PMS Data Quality
PMS Subgroup meeting March 20-21 2018

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LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Issues regarding good quality PMS data

- Data standardisation
- Data pilot
- Target Operating Model (TOM) for new products
- TOM for variations
- Dealing with the legacy Art 57 data

Data Standardisation: The Problems

- No agreement on expression of strength due to national needs
  - Generics – according to new standards, or same as original product?
- Details in section 1 vs section 2 of SmPC
- Issue has been discussed extensively in CMDh (ca 2012-2013)

Member state	List of proposed product names at day 210	List of reference products according to the AF
NL	Terlipressine acetaat SUN 1 mg oplossing voor injectie (note: again under discussion in NL)	Glypressin, oplossing voor injectie 0,1 mg/ml
DE	Terlipressin SUN 0,1 mg/ml Injektionslösung	Glycylpressin® 0,1mg/ml Injektionslösung
DK	Terlipressinacetat SUN 1 mg injektionsvæske, opløsning	Glypressin, injektionsvæske, opløsning
ES	Terlipresina SUN 0,12 mg/ml solución inyectable EFG	Glypressin 0,12 mg/ml solución inyectable
FI	Terlipressiini SUN 0,1 mg/ml injektioneste, liuos	Glypressin 0,1 mg/ml injektioneste, liuos
FR	Terlipressin SUN 0,12 mg/ml, solution injectable	Glypressine 1 mg/8,5 ml, solution injectable
IT	Terlipressina SUN 0,1 mg/ml soluzione iniettabile	Glipressina 1 mg/5 ml polvere e solvente per soluzione iniettabile per uso endovenoso
NO	Terlipressin SUN 1 mg injeksjonsvæske, oppløsning	Glypressin 1 mg injeksjonsvæske, oppløssning
SE	Terlipressin SUN 1 mg injektionsvätska, lösning	Glypressin 1 mg injektionsvätska, lösning
UK	Terlipressin acetate SUN 0.12 mg/ml solution for injection	Glypressin 0.12 mg/ml solution for injection

Data Standardisation: The Problems

- Problem 1: Different expectations or traditions from stakeholders how composition is presented (e.g. per concentration or e.g. per presentation)
- Problem 2: Composition elements are used for automated calculation of the PhPID. If not standardised different IDs would be generated for the same composition
- Problem 3: How do we compare products cross-border without standardisation?

Example

- Human readable:
  - Klexane 8000 IU (80 mg)/0.8 mL solution for injection, prefilled syringe
  - Klexane 8000 IU solution for injection, prefilled syringe
  - Klexane 100 mg/mL solution for injection, prefilled syringe

Manufactured item – structured information

Full name	Klexane 8000 IU (80 mg)/0.8 mL solution for injection, prefilled syringe
Manufactured dose form	solution for injection
Unit of Presentation	syringe
Ingredient role	ACTIB
Ingredient	enoxaparin sodium
Strength (pres)	8000 Anti Xa IU/0.8 mL
Strength (conc)	10 000 Anti Xa IU/1 mL
Reference ingredient	enoxaparin sodium
Reference strength (pres)	80 mg/0.8 mL
Reference strength (conc)	100 mg/1 mL

Pharmaceutical product – structured information

Full name	Klexane 8000 IU (80 mg)/0.8 mL solution for injection, prefilled syringe
Administrable dose form	solution for injection
Unit of Presentation	Syringe?
Route of administration	Subcutaneous use
Ingredient role	ACTIB
Ingredient	enoxaparin sodium
Strength (pres)	8000 Anti Xa IU/0.8 mL
Strength (conc)	10 000 Anti Xa IU/1 mL
Reference ingredient	enoxaparin sodium
Reference strength (pres)	80 mg/0.8 mL
Reference strength (conc)	100 mg/1 mL

PhPIDs for liquid solutions

- From 20451:2017 (IG for 11616:2017 – Pharmaceutical product), section 6.5
- “For liquid preparations, strength shall be represented by **both** the **total volume of the container** as authorised by a Medicines Regulatory Authority using strength (presentation) and **strength concentration per unit volume** (e.g. 1 ml) using strength (concentration).”
- Strength per total volume (presentation): standard PhPID
- Strength per unit volume (concentration): abstract PhPID and shall be referred to as a pharmaceutical product concept code (**PPCC**)

Alternatives for PhPID

- Alternative PhPIDs
  - PhPID 123 = 8 000 IU/0,8ml
  - **PPCC ABC** = 10 000 IU/ml
  - PhPID 789 = 80 mg/0,8 ml
  - **PPCC XYZ** = 100 mg/ml
- Should have the same PhPID and PPCC!
  - PhPID 123 = 8 000 IU/0,8ml (80 mg/0,8 ml) - presentation
  - **PPCC ABC** = 10 000 IU/ml (100 mg/ml) -- concentration

- Norwegian product in PMS
  - Strength 8000 IU/0,8 ml
- Swedish product in PMS
  - Strength 80 mg/0,8 ml
- How to ensure that identical products get the same set of PhPIDs?

