Therapeutic Innovation & Regulatory Science (2024) 58:242–257
https://doi.org/10.1007/s43441-023-00593-3

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REVIEW

Regulations Governing Medicines for Maternal and Neonatal Health: A Landscape Assessment

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Received: 13 July 2023 / Accepted: 27 October 2023 / Published online: 17 December 2023

Abstract

Limited evidence related to the safety or efficacy of medicines in pregnancy and during breastfeeding is available to inform patients and healthcare professionals. Understanding the current regulatory landscape in the clinical trial and postmarketing settings is critical to facilitate the development of applicable processes and tools for studying medicine use during pregnancy and breastfeeding and comply with health authority expectations. This review summarizes key findings from a landscape assessment of regulations, guidelines, and guidance on the use of medicines in pregnancy and breastfeeding issued by health authorities in various territories (including the Americas, Europe, Africa, and Asia Pacific) and outlines relevant initiatives undertaken by health authorities, academic institutions, industry consortia, and public–private organizations. While global pharmacovigilance legislation regarding medication use during pregnancy and breastfeeding exists and continues to evolve, the landscape assessment revealed that there is a lack of global legislative harmonization in both the clinical trial and postmarketing surveillance settings and regulatory gaps still exist in many countries/regions. Despite ongoing efforts from health authorities and public and private organizations, intensive efforts for legislation harmonization and stakeholder collaboration are required to improve the current environment of medication safety in pregnancy and breastfeeding.

Keywords Pharmacovigilance regulations · Patient safety · Pregnancy · Breastfeeding

Introduction

Each year, approximately, 140 million births occur worldwide [1]. Yet while 44% to 99% of pregnant women take medications during their pregnancy, pregnant women remain an understudied population [2]. For example, in the last 40 years, only one medicinal product (atosiban) was developed and approved for use during pregnancy in the United Kingdom (UK) to halt premature labor, and only five other medications (for various indications) are currently licensed for non-obstetric use during pregnancy [3]. Thus, limited evidence related to the safety or efficacy of medicines in pregnancy is available to inform patients and healthcare professionals on the benefit/risk balance to the mother and fetus. Consequently, some women with chronic diseases are nonadherent to maintenance treatment during pregnancy due to a fear that their medications are unsafe for their unborn child [4].

The topic of medication use during pregnancy and while breastfeeding continues to evolve as the regulatory environment includes both established standards, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines [5], as well as newly emerging standards, including the soon to be effective European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Chapter P.III [6]. Globally, various initiatives exist to improve this knowledge gap,

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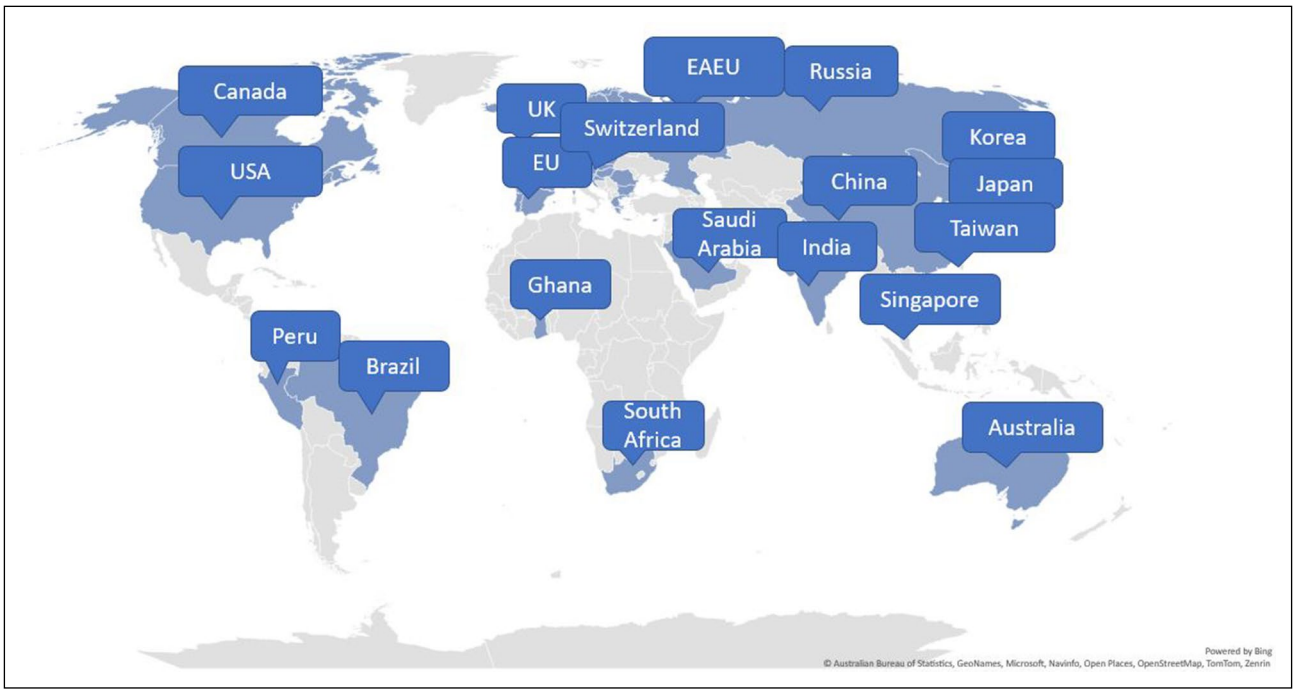

