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Global Perspective of Paediatric Pharmacovigilance and its Importance: Where Have We Reached?

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Authors' contributions

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ABSTRACT

Pharmacovigilance is a tool proposed during the post-marketing process of the pharmaceutical product lifecycle to monitor drug safety in everyday life and to identify adverse drug reactions. The identification of adverse reactions, however, is a significant cause of concern and a challenge to pharmacovigilance structures. Regulators use three basic principles in determining the risk-benefit balance to decide whether to approve a drug or a biological product and to maintain it on the market: safety, quality and effectiveness. In particular, paediatric patients, especially new-borns and infants, are at risk of drug-related adverse reactions. Drugs are also prescribed in an unlicensed and/or off-label manner to new-borns, infants and teenagers, leading paediatric patients to a higher risk of experiencing adverse drug reactions (ADRs). ADRs in children < 2 years of age are often reported and can often be alarming. The practise of paediatric pharmacovigilance needs to be strengthened by stimulating spontaneous paediatric reporting and successful post-marketing surveillance. The current study highlights the importance of paediatric pharmacovigilance and the role of different stakeholders like healthcare providers, regulators, and consumers in increasing the ADR reporting rate. Also, it discusses the pharmacovigilance tools and various initiatives that are

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taken by various regulatory authorities like the United States, the United Kingdom, Japan, and India.

Keywords: Paediatric pharmacovigilance; adverse drug reactions; off label use; spontaneous reporting; paediatric population.

1. INTRODUCTION

It is of vital importance to track the safe use of medicines in children because, during the clinical development of medicines, only limited data on this aspect is provided through clinical trials. Off-label and off-license use of pharmaceutical products beyond the conditions described in the license e.g., in terms of formulation, indications, contraindications, or age, is a major area of concern. A wide variety of different physiologies are found in the paediatric population, representing the extremely varied duration from the fatal and embryonic stages, through birth and infancy, through puberty and adolescence. This makes children very susceptible to ADRs [1].

According to the World health organization (WHO) "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible medicine-related problems, An ADR to a medicine includes not only reactions occurring during normal use of medicines, but also reactions due to errors in medicine administration, non-adherence, overdose, off-label use, drug abuse, and adverse effects due to the use of traditional and complementary medicines" [2].

It is not possible to extrapolate the efficacy of medications used in patients in an adult age group to a paediatric age group. The pharmacokinetics and pharmacodynamics of several widely used medicines differ considerably between these two patient age groups. In addition, as compared to adults, ADRs in children may have a relatively more serious effect. Thus, among children, ADRs can lead to severe morbidity. ADRs in children have been found to result not only in hospital admissions or prolonged hospitalization, but can also lead to permanent disability or even death. It is of particular interest to provide information on the frequency, severity and types of medications most commonly involved in ADRs in the paediatric age group, as pre-marketing clinical trials are often performed in adults. They represent a reported 9.5 percent of occurrences, including 2.1 percent of hospital admissions, with 39.3 percent of them being life-threatening. When used in infants, the safety profile of a medication thus marketed with its testing on adults can differ considerably. For newer medications, this feature of drug therapy is also hard to foresee. To collect risk information on children, an active system of drug surveillance is required [3].

Medicines which have been properly tested for their use should be given to paediatric patients. Safe and efficient pharmacotherapy in paediatric patients demands that knowledge of the appropriate use of pharmaceutical products in paediatric patients of different ages be established in a timely manner and the paediatric formulations of such products be developed. Advances in formulative chemistry and the design of paediatric trials can further promote the production of safe paediatric medicinal products. The paediatric patient population should normally be included in drug development programs when a medication is being produced in adults for a disease or disorder and the product is intended to be used in the paediatric population. The following ICH Guidelines are applicable throughout the paediatric drug development process including the risk management plan and post marketing surveillance [4].

For paediatric research, ICH guidelines on E2 topics and ICH E6, define adverse event reporting (AER) for adults and the Paediatric Population. In AER, age-appropriate, standard laboratory values and clinical measurements should be used. Unintended exposure (accidental ingestion, etc.) to medicinal products can provide a chance to obtain safety and pharmacokinetic information and to maximize understanding of side effects associated with the dosage. Physical and cognitive growth and development may be impaired by pharmaceutical products, and in paediatric patients, the adverse effect profile can vary [5]. Some adverse effects and drug interactions that occur in paediatric patients may not be detected in adult studies, as developing systems may react differently from mature adult organs. Furthermore, the complex growth and development processes do not instantly experience an adverse event but at a later stage of growth and maturation. To evaluate

potential effects on skeletal, mental, cognitive, sexual, and immune maturation and development, long-term studies or surveillance data may be required, either while patients are on chronic therapy or during the post-therapy period. It is an essential objective to gain awareness of the effects of pharmaceutical products in paediatric patients. However, without compromising the (6) well-being of paediatric patients involved in clinical trials, this should be achieved. Companies, regulatory agencies, health care providers, and society as a whole share this responsibility [6].