Data Standardisation

- QRD issued recommendations 2009 for the expression of strength in the name of centrally authorised human medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500056428.pdf)
- These could be used as a basis for a standardised representation for all products
  - Spain is already doing this for generic substitution use

Solution – save some of the key attributes twice

- Composition saved twice:
  - National use
    - 80 mg/0.8 ml
  - EU standardised
    - 8 000 IU/0.8 ml

This would ALWAYS be used to calculate the PhPID and the PPCC

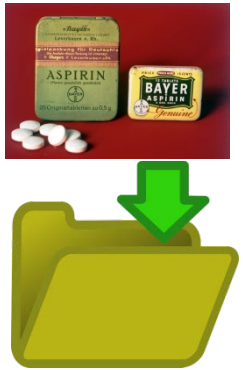
- The EU IG will have to define the rules in collaboration with CMDh, CMDv, QRD, SmPC Advisor Group, etc.

Data standardisation

- Probably need to define a ”standard EU product” for MRP products
- Should this be saved as a separate entity somewhere?
- NCAs and PMS: save some information twice
  - in EU standardised format
  - in national expression
- Minor adjustment to the LDM
  - A little more adjustment to a GUI
  - Need to store PhPIDs AND PPCCs (PhPID not in PNS Iteration 1)

PMS Data Pilot

- IDMP very complex – understanding is still poor
- ISO starting an IDMP Adoption Expert Group
  - Probably not deliver in our timeframe
- Need to put data into the model to properly understand what data goes where
  - ISO IGs not detailed enough
- EMA asked us to do the data pilot
- Industry did a data pilot in late 2017 – a number of issues were raised



NCA group will organise a data pilot

- 20(?) products from simple to very complex, including
  - Multiple manufactured items (e.g. birth control pills)
  - Solid and Liquid forms, patches
  - Vaccines, combined Advanced Therapies
  - Different procedures (CAP, DCP, NAP)
  - Human and veterinary products
- NO and SE willing to lead
  - Other NCAs willing to help!
- Timeframe – deliver summer (?)

Data Pilot Organisation (proposal)

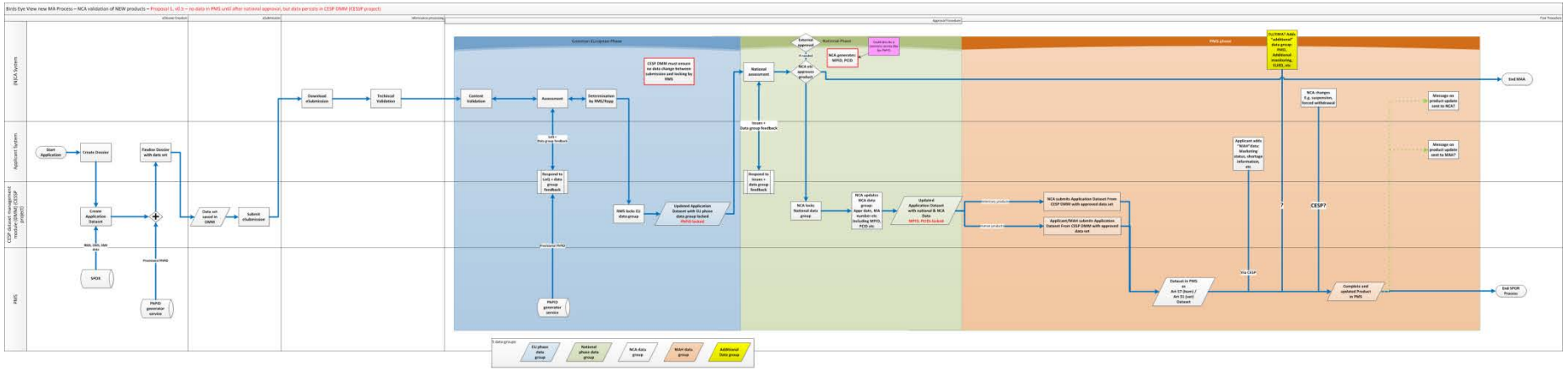
- Real products from different countries
- All data from public sources
- Openness and transparency important
- **SMALL group with representatives from NCAs, EMA, Industry, ISO authors**
  - **SE, NO, ES, EE, DE, AT, FR (vet)**
  - **EMA to be confirmed**
  - **ISO by invitation**
  - **Industry – how to get involved?**
- Share documents on a collaboration site
- Telephone meetings
- One or two face to face meetings
- Issues – funding for consultants and face to face meetings

Data pilot deliverables

- Keep it simple!
- Written report with identified problems and suggestions for solutions
- Excel sheet with example products
- Presentation of results from the pilot at EUNDB and Task force meetings
- Input to EU IG – Annex?