Figure 1 Map of the countries and regions included in the landscape assessment. EAEU, Eurasian Economic Union; EU, European Union; UK, United Kingdom; USA, United States of America.

with diverse efforts spanning health authorities, academic institutions, industry consortia, and public–private organizations to meet this challenge (e.g., Innovative Medicines Initiative [IMI] ConcePTION, Association of the British Pharmaceutical Industry [ABPI] Maternal Health Project Group, United States [US] Task Force on Research Specific to Pregnant Women and Lactating Women [PRGLAC]) [7–9]. Moreover, the conventional attitude to protect pregnant women from participation in clinical trials has evolved to carefully consider the inclusion of pregnant women based on clinical need and ethical considerations [10].

Understanding the current regulatory landscape in the clinical trial and postmarketing settings is imperative to facilitate the development of applicable processes and tools for studying medicine use during pregnancy and breastfeeding and to comply with health authority expectations. TransCelerate BioPharma is a non-profit organization with more than 20 biopharmaceutical member companies that aim to streamline and accelerate the research and development of new therapies around the world. To meet the need for a regulatory landscape assessment on this topic, TransCelerate formed the Pharmacovigilance Pregnancy and Breastfeeding Topic Team to map existing global regulations,guidelines, and guidance on the use of medicines in pregnancy and breastfeeding, with the ultimate goal of using this understanding to propose solutions with a patient-centric approach [11]. This review summarizes key findings from the landscape assessment of regulations, guidelines, and guidance concerning the use of medicine during pregnancy and breastfeeding issued by health authorities in various countries. This paper also outlines relevant initiatives undertaken by health authorities, academic institutions, industry consortia, and public–private organizations.

Methods

For the landscape assessment, an in-depth search and review of global regulatory guidance and legislations were conducted following the "four-eyes principle" (reviewed by two team members). Findings were consolidated following an independent review. Territories in scope included the Americas, Europe, Africa, and Asia Pacific (Fig. 1). In and out of scope topics for the reviewed regulations, guidelines, and guidance covering clinical trial and postmarketing settings are outlined in Table 1. The ICH standards and the Council for International Organizations of Medical Sciences (CIOMS) guidelines served as benchmarks for national safety regulations, guidelines, and guidance [5, 12]. To provide a comprehensive evaluation, initiatives across private consortia, health authorities, and academia have also been included in this landscape assessment. The landscape assessment was conducted based on information that was available as of March 2022. Further changes in the regulatory landscape after March 2022 are not comprehensively reflected in this review.

Table 1 In and out of scope topics for the regulations, guidelines, and guidance landscape assessment

In scope	Out of scope
Maternal, breastfeeding, and paternal exposure	Preclinical safety regulations
Case reports	Regulations on contraception
Aggregate reports	Medical device regulations
Enhanced pharmacovigilance	Submission requirements for clinical trial case reports
Signal detection	
Risk management	
Inclusion/exclusion criteria and enrollment in clinical trials	
Postmarketing surveillance	
Pregnancy registries	
Labeling regulations	

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Results

Regulations, Guidelines, and Guidance

Key results from the TransCelerate landscape assessment are summarized below [13]. These results provide information on which topics in the clinical trials and postmarketing settings (Table 1) have regulations, guidelines, and guidance from ICH, CIOMS, or at a national/regional level.

The following should be noted regarding regulations, guidelines, and guidance at a national/regional level:

- ICH guidelines are adopted by Brazil, Canada, China, the European Union (EU), Japan, Korea, Saudi Arabia, Singapore, Switzerland, the UK (which became a member in June 2022), and the US [14]
- Eurasian Economic Union (EAEU) regulations, guidelines, and guidance apply to Armenia, Belarus, Kazakhstan, Kyrgyzstan, and Russia [15]

Detailed specifics of the reviewed regulations or guidances can be found in the complete TransCelerate landscape assessment output [13].

Clinical Trials Regulations, Guidelines, and Guidance

Regulations, guidelines, and guidance specific to the clinical trial setting are summarized in Tables 2 and 3 (topics: enrollment in studies, follow-up, lactation studies) and in Table 4 (topics: case reports, aggregate reports, risk management). When available, requirements from ICH and CIOMS regulations for each topic are presented in the summary tables alongside country-specific legislation (denoted by filled in boxes). ICH member status of the countries/regions included in the landscape assessment (Fig. 1) is also noted, as membership indicates adoption of ICH guidelines in that country.

Regulatory gaps (denoted as blanks in the tables) as well as inconsistencies among territories were observed (Tables 2, 3, and 4) [6, 16–21]. Additionally, ICH regulation lacks granularity in the clinical trials setting and enrollment regulations vary among countries (Table 2). Risk management measures are generally focused on contraception, which was an out of scope topic for the landscape assessment (Tables 1 and 4).