2. AGE CLASSIFICATION OF PAEDIATRIC PATIENTS

To some extent, any classification of the paediatric population into age groups is subjective, but a category such as the one below offers a framework for thinking about paediatric patient study design. Developmental biology and pharmacology must be taken into account in decisions about how to stratify research and data by age. A versatile approach is therefore required to ensure that studies represent current paediatric pharmacology awareness. If the clearance pathways of a medicinal product are well defined and the oncogenicity of the pathways understood, age categories for pharmacokinetic evaluation may be selected based on the 'break point' where clearance is likely to change dramatically. If the clearance pathways of a medicinal product are well established and the oncogenicity of the pathways understood, the age categories for pharmacokinetic evaluation may be selected. Often, collecting data across wide age ranges and analysing the impact of age as a continuous covariant might be more fitting [7].

The number of patients required could unnecessarily be increased by splitting the paediatric population into several age groups. In longer-term studies, paediatric patients will shift from one age group to another; changes in the number of patients within a given age category must be prospectively taken into account in study design and statistical plans. In developmental (e.g., physical, cognitive, and psychosocial) problems across the age groups, however, there is significant overlap. Ages are specified in the days, months, or years completed. One potential categorization is the following [8].

3. HISTORY OF PHARMACOVIGILANCE IN PAEDIATRICS

The first example of a safety problem that contributed to a reflection of pharmacovigilance was published in chloroform problems in the British Medical Journal in 1877. In 1898, the second issue emerged with the commercialization of diacetylmorphine, dubbed heroin Pharmacovigilance, which began to be addictive at the beginning of the 1910s (500,000 dependent patients reported only in the US). In 1937, diethylene glycol was used to solubilize sulphanilamide without any previously tested toxic examination, with a series of 34 kidney failure deaths among children (of 103 cases). Stalinon®, a topical skin product, was applied to diiodo diethyl tin at the beginning of the 1950s (1954), resulting in 102 cases of encephalopathy-related deaths, and a hundred patients with developed serious, permanent, neurological life – threatening adverse effects [9].

Table 1. List of ICH Guidelines applicable for Paediatric Populations

E2	Clinical Safety Data management
E3	Structure and Content of Clinical Study Reports
E4	Dose-Response Information to support Drug Registration
E5	Ethnic factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice: Consolidated Guideline
E8	General Considerations for clinical Trials
E9	Statistical Principles for Clinical Trials
E10	Choice of Control Group in Clinical Trials
E11	Clinical Investigations of Medicinal Products in Paediatric Population
S11	Non-Clinical Safety testing in support of Development of Paediatric medicines
Q1	Stability Testing
Q2	Validation of Analytical Procedures
Q3	Impurity Testing

Table 2. Age Classification of Paediatric Population by WHO

Pre term New born infants	**--------**
Term new born infants	0 to 27 days
Infants and toddlers	28 days to 23 months
Children	2 to 11 years
Adolescents	12 to 16-18 years [Dependent on Region]

