Breakout session 3 - Process Optimisation

Introductory presentations

- Helga Gardarsdottir, Utrecht University
- Solange Corriol Rohou, Astra Zeneca/EFPIA

Chair: Inka Heikkinen, MSD/EuropaBio

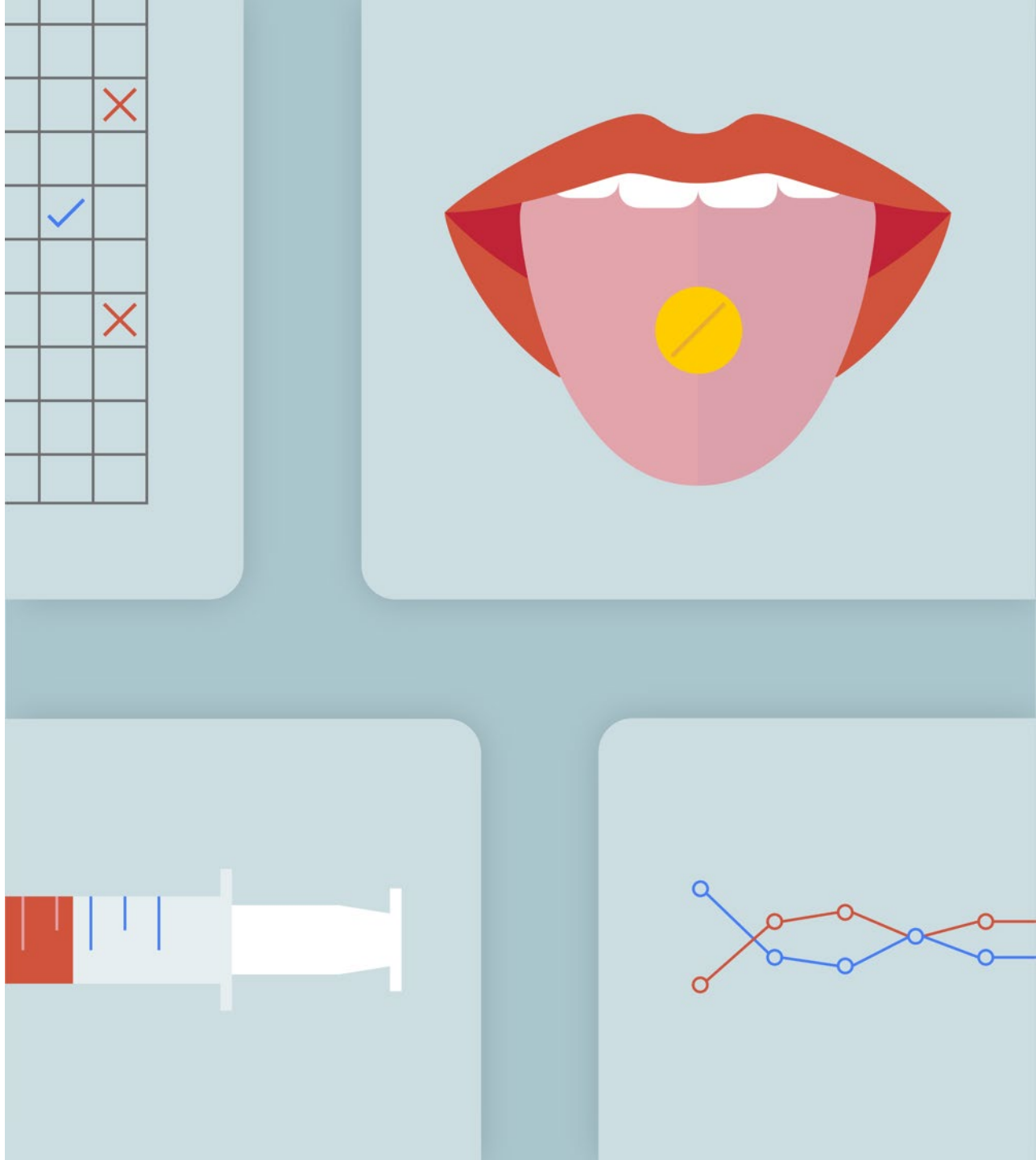
Rapporteur: Andrej Segec, EMA

Learnings Initiative for Optimal Use of Big Data for Regulatory Purpose

30 November 2021
Virtual meeting, European Medicines Agency

Use of RWD for regulatory decision making

Helga Gardarsdottir, PharmD, PhD, FISPE
Associate professor



Utrecht University

Pharmacoepidemiology
and Clinical Pharmacology

Review of studies evaluating the effectiveness of risk minimization measures assessed by PRAC