Postmarketing Surveillance Regulations and Guidelines

Regulations, guidelines, and guidance specific to the postmarketing surveillance setting are summarized in Table 5 (topics: case reports, follow-up reports), Tables 6 and 7 (topics: postmarketing studies, pregnancy registries), Tables 8 and 9 (topics: risk assessment and planning, signal detection, aggregate reports), and in Table 10 (topic: labeling). When available, requirements from ICH and/or CIOMS regulations for each topic are presented in the summary tables alongside country-specific legislation; filled in boxes denote available regulation/guidance, whereas blanks in the tables denote regulatory gaps. When relevant, the tables also specify which countries/regions follow ICH guidelines (ICH member status).

With regard to different types of case reports, ICH guidelines mention maternal exposure and paternal exposure to a drug but do not address drug exposure via breastfeeding

Table 2 Clinical Trials: Summary of regulations, guidelines, and guidance by country and topic (enrollment in studies, follow-up, lactation studies) and comparison to ICH/CIOMS guidelines

Country/Region	ICH Member*	Enrollment in Studies	Follow-up	Lactation Studies
ICH/CIOMS	*ICH guidelines are adopted	**ICH E8 (R1):** "Investigation of drugs that may be used in pregnancy is important. Where pregnant women volunteer to be enrolled in a clinical study, or a participant becomes pregnant while participating in a clinical study, follow-up evaluation of the pregnancy and its outcome and the reporting of outcomes are necessary." [16] **International Ethical Guidelines for Health-Related Research Involving Humans (CIOMS & WHO):** Extensive guidance regarding enrollment of pregnant women in clinical trials is given. "Research in pregnant and breastfeeding women must be initiated only after careful consideration of the best available data from preclinical research in pregnant animal models, research in non-pregnant women, retrospective observational studies, and pregnancy registries." "She is the one to make the final decision about the acceptability of these risks to her and her fetus or infant. Women must also be informed that it is often difficult to determine causality in cases of fetal or infant abnormalities." "Pregnant women must not be considered vulnerable simply because they are pregnant." "When participation in research might be hazardous to a fetus or a woman if she becomes pregnant, sponsors and researchers must guarantee access to pregnancy tests, effective contraceptive methods before and during the research and to safe, legal abortion." [17]	**ICH E8 (R1):** "Where pregnant women volunteer to be enrolled in a clinical study, or a participant becomes pregnant while participating in a clinical study, follow-up evaluation of the pregnancy and its outcome and the reporting of outcomes are necessary." [16] **CIOMS VI:** "Pregnancies occurring during clinical trials present a unique situation. Any pregnancy that occurs in a female trial participant during a clinical trial should be followed to termination or to term. Under special circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery. There may also be special situations when it will be necessary to monitor the pregnancy of a woman whose male partner is the trial participant (e.g., class effects, evidence from animal reproductive studies). Partner privacy may become an issue in follow-up for these situations. The protocol should describe in detail the process for monitoring and managing pregnancy occurrences." [18]	**International Ethical Guidelines for Health-Related Research Involving Humans (CIOMS & WHO):** "Research in pregnant and breastfeeding women must be initiated only after careful consideration of the best available data from preclinical research in pregnant animal models, research in non-pregnant women, retrospective observational studies, and pregnancy registries." "She is the one to make the final decision about the acceptability of these risks to her and her fetus or infant. Women must also be informed that it is often difficult to determine causality in cases of fetal or infant abnormalities." [17] **ICH E8 (R1):** "When nursing mothers are enrolled in clinical studies, their babies should be monitored for the effect of the drug." [16]
Australia	no			
Brazil	yes			
Canada	yes			
China	yes			
EAEU	no			
EU	yes			O [6]
Ghana	no			
India	no	X		
Japan	yes			
Korea	yes			
Peru	no	X		
Russia	no	X		
Saudi Arabia	yes			
Singapore	yes			
South Africa	no			
Switzerland	yes			
Taiwan	no			
UK†	yes			
USA	yes			O [19]

= Specified in local regulation or guidance.
= Not mentioned in regional or national regulations or guidance.
X = Inclusion of pregnant women in clinical trials is permitted only when the drug is designed to be used by pregnant/nursing women.
O = Contains additional information compared to ICH/CIOMS (Table 3).
†As of June 2022, became a member of ICH.

CIOMS: Council for International Organizations of Medical Sciences; EAEU: Eurasian Economic Union; EU: European Union; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; UK: United Kingdom; USA: United States of America; WHO: World Health Organization.

