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BELpREG

Experiences and Perspectives of the Pharmaceutical Industry on the Safety Monitoring of Medication Use during Pregnancy

An international and qualitative exploration

Laure Sillis - PharmD, PhD Candidate

Veerle Foulon - PharmD, PhD

Jan Y Verbakel - MD, PhD

Michael Ceulemans - PharmD, PhD

27/06/2022

OTIS / MotherToBaby

34th Annual Conference

Disclosure

No conflicts of interest to disclose.

The research activities of Laure Sillis, and the overall BELpREG research project, are supported by an internal KU Leuven research grant (C3/20//095).

Introduction

Regulators hold Marketing Authorization Holders (MAHs) responsible for:

Monitoring of medication safety in pregnancy
Adaptation of the **label** accordingly

Exclusion of pregnant persons from clinical trials[1,2] → MAHs rely on **observational data**:

- Post-approval surveillance through **spontaneous reporting**
- Product-specific pregnancy **registries** (sometimes imposed by regulators)

Paucity of data in the labels/product information on the safety of medicines during pregnancy:

- 98% of 172 medicines approved by the FDA between 2000 and 2010 lacked information on the teratogenic risk[3]
- Also for most commonly medicines used during pregnancy[4]
- 27 years to assign risk category: undetermined → more defined[3]

How do MAHs experience their current safety monitoring experiences?
How do they reflect upon their responsibilities?

Aim of this study: To gain insight in the **current initiatives**, **needs**, **obstacles**, **expectations**, and **future preferences** of MAHs regarding **medication safety and pharmacovigilance in pregnancy**

[1]*Shields K et al. 2013* , [2]*Scaffidi J et al. 2016*, [3]*Adam MP et al. 2011*, [4]*Thorpe PG et al. 2013*

Clinical Pharmacology and Pharmacotherapy
Department of Pharmaceutical and Pharmacological Sciences
KU LEUVEN

Full text – Open access

International Journal of
Environmental Research and Public Health

MDPI

Article

Experiences and Perspectives of Marketing Authorisation Holders towards Medication Safety Monitoring during Pregnancy: A Pan-European Qualitative Analysis

Laure Sillis [1], Veerle Foulon [1], Jan Y. Verbakel [2,3] and Michael Ceulemans [1,4,*]

Scan me!

Methods

Online **focus group discussions** (June – July 2021)

Study population:

Employees of **pharmaceutical companies** (employed at Belgian or global departments)
Employees of the **umbrella organisation** of pharmaceutical companies in Belgium

- ✓ Professional activities closely related to medication safety and pharmacovigilance in pregnancy
- ✓ Speaking sufficient Dutch and/or English

- Purposive sample technique
- Employees of one organization took part in the same interview
- GDPR and ethical approval obtained *(G-2021-3245 on 23/04/2021);* informed consents were obtained

- Data analysis: inductive thematic approach (framework method[1]), Nvivo® software

[1]*Gale et al. 2013*

Results

- ✓ 9 different organisations included
  → 8 MAHs and 1 umbrella organisation
- ✓ 38 representatives participated

Demographics of Participants (N = 37) [1]	
Gender	
Female	26 (70.3%)
Male	11 (29.7%)
Highest educational level	
Bachelor	2 (5.4%)
Master	19 (51.4%)
PhD	16 (43.2%)
Department of the current function	
Pharmacovigilance	19 (51.4%)
Medical affairs	6 (16.2%)
Epidemiology	4 (10.8%)
Regulatory affairs	2 (5.4%)
Other	6 (16.2%)
Location current function	
Belgium	15 (40.5%)
USA	11 (29.7%)
Other European countries	11 (29.7%)
Information on the Organisations (N = 9)	
Departments in different countries	7 (77.8%)
Location headquarters	
USA	3 (33.3%)
Belgium	2 (22.2%)
Switzerland	2 (22.2%)
UK	1 (11.1%)
Japan	1 (11.1%)
Participation in IMI ConcePTION [2]	5 (55.6%)

Results are shown as absolute numbers (%). [1] Information on the demographics of one participant is missing; [2] IMI ConcePTION is a public–private partnership launched in April 2019, aiming to build an ecosystem for medicine safety in pregnancy and breastfeeding

Results

Difficulties with the **collection of exposure and outcome data**

> Both routine pharmacovigilance practice and company-based registries

*“There is a big black hole of missing information. It is not because exposures aren’t happening, it is because we are **not able to collect them efficiently**.” [IT06 – PP04]*