Helga Gardarsdottir, Jarno Hoekman, Jet Scheffers (Utrecht University)
Simone Bergner, Wiebke Seemann (BfArM, Germany)
Valerie Straßmann, Thomas Goedecke (EMA)

This study is a deliverable of the PRAC IG Impact work plan to support the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities (Rev 1) (EMA/165407/2017).

The aim of this review of industry-sponsored PASS evaluating the effectiveness of risk minimisation measures is to improve regulatory decision-making by providing a better understanding of factors associated with the implementation and effectiveness of risk minimisation measures.

Main objectives

- identify all industry-sponsored PASS conducted in EU that evaluated the effectiveness of Risk-minimization measures (RMMs) and to describe their designs and analytical methods and chosen measures for effectiveness evaluation,
- determine the types of RMMs, the proportion of effective RMMs and how effectiveness was defined,
- compare characteristics of effective RMMs with non-effective RMMs,
- identify factors associated with PASS where PRAC could draw a conclusion on RMM effectiveness.

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- **identify factors associated with PASS where PRAC could draw a conclusion on RMM effectiveness.**

Approach

Step 1: PRAC meeting agendas were screened for the identification of industry-sponsored PASS evaluating the effectiveness of RMM

Step 2: Final study reports of PASS (EU RMP categories 1, 2 and 3) included if:
- objective of the PASS is the evaluation of the effectiveness of routine and/or additional RMM
- assessed by PRAC between 1st January 2016 and 31st December 2019

Step 3: Development of a standardized extraction form used to extract information from the final PASS study reports

Step 4: Information on included studies extracted from DREAM

Step 5: Random validation by EMA staff

Results – PASS characteristics

In total, **72 PASS** were included for 66 products

		N	%
EU PAS registration		57	79.2
PASS category	Imposed (category 1)	15	20.8
	Specific obligation (category 2)	2	2.8
	Required (category 3)	55	76.4
Joint PASS		13	18.1
PASS Objective*	Measuring HCP awareness/behavior/knowledge	42	58.3
	Measuring patient risk awareness/behavior/knowledge	16	22.2
	Measuring patterns of use in clinical practice	25	34.7
	Measuring health outcomes pertaining to implementation	11	15.3
	Measuring health system utilization pertaining to implementation	10	13.9
	Other measures	3	4.2

* Categories are not mutually exclusive, total >100%

Results – Study characteristics

		N	%
Included countries	Single country studies	6	8.3
	Included at least one country from each European region**	17	23.6
Time period	post-intervention	60	83.3
Outcome*	(Change in) awareness/knowledge, self-reported behavior, attitudes	41	56.9
	(Change in) prescribing/dispensing pattern	30	41.7
	Health outcome (mortality, morbidity etc)	30	41.7
	Change in ADR reporting	3	4.2
	Other	13	18.1
PASS performance	RMM effectiveness criterion defined a priori	18	25.0

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** Based on the United Nations Geoscheme

Of all the 72 PASS, conclusions on RMM effectiveness could be drawn for **56.9%** (n=41) of the PASS while **43.1%** (n=31) were inconclusive

Results – Characteristics, stratified by conclusive/inconclusive

		Conclusive RMM assessment (n=41), N(%)	Inconclusive RMM assessment (n=31), N(%)
REGULATORY BACKGROUND			
PASS Objective*	Measuring HCP awareness/behavior/knowledge	24 (58.5)	18 (58.1)
	Measuring patient risk awareness/behavior/knowledge	11 (26.8)	5 (16.1)
	Measuring patterns of use in clinical practice	9 (22.0)	16 (51.6)
	Measuring health outcomes pertaining to implementation	6 (14.6)	5 (16.1)
	Measuring health system utilization pertaining to implementation	4 (9.8)	6 (19.4)
	Other measures	3 (7.3)	0 (0)
STUDY CHARACTERISTICS			
Sources for data collection*			
	Primary data collection	**33 (80.4%)**	**19 (61.3%)**
	- Survey	*25 (75.8%)*	*17 (89.5%*
	- Interview	*3 (9.1%)*	*0 (0.0%)*
	- Prospective observational study	*6 (18.2%)*	*2 (10.5%)*
	- Registry	*1 (3.0%)*	*0 (0.0%)*
	Secondary data collection	**11 (19.6%)**	**15 (38.7%)**
	- Patient medical records (including prescribing data)	*8 (72.7%)*	*12 (80.0%)*
	- Administrative claims records/pharmacy records	*3 (27.3%)*	*10 (66.7%)*
	- Healthcare records linkage	*3 (27.3%)*	*4 (26.7%)*
	- Registry/registry-based	*2 (18.2%)*	*1 (6.7%)*