Table 3 Clinical Trials: Additional regional guidances on lactation studies beyond ICH/CIOMS guidelines

Country/region	Lactation studies
EU	EMA Guideline of GVP Chapter P.III.B.4.3 Clinical Lactation Studies: "In cases where no human data are available on the extent of medicine transfer into breast milk, where use by breastfeeding women is expected to be common, and based on the medicinal product's pharmacological properties, it is considered plausible that there is a risk to breastfed infants, a PK study amongst breastfeeding women should be considered. This is expected to be the case when a medicinal product is commonly used by women of reproductive age (e.g., antidepressants, anti-infectives, diabetes medications, pain medications) or when there is evidence of use or anticipated use of the medicinal product by lactating women." "Medicine concentration levels in breast milk samples should be measured and a relative infant dose calculated, to obtain information for supporting the risk assessment and provision of advice on timing of medicine intake relative to breastfeeding where this may be feasible (e.g., for short-term or single-dose treatments). Moreover, data on the effect of the medicine on milk production or composition should be collected, if potentially clinically relevant." "In the case of a medicine highly used in women who could breastfeed, with an unknown potential for serious adverse reactions in breastfed children, establishing safety information in the post-authorisation phase should be considered as an important source of information. This may include the clinical follow-up of breastfed children whose mothers are treated with a specific medicine. Pregnancy registries in which newborns are further observed could include the collection of information on breastfeeding to allow a comparison of a group of breastfed children to those not breastfed and those breastfed in mothers who are not treated with the product of interest. In case a medicine is used during breastfeeding and questions arise regarding a potential long-term impact on child's growth, neurodevelopment, or other adverse events with a prolonged latency, it should be considered to carry out long-term follow-up in those children." [6]
USA	FDA Guidance for Industry—Clinical Lactation Studies—Considerations for Study Design: Detailed design considerations for lactation studies are provided, including sample collection, pharmacokinetic and pharmacodynamic considerations. [19]

CIOMS council for international organizations of medical sciences, *EMA* European medicines agency, *EU* European union, *FDA* food and drug administration, *GVP* good pharmacovigilance practices, *ICH* international council for harmonisation of technical requirements for pharmaceuticals for human use, *USA* United States of America

Table 4 Clinical Trials: Summary of regulations, guidelines, and guidance by country and topic (case reports, aggregate reports, risk management) and comparison to ICH/CIOMS guidelines

Country/Region	ICH Member*	Case Reports	Aggregate Reports	Risk Management
ICH/CIOMS	*ICH guidelines are adopted	**ICH E2B (R3):** Contains detailed instructions on what to provide in a case report. [20]	**ICH E2F:** Risk evaluation should include pregnancy and lactation exposure and outcomes. Safety findings related to medication administration to special populations, including pregnant women, should be included in report, under section `Safety findings from marketing experience`. [21]	Guidelines not provided
Australia	no			
Brazil	yes			
Canada	yes			
China	yes			
EAEU	no			
EU	yes			
Ghana	no			
India	no			
Japan	yes			
Korea	yes			
Peru	no	X		
Russia	no			
Saudi Arabia	yes			
Singapore	yes			
South Africa	no			
Switzerland	yes			
Taiwan	no			
UK[†]	yes			
USA	yes			X

= Specified in local regulation or guidance.

= Not mentioned in regional or national regulations or guidance.

X = When Sponsor becomes aware of pregnancy cases, must submit a report within 7 days.

[†]As of June 2022, became a member of ICH.

CIOMS: Council for International Organizations of Medical Sciences; EAEU: Eurasian Economic Union; EU: European Union; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; UK: United Kingdom; USA: United States of America.

(Table 5) [22, 23]. Nonetheless, national/regional regulations or guidances address these types of case reports with exception of Korea, Taiwan, and the UK (Table 5). With regard to different types of follow-up reports, there are no ICH guidelines for follow-up reports on pregnancy outcomes or child development but ICH does instruct to follow-up all reports of possible fetal exposure to the medical product and to consider product half-life [22, 23]. Conversely, some national/regional guidances specifically require follow-up on pregnancy outcomes and/or monitoring of child development (Table 5).

There are ICH or CIOMS guidelines, as well as regional regulations or guidances, for postmarketing studies, pregnancy registries, risk assessment and planning, signal detection, and aggregate reports [24–35]. Tables 6 and 8 summarize which countries/regions have regulations or guidances for these topics. If national/regional regulations or guidance exist, they follow ICH, although some may have additional details for these topics (e.g., organization

Table 5 Postmarketing surveillance: summary of ICH and regional/local regulations, guidelines, and guidance for specific types of case reports and follow-up reports

Country/Region	ICH Member*	Case Reports			Follow-up Reports		
		Maternal Exposure	Paternal Exposure	Breastfeeding	Fetal Exposure	Pregnancy Outcome	Child Development
ICH [22, 23]	*ICH guidelines are adopted	■	■		■		
Australia	no	■			■	■	■
Brazil	yes	■					
Canada	yes	■			■		
China	yes	■			■	■	
EAEU	no	■		■	■	■	X
EU	yes	■	■		■	■	X
Ghana	no	■					
India	no	■		■			
Japan	yes	■					
Korea	yes						
Peru	no	■	■	■	■	■	XX
Russia†	no	■					
Saudi Arabia	yes	■	■				
Singapore	yes	■		■	■	■	■
South Africa	no	■		■	■	■	■
Switzerland	yes	■					
Taiwan	no						
UK‡	yes						
USA	yes	■					

■ = Specified in regulation or guidance.
□ = Not mentioned in regional or national regulations or guidance.
X = Development of child after birth.
XX = Within 6 months of newborn life.
†Follows EAEU.
‡As of June 2022, became a member of ICH.

