pilot but are pre-conditions for the implementation in SMS

April 2017 – September 2017

Development of Substance list
Enhancement with FDA and NCA data

Mid September 2017

- First result of mapping completed
- List does not include SSG2 and SSG3 (SSG3 needed for some substances e.g. Water for Injections, purified water)
- Gaps and misalignments will be known
- Key areas of concern identified
- Products for pilot identified.

November 2017

- Report interim findings to IT Directors

End September 2017 – End November 2017

- Based on selected product and substances regulators will have identified what is not in their database including information extracted from submission dossiers
- Hand over of activity of finding missing data to participating pilot companies
 - Don't have to wait until the end of this phase to start the next

End November 2017 – End January 2018

- Pilot companies check regulators work and fill in remaining gaps

End February 2018

- Consolidate pilot data

March - May 2018

- Outcome will be documented in consolidated report and will be handed over to ROG
- ROG proposal - 1 month for prep. Look at how we present the information.



Pilot Steps and Timelines

	2017										2018				
	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	
Call for Volunteers	█														
Source EU lists	█														
Match FDA & NCA data (autom)	█	█	█	█	█	█									
Training		█				█									
Issue identification						█									
Confirm pilot products/Sample						█									
Interim report to IT Directors								█							
Regulator enhance pilot substance data							█	█							
Industry enhances pilot substance data								█	█	█					
Analyse results											█				
Report to ROG												█			
Report to HMA														█	



Resources

- NCAs/EMA data (5 to 6 NCAs with the ability to output data in a 'consumable' format)
 - Survey to collect information on other possible sources and NCAs that don't have substance databases
- NCA commitment to participate in evaluation
 - Request at Task Force today
 - Via NCA change liaisons if not enough via EUNDB reps on Task Force
- Industry commitment to participate
 - Match to areas of concern



What happens next

- Proposal to ROG/HMA to complete the list for Iteration 1
 - Substances/SSGs comprehensive of what is in Authorised MPs
 - With minimum set of data to be workable
- How SMS will consume 'simple' list
- How naming conventions will work for PMS/simple SMS
 - Can SMS cope with simple ID + name (assumed that naming convention is such that users can differentiate similar substances/SS by name)
 - If not, it may be that SMS will require additional fields, this needs to be known at the latest by Sep 17
- How Substance/Reference Substance/Strength can be managed
- How multiple SSGs for a Substance in a Product will be managed
 - To ensure that these are considered as 'or' not 'and'




Survey (1)

Why are we doing this?

- Gather information to help on set up of SAB and associated processes
Action: Consideration of who should be the sender of the survey? Make sure the sender has the right impact (could be telematics office?)

Scope of questions **(simple survey of 5-6 questions to collect responses from NCAs)**

- Existence of NCA substance database
 - Type of database/spreadsheet/none....
 - How is it managed
- **Process and** Effort in managing substances at present
 - Team, numbers, expertise/**profile, experience**, etc
 - **Division of work? 1 step vs 2 step approval?**
- Opportunities for improvement/centralisation
- Legal obligations to have local database
-  Volume of new and updated substances **(incl. updates, names, translations, attributes)**



Survey (2)