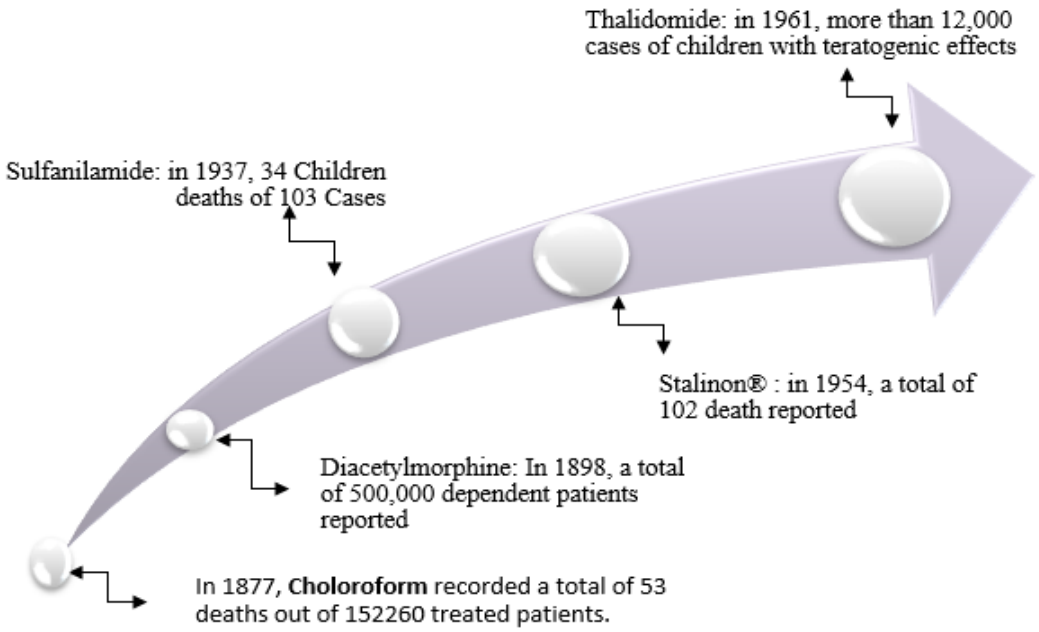

Fig. 1. Significant milestones of history of Paediatric Pharmacovigilance

As a side effect of thalidomide, several children were born with phocomelia and agenesis of the limbs during the 1960s. Thalidomide was marketed as an over-the-counter (OTC) hypnotic/sedative and a safe medication in 1957, which was later used in pregnant women to treat nausea. More than 12,000 cases of teratogenic effects in children were the result (not only limbs malformations) [10].

In 1968, the WHO established its Program for the International Drug Monitoring following the thalidomide's tragedy. The organization also established its own Pharmacovigilance Centre in 1978. It was created to support the development of this field. It was important to examine the effectiveness and safety of the medication in the population for which it is intended and marketed. Therefore, special strategies for developing medication for children are needed [11].

4. DISCUSSION

The study highlights the current measures that has been taken to improve the Pharmacovigilance activities in Paediatric Population by different regulatory authority such as the European Medicines Agency (EMA), the United States Food and Drug Authority (USFDA), the Medicines and Healthcare products Regulatory Agency (MHRA), the Pharmaceutical and Medical Devices Agency (PMDA), Pharmacovigilance Program of India (PvPI), the Central Drugs Standards and Control Authority of India (CDSCO).

4.1 European Union

The Paediatric Regulation (EC) (No. 1901/2006) was conceived and adopted by the EMA to address the challenges of differing pharmacokinetic and pharmacodynamic profiles compared to adults, uncertainty about the long-term drug risk-benefit profile and the additional risks due to off-label medicine use, to identify research priorities and increase the volume and quality of paediatric research [12].

The Paediatric Regulation (EC) (No 1901/2006) was formulated and adopted by the EMA to

resolve the difficulties of different pharmacokinetic and pharmacodynamic profiles compared to adults, the ambiguity of the long-term risk-benefit profile of medicinal products and the additional risks resulting from off-label use of medicinal products, to define research priorities and to increase the amount and quality of paediatric research. The newly published Good Pharmacovigilance Practices (GVP) Chapter "Product- or Population-Specific Considerations IV: Paediatric Population', hereinafter referred to as Paediatric GVP (PGVP), was accompanied by many European regulatory milestones. In October 2018, following public consultation, the PGVP was formally adopted with the goal of increasing the use of existing pharmacovigilance resources and procedures, while clarifying the role and responsibilities of each stakeholder in paediatric healthcare. The PGVP broadly consists of two parts focused on the paediatric community, relating to pharmacovigilance issues and pharmacovigilance frameworks and processes [13].