*“For 2020, we got overall approximately **90 reports** of pregnancy exposure worldwide. Nine zero. This out of an estimated exposure of roughly **half a million patients** worldwide.” [IT07-PP03]*

Collection of data
- Underreporting and slow recruitment
- Incomplete reports: lack of confounders and clinical information
- Loss to follow-up

Processing of data
- No denominator
- No comparator (diseased non-exposed)
- Insufficient number: lack of power
- No corrections for confounders

Communication of data: the label
- No directive evidence in the label: only insufficient or poor quality data available
- Uncertainties about what can be included
- Ambiguities in regulatory guidance and slow procedures for SmPC updates

Results

Possible contributing factors to poor data collection via spontaneous reports	Identified issues with data collection by marketing authorisation holders on medication use during pregnancy	Consequences related to the issues with data collection
▪ Mistrust by patients and healthcare professionals (HCP) ▪ No return of information to the reporter ▪ Data collection not structured in clinical care setting ▪ Regulatory aspects	**Collection of data** ▪ Underreporting and slow recruitment ▪ Incomplete reports: lack of confounders and clinical information ▪ Loss to follow-up	▪ Long time period before sufficient data are collected ▪ Imbalance between invested resources and created output

"I don't mind having to do all sorts of work and invest time in a pregnancy registry. My issue with that, ***still after all these resources and time****, lot of interim assessments,* ***you still don't have a handle*** *on how safe it this." [IT09 – PP03]*

Results

Challenges associated with **processing of observational data** to acquire evidence

*"From the time that the information is available, I can tell you, it is a **nightmare**. We cannot really get a hold of the data, we conduct studies, but most of the times they have a lot of **shortcomings**." [IT02 -PP04]*

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Results

The **label** (SmPC - section 4.6)

Often *vague* statements → unfavorable consequences in practice

- Patients and HCPs unable to appropriately weigh risks and benefits
- Deprive patients from medication ↔ Inability to precaution timely

How to improve medication safety monitoring in pregnancy in the future?

*"I think **partnership** between academia, industry and regulators is quite key. Ultimately, we all have sort of the **same interest** in mind, especially around a project like pregnancy. **We can't do it ourselves** for sure." [IT08-PP03]*

Collection of data
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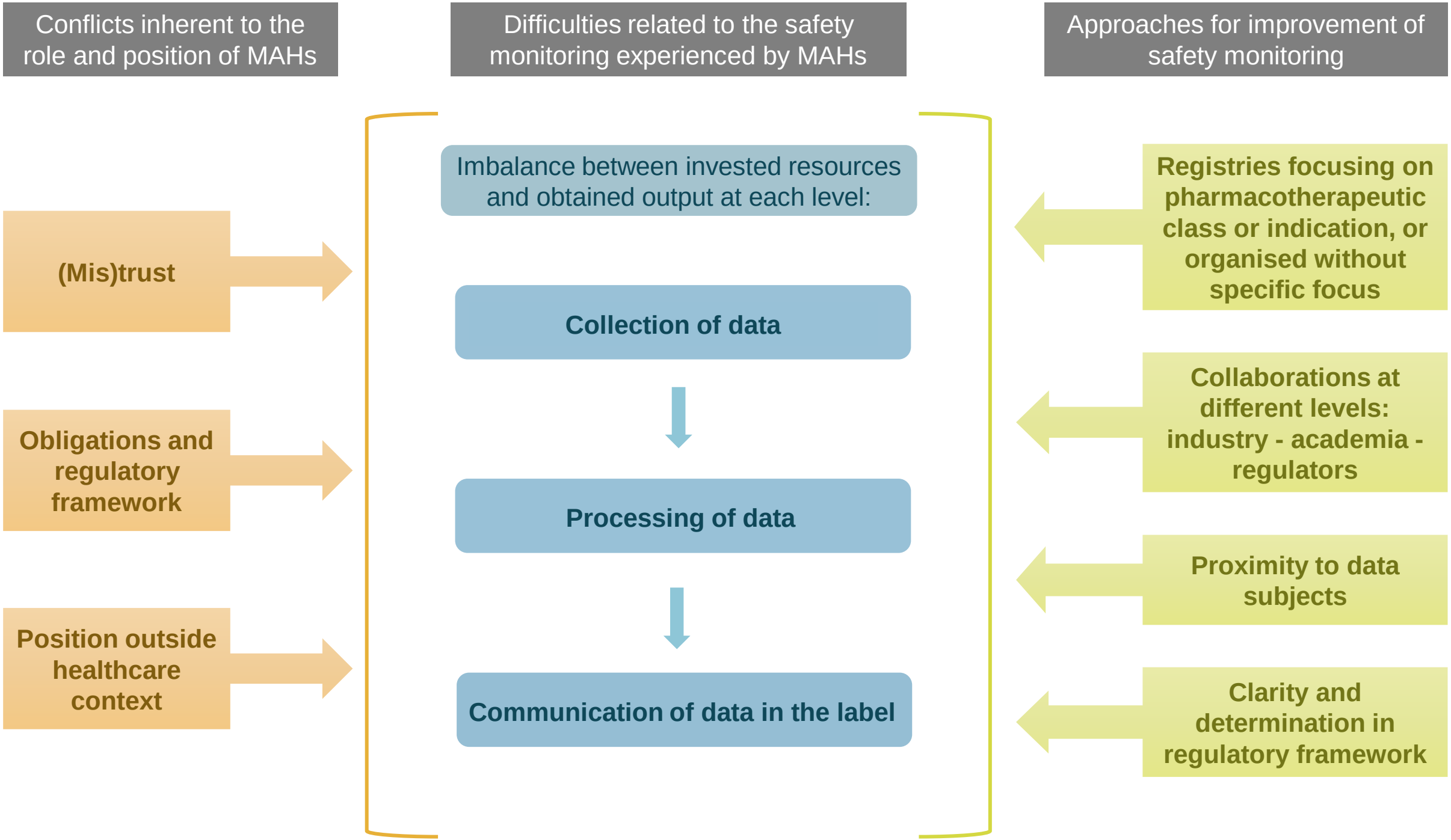
Conflicts inherent to the role and position of MAHs
Difficulties related to the safety monitoring experienced by MAHs
Approaches for improvement of safety monitoring
(Mis)trust
Obligations and regulatory framework
Position outside healthcare context
Imbalance between invested resources and obtained output at each level:
Collection of data
Processing of data
Communication of data in the label
Registries focusing on pharmacotherapeutic class or indication, or organised without specific focus
Collaborations at different levels: industry - academia - regulators
Proximity to data subjects
Clarity and determination in regulatory framework