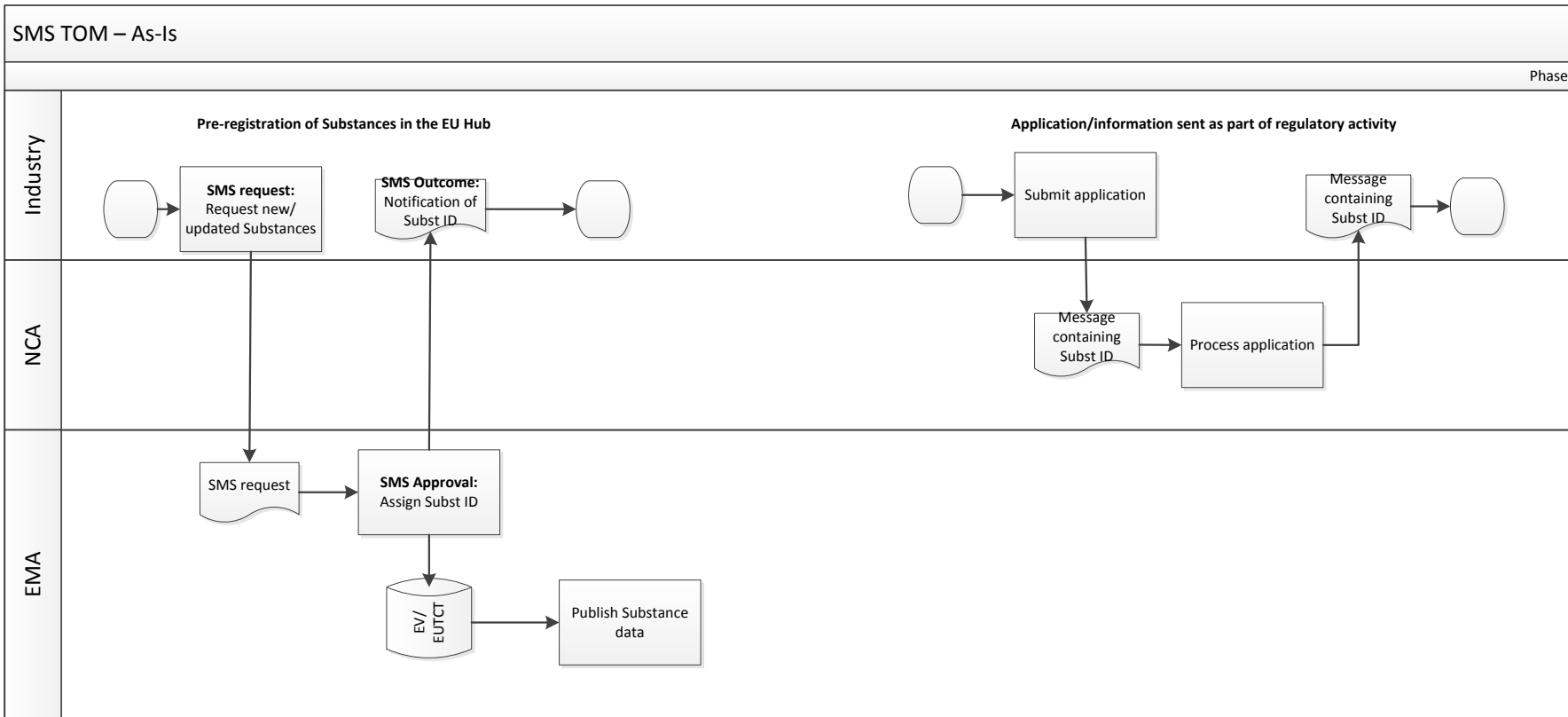
Target

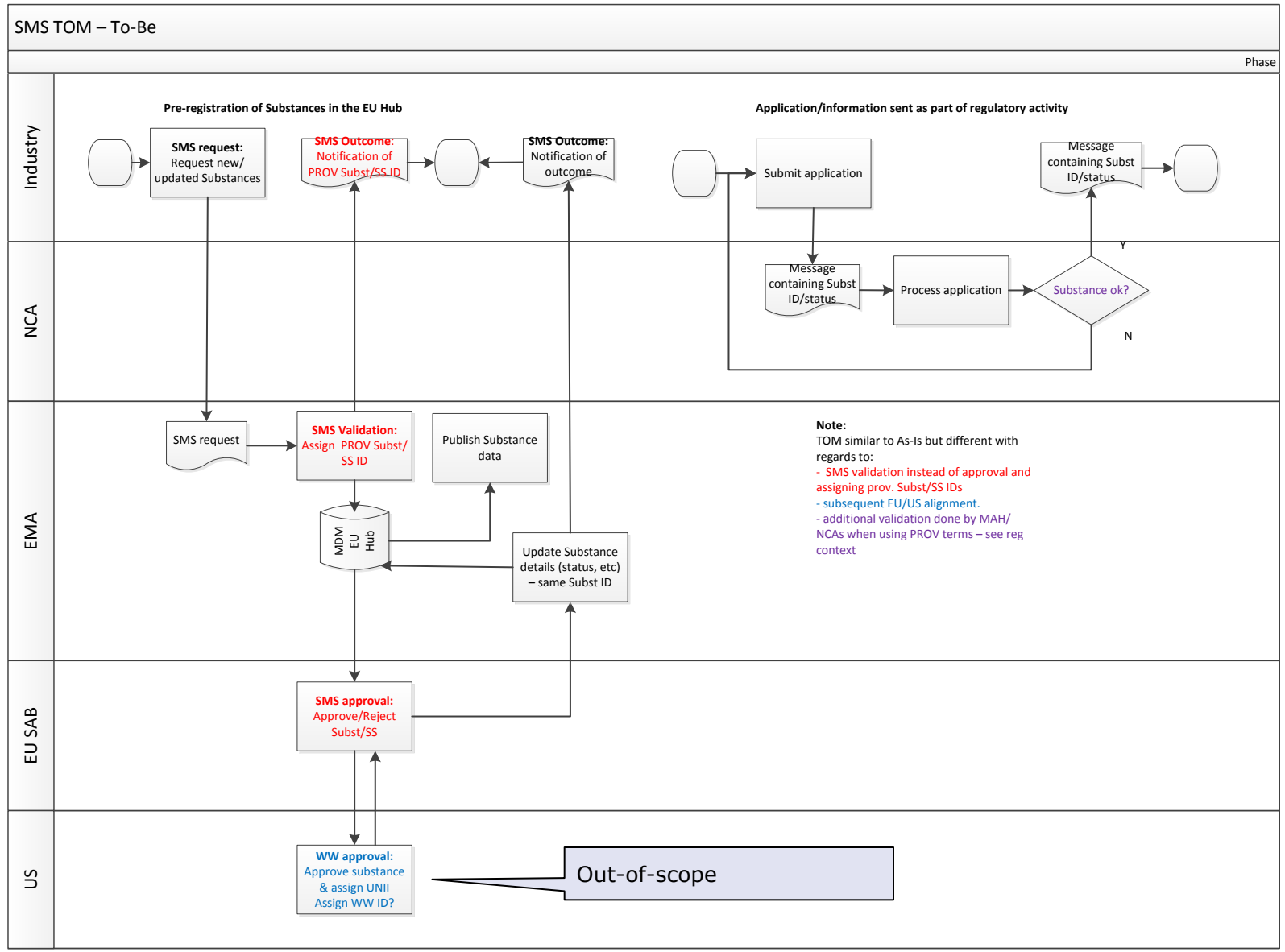
- All NCAs
- Experts within NCAs who can answer the questions
- Via NCA change liaisons
 - With IT Directors support
- Mechanism to be determined
- Timescale – April/May
 - Feeding into processes considerations May-November 2017
- Volunteers to work on survey development/analysis from S-subgroup
Potential volunteers to lead activity: Rune, Anjana, Herman, Dave.
Need other NCA representatives.