EAEU: Eurasian Economic Union; EU: European Union; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; UK: United Kingdom; USA: United States of America.

or design of registries, reporting timeline to health authorities for a signal, additional guidance for signal detection) that are described in Tables 7 and 9 [26–31, 33–35].

Lastly, while CIOMS has recommendations on labeling, several countries/regions also have labeling regulations or guidances that provide more detailed information compared to CIOMS (Table 10) [36–42].

Pregnancy- and Breastfeeding-Related Initiatives

Related initiatives conducted by health authorities, industry associations, and research/academic groups focus on a wide array of objectives, including pregnancy/breastfeeding data, policy information, clinical trials, and patient communication. Most initiatives are led by research/academic groups or health authorities and primarily focus on data collection or provision of information (Fig. 2) [7–9, 43–54]. Details on specific initiatives can be found in the complete TransCelerate landscape assessment output [13]; this output should not be considered a comprehensive list of initiatives, but an overview of main associations that aim to improve

Table 6 Postmarketing surveillance: summary of regulations, guidelines, and guidance by country and topic (postmarketing studies, pregnancy registries) and comparison to ICH/CIOMS guidelines

Country/Region	ICH Member*	Postmarketing Studies	Pregnancy Registries
ICH/CIOMS	*ICH guidelines are adopted	**ICH E2E:** Guidance mentions pregnant women as a special population (safety information should be stratified for special populations). [24]	**CIOMS V:** Guidance mentions pregnant women as a population that may warrant additional studies. Distinction between pregnancy follow-up studies, pregnancy registries, and congenital anomaly/birth defect registries are made. "A pregnancy registry generally is a cohort of women who are known or possibly expected to be pregnant and are followed for both positive and negative outcomes. This is not the same as a congenital abnormality/birth defect registry, which is a repository of established cases of children born with defects/abnormalities." [25]
Australia	no		
Brazil	yes		
Canada	yes		O [26]
China	yes		
EAEU	no		O [27]
EU	yes	O [28, 29]	O [29]
Ghana	no		
India	no		
Japan	yes		
Korea	yes		
Peru	no		
Russia	no		O [27]
Saudi Arabia	yes		
Singapore	yes		
South Africa	no		
Switzerland	yes		
Taiwan	no		
UK*	yes		
USA	yes	O [30]	O [30, 31]

= Specified in local regulation or guidance.
= Not mentioned in regional or national regulations or guidance.
O = Contains additional information compared to ICH/CIOMS (Table 7).
*As of June 2022, became a member of ICH.

CIOMS: Council for International Organizations of Medical Sciences; EAEU: Eurasian Economic Union; EU: European Union; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; USA: United States of America.

understanding of medication efficacy and safety in pregnancy and breastfeeding.

Discussion

Limited evidence related to the safety or efficacy of medicines in pregnancy is available to inform patients and healthcare professionals on the benefit/risk balance to the mother

Table 7 Postmarketing surveillance: additional regional guidances on postmarketing studies and pregnancy registries beyond ICH/CIOMS guidelines

Country/Region	Postmarketing Studies	Pregnancy Registries
Canada		**Health Canada Guidance Document:** Guidance encourages the gathering of data on pregnant and breastfeeding women. [26]
EAEU		**Rules of GVP of EAEU No. 87:** Organization and the design of the pregnancy register that would cover all patients who got pregnant during the treatment or within the relevant period following the completion of treatment (e.g., 3 [three] months) should be considered. [27]
EU	**EMA Guideline of GVP Module VIII (Rev 3):** Outlines the purpose and requirements of a post-authorization safety study (PASS) with specific focus on noninterventional PASS. Prioritization should be given to vulnerable patient populations/poorly studied patient populations, missing information (e.g., pregnant women) as these populations are likely to be exposed in the post-authorization setting. Outlines the details of registries and their use. [28] **EMA Guideline on the Exposure to Medicinal Products During Pregnancy – Need for Post-Authorisation Data:** Sources of pregnancy outcome data are discussed briefly (spontaneous reports, record linkage, registries, clinical studies, comparative observational studies). Study areas of specific interest include foetal therapy studies and pharmacokinetic studies. [29]	**EMA Guideline on the Exposure to Medicinal Products During Pregnancy – Need for Post-Authorisation Data:** Source of data information may include birth defect registries or/and pregnancy registries. [29]
Russia		**Rules of GVP of EAEU No. 87:** Organization and the design of the pregnancy register that would cover all patients who got pregnant during the treatment or within the relevant period following the completion of treatment (e.g., 3 [three] months) should be considered. [27]
USA	**FDA Guidance for Industry – Post-Approval Pregnancy Safety Studies:** Guidance on considerations for planning post-approval pregnancy studies (including study design, data sources). [30]	**FDA Guidance for Industry – Post-Approval Pregnancy Safety Studies; Establishing Pregnancy Exposure Registries:** Guidance on strength, limitations, design consideration of pregnancy registries. [30, 31]

[ ] = Not mentioned in regional or national regulations or guidance.