4.2 Paediatric Pharmacovigilance Processes

For clinical study sponsors, healthcare practitioners, parents, caregivers and their respective organizations, the PVGP offers guidance on paediatric medicines on the effect of emerging safety problems and the need to encourage early implementation of risk management strategies. The PGVP advises how to implement current tools and procedures for pharmacovigilance, including Risk Management Plans (RMPs), Periodic Safety Update Reports (PSURs), Post-Authorisation Safety Studies (PASS) and Signal Management, to meet the needs of the paediatric population. Module V of the GVP and Guidelines on the format of the RMP discuss specific issues relating to paediatric RMPs. Risks must be established in view of age-related changes in pharmacokinetics and pharmacodynamics, metabolite-related ADRs present in children but not in adults, and long-term effects on the reproductive and neuro-developmental systems (i.e., fertility and cognition), the musculoskeletal system (i.e., growth), and the immune system. Even though it may be agreed that, in terms of physiological/pharmacological features, some paediatric groups, such as teenagers, are identical to adults, this should be validated by empirical evidence when filing for initial marketing authorisation. A PASS can be warranted if further investigation is needed, as per GVP Module VIII [14].

4.3 Implications for Marketing Authorisation Holders and National Competent Authorities

The scope of the PGVP includes many processes that are designed to implement pre-existing legal structures. These include the need for the submission of a patient safety assessment (PRA) and the establishment of an approved protocol. The goal of the PGVP is to promote the creation of a more accurate and effective pharmacovigilance system that is capable of providing relevant post-authorisation information. Another example is the preparation of a Paediatric Investigation Plan (PIP). The topic of the article also touches on the various steps that a pharmacovigilance specialist can take to support the detection of safety signals [7].

In order to establish consistency between pre-marketing and post-marketing research on paediatric drug safety, the value of good planning is emphasized. If a paediatric indication is applied to an already approved medication, as well as when new safety evidence occurs from off-label usage linked to paediatric ADR signals, more frequent PSURs might be needed. Detailed documentation on the paediatric population exposed, with appropriate age or weight ranges, should be included in PSURs. The PGVP encourages both the holder of the marketing authorisation (MAH) and the competent national competent authorities (NCA) to tailor communications relating to the protection of drugs to the needs of children and adolescents. Details on the possible effects of the medication on school performance and sports-related behaviour will be an example. Similar notions of communication targeting children and teenagers also refer to risk minimization steps (RMMs) [15].

4.4 USFDA

Paediatric Pharmacovigilance is the outcome of discussions between OPT, DPMH and OSE about how to increase the efficiency of paediatric pharmacovigilance by the FDA while preserving or improving the accuracy of safety signal detection for products used in the paediatric population.

Congress passed the Food and Drug Administration Modernization Act (FDAMA) in

1997 in response to challenges that are actual and perceived, to carrying out drug trials in the paediatric population. FDAMA offers an additional 6-month marketing exclusivity duration for an emerging drug manufacturer responding to a written request by the FDA for trials of its drug in paediatric patients. Fewer than 1000 children are involved in most paediatric trials performed for FDA approval of an individual medication, and medications are used after marketing in a population of children more complex and multiple than those in controlled studies. Thus, after the introduction of a product to the market, safety issues could become apparent [16].

Since children constitute a smaller percentage of the population receiving drugs that are reported to the FDA for adverse effects, the detection of paediatric-specific issues is often more difficult since they are 'submerged' in the greater number of adult reports submitted. Furthermore, voluntary adverse event reporting (AER) is a passive method. In order to resolve these issues, Congress provided a provision for the FDA to report to the Paediatric Advisory Committee (PAC) in the Best Pharmaceuticals for Children Act (BPCA) of 2002 to review safety problems found in the 1-year cycle following the granting of exclusivity and to seek suggestions for action from the PAC [.17].

The PAC consists of 14 voting members, including the chair. The FDA Commissioner chooses representatives and chairs from bodies with experience in paediatric research, paediatric subspecialties, statistics, and/or biomedical ethics. Some of the responsibilities assigned to the PAC include advising and giving suggestions to the FDA Commissioner regarding: (1) paediatric research; (2) the ethics of paediatric therapeutics-related clinical trials; (3) paediatric labelling disputes; and (4) AE reports of paediatric exclusivity given drugs and any potential safety concerns.

The electronic Adverse Event Reporting System (AERS) obtains safety information for these reports. AERS is a computerized database of information intended to support the post-marketing safety monitoring program of the FDA for all licensed drugs and biological therapeutic products. By offering a system for collecting post-marketing AEs, the ultimate aim of AERS is to boost public health. As mandated by law, safety reports are obtained by the FDA from manufacturers as well as from patients and health care professionals. Protection evaluators, medical reviewers, and epidemiologists at the FDA test the AEs submitted to AERS in order to identify safety signals.[18].