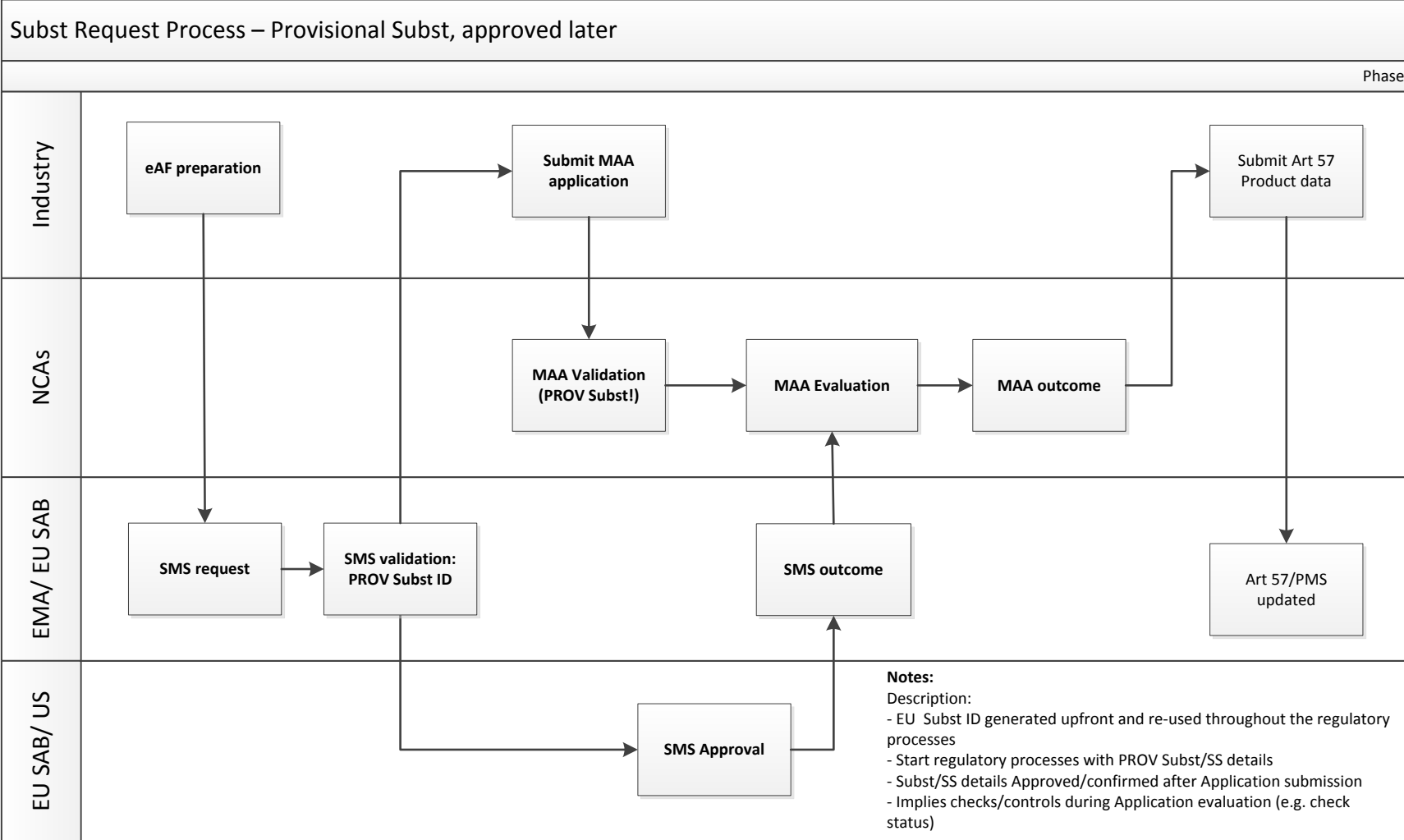
Target Operating Model

- Involving Substance Advisory Board/Substance Validation Group for 2019
 - Will need HMA nominations
- Two step approval process
 - Provisional terms – approved terms (ID remains the same)
- Not pursuing US alignment at this stage
- Need some survey results to help define TOM





SMS in the regulatory context (It1) – 1/2



Assumptions:
 - SLAs assumed to be acceptable for variations and shorter procedures
 - Valid for both H&V, with the exception that Art 57 does not apply for V

TBD:
 - Does not cover early stages of P lifecycle - CT
 - Does not cover translation aspect
 - Does not cover PMS TOM e.g. NCAs involvement as still WIP!





High-level business processes 1/2

- Request
Action: Need to identify types of request and identify who can validate/approve – define the number of experts needed.
- Validation
- Approval
 - Needing SAB/SVG
 - Not-needing SAB/SGV (administrative)
- Some initial thoughts considered
- Need more information from the NCA survey to further develop business processes