Getting the data into PMS

- Problem – how to make sure the data the companies put into PMS is the same as what NCAs approve?
- Answer – check the data as part of the approval process: Target Operating Model (TOM)



Target Operating Model (TOM)

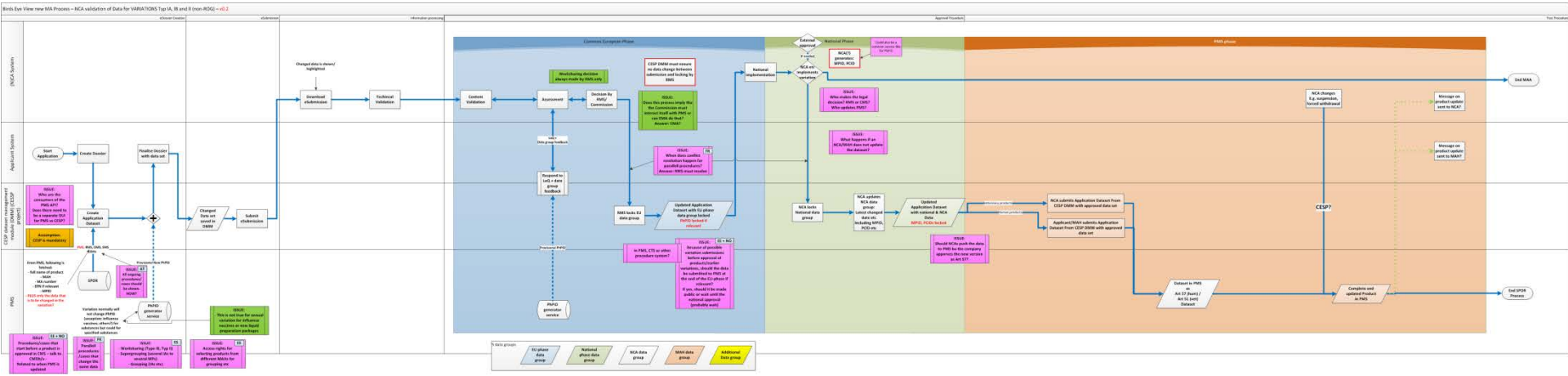
- Objective – minimum impact on NCAs and industry
- No demand for NCAs to have an IDMP database
- All NCAs will have to adjust their processes slightly to include data quality check as part of approval process
- Divide the data into groups that would be checked in different phases
  - 5 groups identified
- BUT – makes significant demands on CESP
  - CESP to control the data validation process
  - Will need to be financed
- Need to get buy-in from CMDh, CMDv, HMA, Industry etc. - started
- Two TOMs – New Applications & Variations (non-ROG)

TOM New products

- Presented to PMS subgroup / EUNDB October 2017
- No significant changes since then
- Human and veterinary processes virtually the same

TOM Variations (excluding ROG)

- Very similar to TOM for New Products
- Basic idea is that eAF/CESP takes product information from PMS and the applicant changes what is necessary for the submission