5. LEGISLATION GOVERNING PAEDIATRIC PHARMACOVIGILANCE IN US

5.1 BPCA (2002) and PREA (2003)

- **Better Pharmaceuticals for Children Act** within Food and Drug Administration Modernization and Accountability Act (1997)

- **The Best Pharmaceuticals for Children Act (BPCA) (2002)**

    - ✓ Established FDA's Office of Paediatric Therapeutics

    - ✓ The FDA Paediatric Advisory Subcommittee Mandated the Anti-Infective Drugs Advisory Committee to review any adverse case report in the year following the date on which a paediatric medication gains market exclusivity.

- **The Paediatric Research Equity Act (PREA),** codifying the 1998 Paediatric Rule (2003)

    - ✓ Established the PAC

- **The Food and Drug Administration Amendments Act** reauthorized BPCA and PREA until 2012

    - ✓ Gave the FDA clear authority (under BPCA and PREA) to label a child-researched medication, regardless of whether the drug has been shown to be safe and successful in paediatrics.

    - ✓ The adverse event reporting requirement persisted (for BPCA) and extended (to PREA) to the PAC during the one-year period after a labelling change

    - ✓ Extended PAC through October 1, 2012

    - ✓ After studies under PREA and BPCA, extended criteria for

paediatric labelling warranted further PAC analysis.

- **Food and Drug Administration Safety and Innovation Act**

  - ✓ Made BPCA and PREA permanent
  - ✓ Extended PAC permanently
  - ✓ Required BPCA requests to provide a justification for not including neonatal studies for paediatric drug studies if none are requested [9].

The following information is considered by FDA for the post market safety evaluations of paediatric formulation and it assesses several data including:

- The product's pre-approval safety profile
- The product's current FDA-approved label
- Reports made to the FDA Adverse Event Reporting System (FAERS), previously known as AERS
- Reports made to the Vaccine Adverse Event Reporting System (VAERS)
- Manufacturer-submitted periodic safety reports
- Medical literature
- Drug utilization databases
- Data from post-approval clinical trials and other studies, when applicable

Postmarked tests are done 18 months after the approval of the medication or following the use of the drug by 10,000 people, whichever is later. Information is reviewed at the outset and no later than 18 months after approval, scientists from the Office of Surveillance and Epidemiology and the Centre for Drug Evaluation and Research (CDER) of the Office of New Drugs jointly evaluate the relevant data, summarize the results, and, if appropriate, establish a plan to further examine possible new safety concerns for CDER-regulated items. Scientists from the Biostatistics and Epidemiology Office of CBER and the related product office are performing this safety analysis and assessment for medical products regulated by the Centre for Biologics Evaluation and Research (Office of Blood Research and Review, Office of Vaccine Research and Review, or Office of Cellular, Tissue and Gene Therapies) [19].

In addition to these, the FDA will use AERS to diagnose extreme and unusual AEs along with retrospective safety review in previously conducted trials (SSRIs and ADHD medications) and sponsor-completed phase IV safety studies. There are phase 4 safety trials ongoing for many of the products brought even before PAC. While the findings of these studies are still pending, the PAC is made aware of these ongoing studies and is unlikely to call for additional studies. However, during this time span, the PAC can ask for additional follow-up.

The BPCA was mandated to report safety issues related to the use of AERS to the PAC in the 1-year period following the approval of exclusivity. However, the committee found that the data needed more context. In order to ensure that the reports were useful, the BPCA has extended the scope of the reporting to include all indications since the product was originally marketed [20].

6. UNITED KINGDOM (MHRA)

By establishing the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in 2006, the Department of Health recognized the importance of developing medicines and the science of drug safety in children. The assessment of the potential harm of medicinal products is as important as the evaluation of their benefits and is an essential component of the proposals under the European Children's Medicinal Products Regulation and the Children's Pharmacovigilance Guidance. New regulations on pharmacovigilance entered into force across the European Union (EU) in July 2012, including consolidated reporting by the ADR industry to the Surveillance database at the EMA and the incorporation of consumer or patients reports as legitimate, reportable ADRs. The Plan for the Outcomes of Children and Young People (commissioned by the Secretary of State for Health) recognized that there is a need to optimize the safe use of drugs. In 2008, there were 33,000 paediatric safety incidents reported by health care providers to the National Monitoring and Learning System, of which 19 percent were for a drug problem. This contributed to the recommendation report that 'with significant consequences, the MHRA prioritizes the pharmacovigilance of children medicinal products, including prescription errors and off-label use, in accordance with the new EU legislation implemented in July 2012. The responsibility for controlling the safety of medicines in the UK lies with the MHRA. In practice, the compilation and review of ADR reports is vital to the duty of the MHRA to track the protection of medicines: this is done by the

submission of spontaneous reports by health care practitioners of suspicious ADRs and by the general population through the Yellow Card Scheme. In order to provide information on any possible adverse effects encountered by women or children involved with medication taken during pregnancy, the Yellow Card Scheme has been revised [21].