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STUDY CHARACTERISTICS (cont')			
Study design*	Cohort study	14 (34.1%)	9 (29.0%)
	Case control	1 (2.4%)	0 (0.0%)
	Cross-sectional	28 (68.3%)	24 (77.4%)
	Time series	1 (2.4%)	1 (3.2%)
Outcome*	(Change in) awareness/knowledge, self-reported behavior, attitudes	24 (58.5%)	17 (54.8%)
	(Change in) prescribing/dispensing pattern	13 (31.7%)	14 (45.2%)
	Health outcome (mortality, morbidity etc)	11 (26.8%)	14 (45.2%)
	Change in ADR reporting	8 (19.5%)	3 (9.7%)
PASS Performance	RMM effectiveness criteria defined a priori	12 (29.3%)	6 (19.4%)
Limitations	Unable to enroll sufficient number of subjects	18 (43.9)	14 (45.2)
	Suboptimal selection of study subjects	5 (12.2)	7 (22.6)
	Limited use of medicinal product in country	1 (2.4)	2 (6.5)
	Imbalanced country distribution of included subjects	4 (9.8)	1 (3.2)

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Conclusion

Almost half of PASS are unable to provide conclusive results allowing for assessment of if an RMM is effective or not.

How to move forward:

- **Plan early** how RMM effectiveness can be measured
- Information presented by companies in study protocols
  - Feasibility assessment, mixed-methods approach
- Study protocol elements where PRAC could pay special attention

Most importantly → keep an **open dialogue** between the different stakeholders

Next steps → Look further into the methodological limitations specifically discussed in the assessment report:

- For inconclusive PASS
- For (in)effective RMM

efpia

European Federation of Pharmaceutical Industries and Associations

Learnings Initiative for Optimal Use of Big Data for Regulatory Purpose

Breakout session 3: Process Optimisation






EMA Virtual Meeting

30 Nov. 2021

Solange Corriol-Rohou, M.D.

Current opportunities to discuss RWD/RWE with regulators and/or HTA Bodies

EMA Innovation Task Force

Scientific Advice with EMA SAWP, incl. Qualification Advice/Opinion

(Multi-) national Scientific Advice

Parallel Scientific Advice with EMA + FDA

Parallel consultation with NA +HTA body

Joint Scientific Consultation with EMA + HTABs

Joint HTA PLEG activities

Obviously some options are more appropriate than others to discuss, e.g., the use of RWE in the pre-licensing

Ongoing initiatives

- The growth of new types of data source and complex analytical methodology, including artificial intelligence or digital health technologies, has highlighted the need to ensure that the regulatory processes reflect this evolution – EMA RSS to 2025 and EMRN Strategy to 2025

- Multi-stakeholders' activities: the GetReal Institute, IMI projects (e.g., Big Data for Better Outcomes; EHDEN; H2O) are useful to share learnings and best practices

- There is limited guidelines ➔ a lack of predictability for applications containing RWE
    - The EMA Registry-based studies guideline was recently finalised
    - Qualification of the Cystic Fibrosis Patient Registry in 2018
    - Qualification of Cellular therapy module of the EU Society for Blood & Marrow Transplantation Registry in 2019