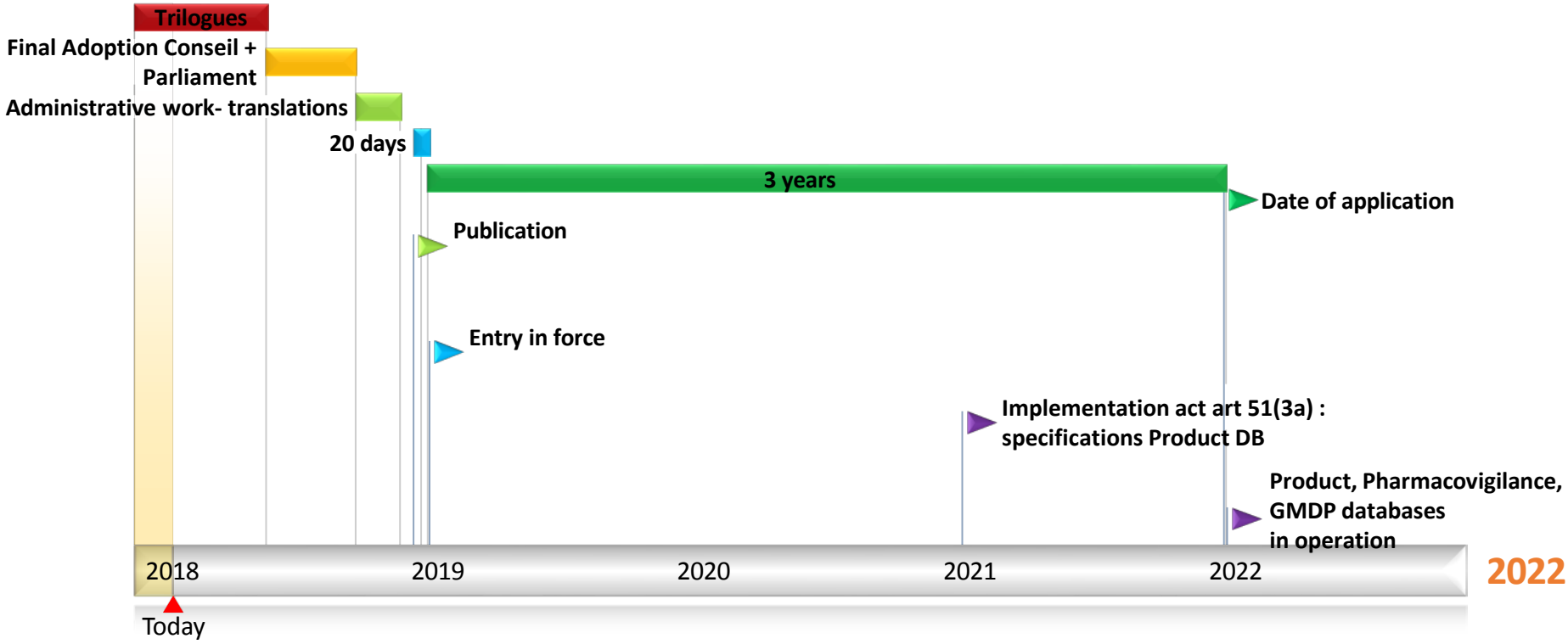


Issues with TOM variations

- Procedures/cases that start before the product is approved
- Management of parallel cases – conflict resolution
- Worksharing/Supergrouping
  - Products belong to different MAHs within the same concern
  - How to grant access rights to use products from other MAHs in an application
- Decision made by the EU Commission – should they interact with PMS directly?
- What happens if MAHs/NCAs do not update PMS with ”their” data (NCA group)?
- RMS makes decisions for CMSs – who does updates?

Many issues have been assigned to different NCAs

Veterinary products – new vet regulation

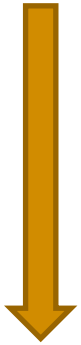


PMS – veterinary products

- Implementing acts expected to say that NCAs will be responsible for filling PMS – Art 51 database
    - Fewer data providers (ca 30 instead of 1000s)
    - Easier to maintain data consistency
    - Simpler process
- Same IDMP database as for human products with vet extensions
    - Fewer mandatory attributes
    - Target species
    - Withdrawal period
    - Maximum Residue Limit (MRL)
    - Minor Use Minor Species (vet equivalent of orphan)

How will we use Art 57 data?

- Different use cases for Art 57 data
  - #1 Pharmacovigilance – mandated by law
  - Regulatory efficiency
  - Cross-border prescriptions



Increased need for good data quality & data standardisation

Validation of Art 57 data today

- 500 000 products from almost 5 000 data providers
- EMA checks via comparison with SmPC
  - SmPC in national language
  - Incomplete / simplified regarding active substances
  - EMA does not validate after every variation
- NCAs have the gold standard

Validation of Art 57 legacy data after migration to PMS – challenges

- NCAs will have to validate all the non-central products authorised in their country
- EMA must validate centrally approved products
- Different NCAs have different capacities and different amounts of data
  - Ad-hoc NCA group has done an informal survey about which data NCAs have
  - No NCA has all the information that is in Art 57
  - Few have structured clinical data, e.g. MedDRA coding of product indications
- Several agencies have gotten dumps of data for products approved in their country
- EMA has measured completeness, usually 90+%

Strategy

- Cannot validate everything
- Break up the data into blocks
  - Name block
  - Composition block
  - Package block
  - Etc
- Find suitable ”blocks” and do validation on block level
  - DE is looking at this
- Very difficult to do automatic validation of existing data
- Different NCAs will be able to validate different combinations of blocks so that we know what we have validated and can have some sort of guarantee for quality

Quality check – phase 1
NCA Validation: On Boarding

- Do a quality test with a very limited amount of data to start with
- Marketing authorisation number (MA) is the primary key to match our data with EMAs data
- Phase 1: Clean the MA numbers in the EMA data in preparation for larger data validation
  - Simple Excel-based comparison
  - Try and get all the (human) NCAs on board
  - Establish process
  - Give NCAs time to better understand what they have to do
    - RMS & OMS mapping, etc.
  - How will we do data correction?
    - TOM should take care of this problem going forward