CIOMS: Council for International Organizations of Medical Sciences; EAEU: Eurasian Economic Union; EMA: European Medicines Agency; EU: European Union; FDA: Food and Drug Administration; GVP: Good Pharmacovigilance Practices; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; USA: United States of America.

and fetus. While the majority of pregnant individuals take at least one medication during their pregnancy, only a few medications were developed to be used by pregnant people [2, 3]. Moreover, less than 25% of the medications available on the market present concrete information regarding risks during pregnancy in the product label. There is a dire need to understand and overcome the scientific, legislative, legal, and ethical challenges preventing the development of safe and effective medicinal products for use during pregnancy and while breastfeeding.

Table 8 Postmarketing surveillance: summary of regulations, guidelines, and guidance by country and topic (risk assessment and planning, signal detection, aggregate reports) and comparison to ICH guidelines

Country/Region	ICH member*	Risk Assessment and Planning	Signal Detection	Aggregate Reports
ICH	*ICH guidelines are adopted	**ICH E2E:** Populations that are not studied should be specifically highlighted and should be considered as populations, which may warrant additional studies. [24]	**ICH E2E:** Best methods to address a situation can vary depending on the product, indication, study objective, and population. Signals observed in vulnerable populations (including pregnant women) are to be prioritized. [24]	**ICH E2C (R2):** Characterization of risk may include relevant patient characteristics, such as pregnancy/lactation. Exposure data for medication use during clinical trials for special populations. If medication is used in special populations, including pregnant women, post-approval exposure data should be provided. [32]
Australia	no		O [33]	
Brazil	yes			
Canada	yes			
China	yes			
EAEU	no			
EU	yes		O [29]	
Ghana	no			
India	no			
Japan	yes			
Korea	yes			
Peru	no			
Russia	no			
Saudi Arabia	yes		O [34]	
Singapore	yes			
South Africa	no			
Switzerland	yes		O [35]	
Taiwan	no			
UK[†]	yes			
USA	yes			

= Follows ICH.

= Not mentioned in regional or national regulations or guidance.

O = Follows ICH with additional information (Table 9).

[†]As of June 2022, became a member of ICH.

EAEU: Eurasian Economic Union; EU: European Union; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; UK: United Kingdom; USA: United States of America.

As a first step toward meeting this challenge, this regulatory landscape assessment, developed by experts in pharmacovigilance and/or maternal and fetal health, focused on regulatory challenges and represents an overview of current safety legislation for pregnancy and breastfeeding [13]. Based on information that was available as of March 2022,

Table 9 Postmarketing surveillance: additional regional guidances on signal detection beyond ICH guidelines

Country/region	Signal detection
Australia	TGA Pharmacovigilance Responsibilities of Medicine Sponsors: Report signal of a possible teratogenic effect (cluster of cases) as a significant safety issue [33]
EU	EMA Guideline on the Exposure to Medicinal Products During Pregnancy—Need for Post-Authorisation Data: Additional guidance on how to perform signal detection for pregnancy cases [29]
Saudi Arabia	SFDA Guideline on GVP (v3.1): Immediately notify about potential signals of teratogenicity [34]
Switzerland	Swissmedic: Additional guidance regarding potential/identified signals of teratogenicity [35]

EMA European medicines agency, *EU* European union, *GVP* good pharmacovigilance practices, *ICH* international council for harmonisation of technical requirements for pharmaceuticals for human use, *SFDA* Saudi food and drug authority, *TGA* therapeutic goods administration

globally, pharmacovigilance legislation regarding medication use during pregnancy and breastfeeding exists (e.g., ICH guidelines, CIOMS recommendations, national legislations) and continues to evolve. For example, the ICH E21 Working Group on Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials was formed in Q4 2022 and the EMA GVP Chapter P.III pregnancy legislation is expected to be launched in Q3 2023 [6, 55].

However, despite ongoing efforts from health authorities and public and private organizations (e.g., EU IMI ConcePTION, US PRGLAC, national and global teratology centers), the landscape assessment revealed that there is currently a lack of global legislative harmonization in both the clinical trial and postmarketing surveillance settings [13]. While ICH/CIOMS regulations include general provisions on safety in pregnancy and breastfeeding, more details would be required to support development in this area [16–18, 20–25, 32, 36].

Additionally, while several health authorities have made immense progress by providing detailed recommendations in their respective territories (Tables 3, 7, 9 and 10), regulatory gaps still exist in many countries/regions that were included in the landscape assessment (Fig. 1) [6, 19, 26–31, 33–42]. In particular, significant regulatory gaps exist in the clinical trials setting [e.g., lack of regulations or granularity in the regulations for pregnancy or lactation studies (Tables 2 and 4)], whereas postmarketing surveillance legislation is generally further developed (Tables 5, 6, 8, and 10). In some instances, local regulations are more specific regarding signal management than ICH guidelines [e.g., focus on fetotoxicity in Australia, Saudi Arabia, and Switzerland (Tables 8 and 9)] [33–35].