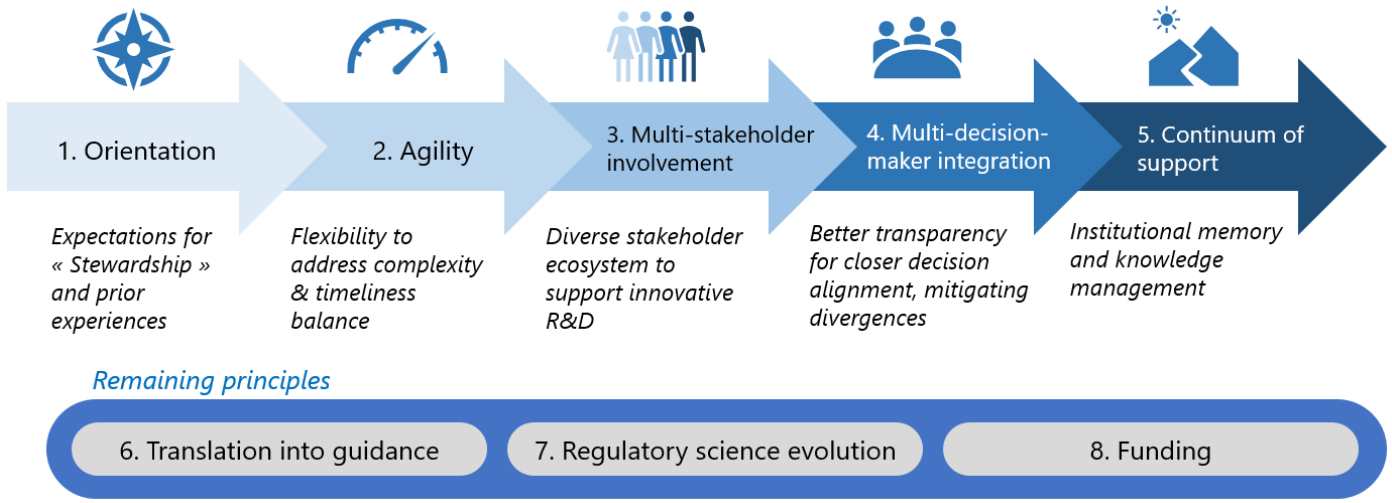
- Ongoing discussion to revamp the SA process – 7th Industry Stakeholder platform on R&D support (Nov. 23)

- Relaunch of the Joint Scientific Consultation involving EMA and HTA bodies

- Creation by EMA of a Methodology Working Party with dedicated expertise in RWE

What the Focus group on the Practical Application of Integrated Development Support identified to revamp the SA process is of interest to the today discussion

Case study collection on the application of **actionable** principles in the context of the PRIME scheme and COVID-19*
(Deadline 20 September 2021)



Output:

- **14 cases received (EFPIA (x10), EuropaBio (x2), EUCOPE (x1) and VE (x1))**
- **6 PRIME, 4 COVID & 4 Non-COVID/PRIME cases**
- Therapeutic areas incl. **COVID-19 infections, Oncology, Haematology & Neurology**
- Most comments received regarding Design Principles "**Orientation/Stewardship**,", "**Agility**" and "**Multi-decision-maker integration**"

** Case studies may relate to e.g., EMNR (EMA and MS) and beyond COVID/ PRIME*

In summary,

- With experience gained, processes can always benefit from optimisation to cope with the evolution in science

- The qualification procedure is an increasingly important regulatory path for tools/methods and registries supporting the development and evaluation of innovative treatments
  - At the 7th Industry Stakeholder Platform on R&D Support, it was mentioned that EMA is planning to set up a focus group and organise a workshop to discuss how to optimise the Qualification procedure framework

- There are already good examples of international collaboration among regulators (e.g., cluster meetings, ICMRA) on various topics including RWD/RWE

- Let's use opportunities for sustainable and transparent learnings initiatives
  - Collaboration should be expanded to include other stakeholders such as Patients or HCPs

- Need for joint discussions to support the evolution of a well-functioning system of scientific dialogue benefits Pharmaceutical Strategy objectives of accelerating development and regulatory approval times

Process Optimisation: some questions to support the discussion

- What is the experience so far?
- At what stage should the use of RWD be discussed with regulators? And with whom?
- Should there be different discussion for technical question and regulatory questions?
- The CHMP guideline on registry-based studies recommends early discussion of proposals for use of registries in regulatory submissions. Should such recommendation be applied to other RWD sources? Should differences be made between data sources?
- How could other stakeholders than pharmaceutical companies contribute to process optimisation and what could be the vehicles through which such input could be provided?
- What else do stakeholders expect from process optimisation, especially in the field of use of RWE?