7. AFTER BREXIT

7.1 Transition between reporting to EU and UK systems

Marketing Authorisation Holders (MAHs) will be required, from 1 January 2021, to send ICSRs directly to the United Kingdom, using the systems mentioned above. The EMA forwards UK ICSRs (individual case safety reports) to the MHRA under current monitoring approaches at the time they are processed via the Surveillance framework. Pharmacovigilance will remain the responsibility of the MHRA in the UK. For goods put on the market in the UK with respect to Great Britain and Northern Ireland, there may be several different criteria. England, Wales and Scotland are Great Britain. As a Marketing Authorisation Holder (MAH) for medicinal products approved in Great Britain, you will be required to apply pharmacovigilance data to the MHRA in compliance with UK regulations, including:

- UK and non-UK Individual Case Safety Reports (ICSRs)
- Periodic Safety Update Reports (PSURs)
- Risk Management Plans (RMPs)
- Post-Authorisation Safety Studies (PASS) protocols and final study reports

In order to better promote patient safety in the UK, it will be analysed taking into account all relevant details and decisions will be taken representing UK clinical practice. The GVP modules will remain in effect, but a clarification note on exemptions and changes to the EU Guidance on Good Vigilance Practices will be published in coming days. All UK (including NI) ICSRs (serious and non-serious) and serious ICSRs from other countries will be required to be submitted through the new MHRA Gateway or/ICSR Submissions Portal that has been established.

PSURs for actives/combinations not currently specified in the EURD (European Union Reference Dates) and thus not subject to the Single Assessment Process should be sent to the MHRA at least six months after marketing during the first two years, once a year for the next two years and every three years thereafter. MHRA has created its own submission platform to be available for use from 1 January 2021 onwards for PSURs. It is possible to send PSURs in PDF or Word or as part of a zip file format to the portal. As part of the CTD lifecycle in the UK, PSUR submissions will not be required and should not be submitted as part of the initiating sequence in the central conversion process [22].

For the evaluation of PSURs for active ingredients/combinations currently listed on the EURD (or potential UK reference date list) submitted to the MHRA, a charge of £ 890 will be payable. For any PSUR where more than one PSUR is involved in the process, there will be a reduction to £ 445. The results of the assessment will be published by the MHRA. When there are concerns about a medicine or class of medicines that are licensed in the United Kingdom, the MHRA may conduct a major safety review to evaluate the existing information and decide what regulatory action may be needed [23].

Table 3. Assessment Fees for conducting the safety review [11]

Fees	Type of Pharmaceutical Form
£51,286	where one or two active ingredients or combinations of active ingredients are included
£59,595	where three active ingredients, or combinations of active ingredients, are included
£67,904,	where four active ingredients, or combinations of active ingredients, are included
£76,213	where five or more active ingredients, or combinations of active ingredients, are included

7.2 Japan

Under the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Department (PMDA) has three systems in place to ensure the safety and effectiveness of drugs after approval: a system for reporting adverse events; a system for re-examination using post-approval data; and a system for re-evaluation The Pharmaceutical Affairs Law (PAL) was updated in 2002 with the majority of revisions. The PAL provides information on the GVP and Good Post-Marketing Research Practice (GPSP) criteria, as well as the framework for re-examination and re-evaluation [24].

7.2.1 Challenges related to paediatric drug therapy

An approximate 60-70% of the medications widely administered in paediatric patients would not indicate paediatric dosage and administration in their product inserts (off-label use prescriptions). Therefore, dosage type modification such as crushing tablets produced for adult patients is a standard procedure in paediatric clinical settings. The scientific evaluation of safety and, stability of such preparations has not been adequately validated. Furtherly, information on possible adverse drug effects is obtained by voluntary reporting or use of pharmaceutical company outcome surveys, and the appropriate safety measures are brought in effect. These surveys, however, require substantial costs and it is often difficult to establish timely correlations between the administered medication and events that occur subsequently, even if the events are observed. As an approach to solving these problems, it is important to develop a system that gathers and analyses various cases automatically and exhaustively, including their controls, allowing an initial evaluation of adverse reaction [25].