Who does what? - NEW

Similar output to be completed after survey

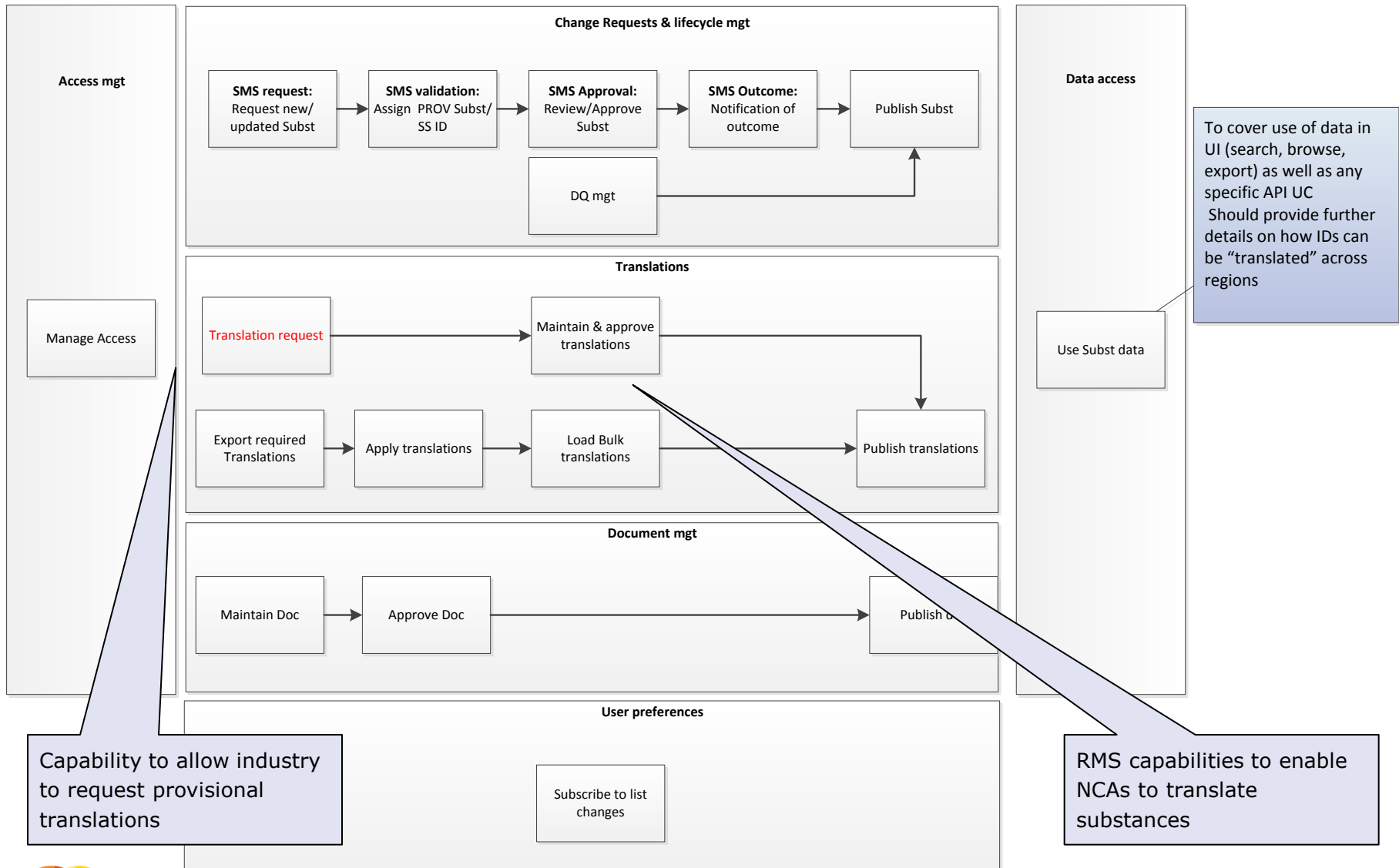
Type of request	Volume/ year	Validation	Aproval
New Subst – Active	<i>TBC</i>	EMA	SAB
New Subst – Excipient	<i>TBC</i>	EMA	SAB?
New SSG1 (of existing Subst)	<i>TBC</i>	EMA	SAB
New SSG1 (of new Subst)	<i>TBC</i>	EMA	SAB
Update names (add/update)	<i>TBC</i>	EMA	SAB?
Complete/update non-defining attributes	<i>TBC</i>	EMA	SAB?
Update defining attributes = NEW!!	<i>TBC</i>		
Update relationships	<i>TBC</i>	EMA	EMA
Merge/splits	<i>TBC</i>	EMA	SAB
New SSG2 – ID/Limited manuf	<i>TBC</i>	EMA	EMA
Update SSG2 – ID/Limited manuf	<i>TBC</i>	EMA	EMA
New SSG2 – extended manuf	<i>TBC</i>	EMA	SAB
Update SSG2 – extended manuf	<i>TBC</i>	EMA	SAB
...	<i>TBC</i>	EMA	SAB