Of note, no end-to-end product development guideline exists for medications to be used by pregnant women. Moreover, where national legislation on related topics exists, global inconsistencies among national requirements in the clinical trials setting were observed. For example, requirements for enrolling pregnant or nursing women into clinical trials vary; in India, Peru, and Russia, enrolling pregnant women into clinical trials is only permitted if the medication is designed specifically for use in this population, while in Canada, EU, Switzerland, and the US, enrollment is permitted after careful benefit/risk assessment, including the mother and the fetus (Table 2). In the postmarketing surveillance setting, requirements for post-authorization study design differ between the EU and US (Table 7). Recommendations for case collection after exposure to medication during breastfeeding or related to longer term follow-up vary as well. These aspects lead to a lack of clarity, uncertainty, establishment of complex pharmacovigilance processes, and delays when it comes to the much-needed product development for this population.

There is an acute need to harmonize global legislation for medication safety in pregnancy and breastfeeding and to provide end-to-end product development guidance for medications to be used in this population. While no investigational plan has been proposed or is required by health authorities in this area, discussions to develop a "maternal" or an "obstetric" investigational plan are currently ongoing in several territories. In 2021, the International Coalition of Medicines Regulatory Authorities (ICMRA) workshop (attended by the EMA and US Food and Drug Administration [FDA] representatives) called for the development of a maternal investigational plan, to

Table 10 Postmarketing surveillance: summary of regulations on labeling by country and CIOMS guidelines

Country/Region	Labeling Regulations
CIOMS	**CIOMS III and V:** Considerations on drafting the Pregnancy and Lactation sections from the Reference Safety Information. [36]
Australia	
Brazil	
Canada	
China	
EAEU	**EAEU No. 88:** Specific details on what information should be included and relevant sections of the label. Principles of presenting of Product Information are provided. [37]
EU	**EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation – from Data to Labeling:** Included a table for risk assessment and recommendation for use based on Nonclinical and Human Data. [38]
Ghana	
India	
Japan	**PSEHB/SD Notification No.0608-1:** Specific details on what information should be included and relevant sections of the label. [39]
Korea	
Peru	
Russia*	
Saudi Arabia	
Singapore	
South Africa	**SAHPRA Package Inserts for Human Medicines (v5):** Expands recommendations to women of childbearing potential and fertility. [40]
Switzerland	
Taiwan	
UK	
USA	**FDA Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format – Guidance for Industry; FDA Content and Format of Labeling for Human Prescription Drug and Biological Products – Requirements for Pregnancy and Lactation Labeling. Final Rule:** Provides detailed guidance on pregnancy and lactation labeling. [41, 42]

[ ] = Not mentioned in regional or national regulations or guidance.

*Follows EAEU.

CIOMS: Council for International Organizations of Medical Sciences; EAEU: Eurasian Economic Union; EMA: European Medicines Agency; EU: European Union; FDA: Food and Drug Administration; PSEHB/SD: Pharmaceutical Safety and Environmental Health Bureau/Safety Data; SAHPRA: South African Health Products Regulatory Authority; UK: United Kingdom; USA: United States of America.

be proposed by sponsors, outlining how these populations will be studied in the product development [48]. Similarly, discussions regarding an obstetric investigational plan, based on learnings from the successful pediatric investigational plans, are occurring in the UK [49].

Based on findings of the landscape assessment, the TransCelerate Pharmacovigilance Pregnancy and Breastfeeding Topic Team has developed a openly available toolkit (called `Points to Consider Concerning the Use of Medicines in Pregnancy throughout the Product Lifecycle`) that aims to provide a holistic view of pregnancy considerations across the lifespan of the drug and aid researchers to optimize their compliance with regulatory authority expectations [56].