7.2.2 Creating and maintaining medical information database (Paediatric Medical Data Collecting System)

Since Fiscal Year (FY) 2012, the Network Implementation Project for Collecting Data on Paediatric Drug Safety has developed and maintained a system at the National Centre for Child Health and Development (NCCHD) to collect and analyze safety information in paediatric populations. A database is developed and maintained to collect and centrally monitor data on the names of illnesses, prescription medications, clinical tests (specimen examinations), signs and symptoms in paediatric patients and the environment to enable the study of the data collected. The Network Implementation Project for the Collection of Paediatric Drug Safety Data (System) gathers medical information (data relating to the names of illnesses, medications and injections received, sample test results, etc.) stored in the paediatric medical facility's electronic health record (EHR) as well as questionnaire data completed by consenting patients (or their proxies). By the end of December 2019, 460,000 medical data from patients and 50,000 questionnaire data from patients had been processed and periodically updated in this framework [26].

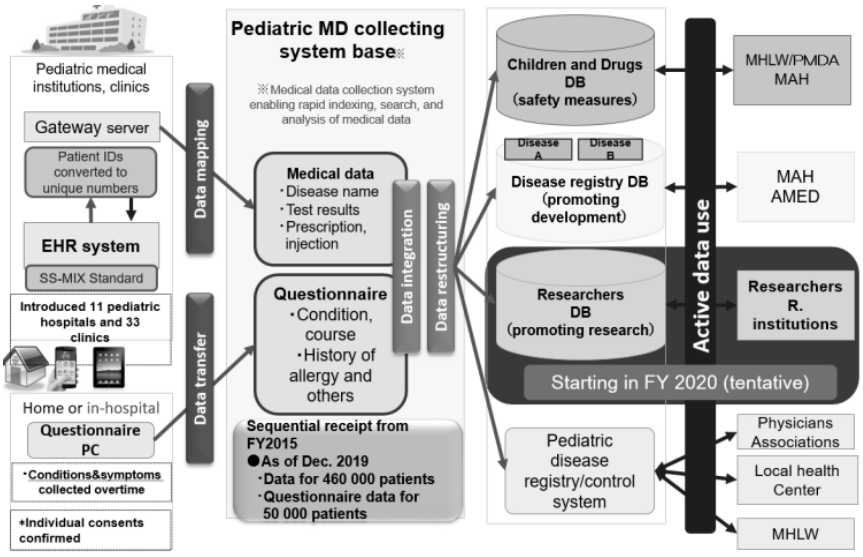

Fig. 2. Paediatric Medical Data Collecting System

The system aims to enhance the clinical development of paediatric patients by a more reliable safety assessment and to encourage the development of the paediatric population through reviewing and evaluating the information gathered by the system. Due to the essence of information treated, patient confidentiality is strictly held in this method. Patients' personal information, such as their names, addresses, postal codes, or telephone numbers, is not received by this method. Actual patient IDs in the system are also not stored. At the conclusion of the NCCHD, the framework is configured to interpret and evaluate the information obtained as data not directly relevant to the patients' confidential details

Objective reactions may occur younger children are more likely to have objective reactions than older children. Also, subjective reactions are more likely to occur in older children [27].

8. INDIA

Back in 1986, under the supervision of the drug controller of India, pharmacovigilance in India was introduced with a standardized ADR monitoring system. In 1998, India joined the WHO's International Drug Monitoring Program. However, it failed to gain full membership due to various factors. In 2005, the program was renamed the Pharmacovigilance Program of India (PvPI). The goal of the PvPI is to safeguard the health of the people of India by ensuring that the use of drugs is conducted in a way that is safe and effective. Through its various programs and centres, the organization has been able to establish a culture of AER. The WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services has now become the IPC-PvPI. Despite these successes, the PvPI faces many challenges, such as the tracking of antidiabetic, cardiovascular and antipsychotic drugs for generic drugs, biosimilars, and disease-specific ADRs and, above all, the creation of awareness, which is an ongoing process. At the same time, other problems, such as counterfeit drugs, antimicrobial resistance and monitoring during mass vaccinations and other national programmes, are being tackled by the PvPI [28].