Conclusions

To enhance the safe use of medication during pregnancy, it is required to have:

- ✓ A large number of registrations/cases: both exposed and non-exposed
- ✓ Complete prospective records, including data on sufficient, potentially relevant confounding factors

MAHs jointly acknowledged **experiencing multiple obstacles regarding data collection, processing, and communication of evidence in the label**

- Several '**conflicts**' explaining these obstacles were identified
- **Suggestions for future improvement** were proposed

Need for **effective, collaborative strategies** to **prospectively** collect (real-world) data to generate new evidence on medication safety in pregnancy

Lessons learned for the BELpREG project

BELpREG

= an academia-initiated data registration system in Belgium collecting data on maternal medication use and mother-infant outcomes by using online questionnaires during pregnancy and after delivery

Presented in 2021:

Start pilot study BELpREG project this summer → **See our poster in the online gallery!**

Lessons learned for the BELpREG project

What we have learned from the experiences of MAHs:	How we will implement this in the BELpREG project / advantages of BELpREG:
Limitations of product-specific registries and/or routine pharmacovigilance	• Both exposed and non-exposed pregnancies will be included in BELpREG, no specific focus on therapeutic group/indication (↗ *guaranteeing comparator group*) • Prospective registrations, including potential confounding variables (↗ *adjustments*) • BELpREG is constructed to facilitate international data pooling (↗ *large numbers*)

Data collection should be structured in the healthcare setting, in close proximity to data subjects	• Pilot study of BELpREG in 5 regions in Belgium, in close collaboration with local HCPs, inviting pregnant persons to participate (↗ *integration in the care setting*)
	• Including consecutive analyses of…
	  • HCPs' experiences with inviting / motivating women for BELpREG data registration
	  • Participants' experiences with data entry and their challenges and barriers

Importance of collaborations between industry and academia	Ambition to conduct joint research projects in the future (including with TIS worldwide) → data sharing purposes described in the informed consent approved by the ethics committee

Laure Sillis – PharmD, PhD candidate

Clinical Pharmacology and Pharmacotherapy

Department of Pharmaceutical and Pharmacological Sciences

Campus Gasthuisberg - O&N II
Herestraat 49 - box 521
3000 Leuven – Belgium

laure.sillis@kuleuven.be

BELpREG

info@belpreg.be

www.belpreg.be

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