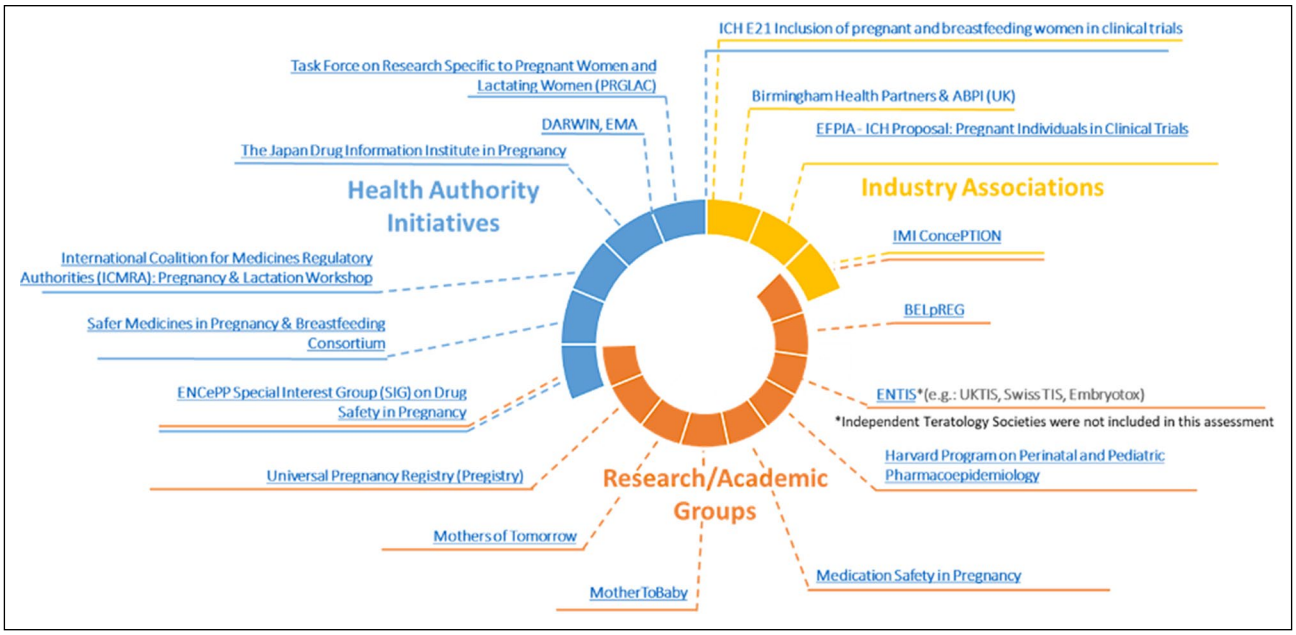

Figure 2 Pregnancy and breastfeeding initiatives from health authorities, industry associations, and research/academic groups. Relevant initiatives include the Association of the British Pharmaceutical Industry (ABPI) Maternal Health Project Group [8], the BELgian interdisciplinary initiative to enhance pregnancy related data REGistration and research on medication use (BELpREG) [43], the European Federation of Pharmaceutical Industries and Associations (EFPIA)—International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Proposal on Pregnant Individuals in Clinical Trials [44], the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Special Interest Group on Drug Safety and Pregnancy [45], the European Network of Teratology Information Services (ENTIS) [46], the Innovative Medicines Initiative (IMI) ConcePTION [7], the United States Task Force on Research Specific to Pregnant Women and Lactating Women [9], the Japan Drug Information Institute in Pregnancy [47], the International Coalition for Medicines Regulatory Authorities (ICMRA) Pregnancy and Lactation Workshop [48], the United Kingdom (UK) Safer Medicines in Pregnancy and Breastfeeding Consortium [49], the Universal Pregnancy Registry (Pregistry) [50], Mothers of Tomorrow [51], MotherToBaby [52], Medication Safety in Pregnancy [53], and the Harvard Program on Perinatal and Pediatric Pharmacoepidemiology [54].

Conclusions

While global pharmacovigilance legislation regarding medication use during pregnancy and breastfeeding exists and continues to evolve, intensive efforts for legislation harmonization and stakeholder collaboration are required to improve the current environment of medication safety in pregnancy and breastfeeding. Sponsors, marketing authorization holders, researchers, healthcare professionals, and patients must work together to enhance medicinal product development, data collection, and transparent risk communication to ultimately improve maternal and fetal health outcomes following medication exposure for the generations to come.

Author Contributions

AA, AG, BK, NA, OA, OE, MFSF, LB-H, KW, and DL contributed to the conception of the work, collection of the information, and the drafting, reviewing, and revision of the article.

Funding

The research for and writing of this article were funded by TransCelerate BioPharma Inc. We wish to thank the following individuals for their expertise, assistance throughout, and help in writing this article: Al Macin, Amy Moon, Anna R. Amato, Christine Taeter, Gary Zuckerman, Joanne Brady, Joyce Miranda, Lisa Schwartz, Maral Zahdei, Pranita Kabadi, Susan Kindig, and Yenlik Zheteyeva.

Data Availability

The data that support the findings of this paper are openly available on the TransCelerate platform at Regulatory Landscape Assessment.

Declarations

Conflict of interest

Amalia Alexe is a full-time employee of Advanced Accelerator Applications, a Novartis Company, and holds shares in Incyte and Novartis. Dr. Anju Garg is a full-time employee of Sanofi and holds shares in Sanofi. Dr. Birgit Kovacs is a full-time employee of Boehringer Ingelheim Pharmaceuticals and holds shares in Eli Lilly. Dr. Nadezda Abramova is a full-time employee of Merck Healthcare KGaA. Dr. Apara is a full-time employee of Merck & Co Inc. and holds shares in Merck & Co Inc. Dr. Eisele is a full-time employee of Amgen Inc. and holds

shares in Amgen. Dr. Maria Fernanda Scantamburlo Fernandes is a full-time employee of Eli Lilly and holds shares in Eli Lilly. Leesha Balramsingh-Harry is a full-time employee of Hoffman LaRoche Ltd. and holds shares in Hoffman-LaRoche AG. Dr. Wurst is a full-time employee of GlaxoSmithKline and holds shares in GlaxoSmithKline. Dr. Lewis is a full-time employee of Novartis Pharma AG and holds shares in GlaxoSmithKline and Novartis.

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