ADR in children, given their reported 9.5 percent incidence, represent a major health concern. They also account for 2.1% of admissions to hospitals, with 39.3% of them being life-threatening. In order to achieve a benefit-risk balance in paediatric populations, the safety data obtained from clinical trials are incapable of detecting rare or late-onset adverse drug reactions; a complex PV cycle is required to facilitate the knowledge improvement and risks management associated with medicines in children. In paediatric pharmacovigilance, that could be a significant new legislative tool [15].

Some legislative tools for improving pharmacovigilance in paediatric population could be

- Fostering study networks and publishing on ADR in children (including pregnancy),
- to create networks of paediatric use of medicine and pharmacovigilance,
- Piloting new techniques to improve signal detection,
- to work on medication error,
- To develop a collaborative work on worldwide benefit risk [29].

8.1 Obstacles to Reporting of Adverse Reactions in Paediatric Population

There are many factors which interferes with reporting of adverse reactions such as

- Severe lack of understanding and knowledge of the presence, purpose and functioning of ADR monitoring systems and national pharmacovigilance programmes.
- The lack of understanding about the incidence of ADRs is a major barrier seen in many studies. Sometimes, healthcare professionals believe that one case does not add to the information pool.
- Obstacles related to possible disputes have also been reported to impair healthcare professionals' reporting. The management of patients has issues.
- There are logistical challenges, such as the shortage of ADR forms available in hospitals and pharmacies. Pharmacists believe that the data necessary to report the ADR is insufficient.
- Clinicians may lack enthusiasm to report an adverse reaction they are experiencing. This is caused by the fact that extra forms for reporting ADRs are required to be filled in. The perception that handling individual ADRs is more

relevant than reporting them has also been illustrated by some studies [30].

9. SOLUTIONS TO UNDER REPORTING

Inadequacy in the reporting of ADRs inevitably leads to the missing or unduly delaying of certain vital signs in the capture of the lacunae, allowing potentially unsafe drugs to remain on the market and posing a danger to patient care. Basis on available data, including conducted surveys among health care professionals, a range of measures that can be taken to improve the spontaneous system of AER in India are identified.

1. **Nurses and Pharmacist** serves as an outstanding supporting resource for ADR identification and monitoring. It is also important to include pharmacists in ADR reporting along with clinicians, as customers are in regular contact with pharmacists who can provide information that is valuable and accurate.

2. **Patients/Consumers** Participation in monitoring ADR is important. In India, less than 12% of PvPI-reported ICSRs come directly from consumers. There have been positive experiences in nations that have incorporated patients/consumers as reporters.

3. **Improving the availability and design of spontaneous reporting form** Also considered critical is wider access to ADR forms. A study evaluating the quality of various countries' ADR reporting forms showed that the best form was in Malaysia. To enhance the reporting process, it is necessary to harmonize the forms & come up with a comprehensive form.

4. **Tools to enhance the pharmacovigilance system and encourage reporting among clinicians,** In all OPDs and hospital wards, drop boxes have been installed, along with simpler reporting forms. This nearly doubled the frequency in the 3-month cycle of ADR reporting. To produce improved reporting outcomes, such creative approaches can be validated and applied in hospital environments.

5. **Educational interventions and training for health care professionals and medical students** Studies carried out in India have explored ways of enhancing the spontaneous reporting of adverse events. Most participants recommended the implementation of educational programs and a series of continuing medical education (CME) programmes. Targeted outreach projects are obviously able to increase ADR reporting rates among doctor [31].

10. CONCLUSION

In Reviewing the existing procedures it indicates that many efforts have been made to improve the safety of pharmacotherapy in paediatric population relevant to paediatric Pharmacovigilance like promoting the effective monitoring of ADRs in Paediatrics. Methodological initiatives and funding are needed to further encourage this approach. For a study that lacks vital information, such as the names of the suspected drugs and the dates of initiation of treatment and onset of reaction, causality cannot be determined. Most important tools for the reports' quality assessment is the completeness of the study. ADRs may occur in children when they are in/out patients in a health care facility or are provided with community medical care, and while they are taking prescription or OTC medicines. Subsequently, the diagnosis and monitoring of paediatric ADR is also the responsibility of health providers and parents/caregivers. All signs of adverse reactions in patients in this group must be clearly observed by health care providers (infants and children in particular that are unable to communicate effectively). In summary, over the past few years, important progress has been made in the production and availability of effective and secure paediatric medication. However, there is still a long way to go until paediatric pharmacovigilance can be seen as 'grown up'; it is crucial that we don't stop 'moving'.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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