High-level business processes 2/2

Translations

- Pilot will look at availability of translations – identification of issues?
- Utilise existing NCA translations
 - Principle of bringing in translations from as many agencies as possible during pilot (expected that all NCAs has English and own language as minimum)
- When not available use XEVMPD translation
 - Will be considered as 'semi-validated' – shouldn't overwrite translations from NCAs
- RMS capabilities (same procedure as for referentials) to enable NCAs to translate substances
- Capability to allow industry to add provisional translations
- NCAs Should translate actives and preferred names, IDMP substance name (recommended – should be looked as as 'best practice')
- NCAs Could translate excipients and synonyms (desirable – not mandatory)
 - Action: Would need some classifier to differentiate active/excipient in SMS (ISO does not split substances in actives and excipients – by working back from product you can find the information in XEVMPD)
 - Action: Explore to have a 'filter' for actives and excipients to distinguish between low and high priority
 - Action: Clarification of process for new substances (incl. identification of if it is active or excipient)





Migration

Migrate records 'as is' (even if deprecated)

Utilise existing records where appropriate

New substances/SSGs will needed

Map substances old to new – all must be there by 2019

- Actives – priority 1
- Excipients – priority 2

Support option to map Products to Substances in two stages
before PMS go-live



	SMS if EU GSRS not in time	SMS if EU GSRS & SAB in time
Description	<ul style="list-style-type: none"> • Minimum Viable Solution delivered 	<ul style="list-style-type: none"> • Solution delivered if: <ul style="list-style-type: none"> • Initial list of all AS (& excipient?) is available in EU GSRS by 2019 • SAB approved by HMA and mobilised by 2019
SMS Migration	<ul style="list-style-type: none"> • Migrate records 'as is' 	<ul style="list-style-type: none"> • Migrate records 'as is' & overwrite with EU-GSRS <ul style="list-style-type: none"> • some xEVMPD/EUTCT codes become deprecated • some xEVMPD/EUTCT codes are updated with new details • new xEVMPD/EUTCT codes will be created for Subst/SS
SMS validation	<ul style="list-style-type: none"> • NA 	<ul style="list-style-type: none"> • NA • New records created upon request to SMS
PMS composition migration	<ul style="list-style-type: none"> • Migrate records 'as is' 	<ul style="list-style-type: none"> • Migrate records 'as is' & overwrite with EU-GSRS <ul style="list-style-type: none"> • some xEVMPD/EUTCT codes become deprecated, • some xEVMPD/EUTCT codes are updated with new details • new xEVMPD/EUTCT codes are not attached to products?
PMS composition validation	<ul style="list-style-type: none"> • NA 	<ul style="list-style-type: none"> • Companies need to review the composition <ul style="list-style-type: none"> • Replace any deprecated record by a new code • Confirm subst/SS details for the product • Request new Subst/SS as needed



Product Group – Touchpoints

Principles for Substances

- Module 3 is the **preferred** source for validation for Human products/Part 2 for Veterinary products
- **Module 3** may have some difference from SmPC
- **Module 3 may have some differences from preferred ISO name**
 - How will initial validation be done?
 - Need to look at the implications and how to align over time
 - New process should avoid any misalignments for new products
 - **It is recommended to look at synonyms and hierarchy**
- Timing for mapping



Coordinating migration, validation and enforcement



Communications (1)

- IT Directors
 - When – November 2017
 - What – interim pilot report and SAB/SVG proposal
 - When - Leading up to HMA (below)
 - Final report of pilot and HMA presentation
 - Approve initial list set up
- HMA
 - When – May 2018
 - What – TOM and SAB/SVG set up
 - Business case development in collaboration with ROG



Communications (2)

- Industry communications Human & Vet
 - Industry not to be asked to fill in the data
 - No more detail than Module 3/Part 2 level of information (current guidance)
 - Any data that the pilot shows may not be routinely in Module 3/Part 2 current guidance would be considered later
 - Pilot is pivotal for deciding how to proceed
 - How far down to the path to IDMP can be achieved in Iteration 1
 - Mapping – timelines - what is feasible?
 - Mapping not in 2017, two step option being considered
- IMPs – start out with Name and ID
 - Longer term consider lifecycle development of data



- Business Cases
 - Confirm MRL business case
- Pilot
 - Pilot detailed Plan
 - Pilot process/working instructions
 - Define pilot consumable format
- Survey of NCAs
 - Draft survey questions
 - Review survey answers
 - Propose profiles, number, request type vs EMA/SAB, process
- Product-Subgroup Touchpoint
 - Discuss Substance and Product Migration
 - Set up dedicated validation discussion