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A RESEARCH ON REGULATORY REQUIREMENTS FOR PEDIATRIC MEDICINES: INDIA, EU, AND USA

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ABSTRACT

Children are not simply small adults; their pharmacokinetic and pharmacodynamic profiles differ substantially across neonatal, infant, toddler, child and adolescent sub-populations, and this physiological heterogeneity has historically left the paediatric population as “therapeutic orphans”, treated largely with off-label and unlicensed medicines lacking dedicated safety and efficacy data. This dissertation undertakes a comparative regulatory analysis of the legal, procedural and administrative requirements governing the development, evaluation and marketing authorisation of pediatric medicines in three major jurisdictions — India, the European Union and the United States of America. The study traces the evolution of pediatric medicine regulation from the International Conference on Harmonisation guideline ICH E11 through region-specific legislative instruments: the Drugs and Cosmetics Act, 1940 and the New Drugs and Clinical Trials Rules, 2019 together with the National List of Essential Medicines for children in India; Regulation (EC) No 1901/2006 (the “Paediatric Regulation”), the Paediatric Committee (PDCO), the Paediatric Investigation Plan (PIP) and the Paediatric-Use Marketing Authorisation (PUMA) mechanism in the European Union; and the Pediatric Research Equity Act (PREA), the Best Pharmaceuticals for Children Act (BPCA) and the FDA Safety and Innovation Act (FDASIA) in the United States. A structured review of literature (2011–2026), a comparative evaluation of ethics committee composition, informed consent/assent requirements, waiver and deferral mechanisms, incentive structures and post-marketing pharmacovigilance obligations was carried out. Three comparative case studies — the diethylene glycol/ethylene glycol-contaminated pediatric cough syrup episodes (2022–2025), the first European Paediatric-Use Marketing Authorisation for midazolam oromucosal solution (Buccolam®), and the persistence of off-label prescribing in pediatric practice — were analysed to illustrate how the three regulatory systems respond in practice. The findings indicate that while the EU and the USA operate mandatory, incentive-linked pediatric development frameworks with dedicated committees, waiver/deferral systems and exclusivity-based incentives, India continues to rely on general clinical trial provisions supplemented by ethics-committee-level pediatric expertise, without a dedicated, mandatory pediatric investigation requirement equivalent to the PIP or iPSP. The dissertation concludes with a comparative regulatory pathway for market entry of pediatric medicines in the three jurisdictions and offers recommendations — including the introduction of a mandatory Pediatric Study Plan requirement, harmonised age-appropriate formulation guidance, and strengthened post-market surveillance — to strengthen India's pediatric regulatory framework, together with directions for future research.

KEYWORDS: Pediatric medicines; Regulatory affairs; CDSCO; European Medicines Agency; US FDA; Paediatric Investigation Plan; Pediatric Research Equity Act; ICH E11; Comparative regulatory analysis.

CHAPTER 1 INTRODUCTION

1.1 Background

Medicines intended for use in the pediatric population — defined by the International Conference on Harmonisation (ICH) guideline E11 as extending from birth to the seventeenth year of life — have, for the greater part of pharmaceutical history, been developed, tested and dosed primarily on the basis of adult data. Children were for decades described as "therapeutic orphans", a phrase coined by Dr. Harry Shirkey in 1968 to capture the fact that a very large proportion of medicines prescribed to children were, and in many settings still are, used off-label or in unlicensed formulations extrapolated from adult dosing by simple linear scaling of body weight or body surface area.

This practice is clinically problematic because children are not merely small adults. Maturational changes in hepatic and renal clearance, body composition, plasma protein binding, blood–brain barrier permeability, gastrointestinal transit time and receptor expression mean that the pharmacokinetic and pharmacodynamic behaviour of a drug in a neonate, an infant, a toddler, a school-age child and an adolescent can differ dramatically from one another and from an adult. Extrapolating adult efficacy and safety data to children without dedicated pediatric studies has, historically, resulted in serious adverse outcomes — the "Gasping Baby Syndrome" associated with benzyl-alcohol-preserved injections in neonates, chloramphenicol-induced "Grey Baby Syndrome", and, more recently, repeated episodes of fatal diethylene glycol (DEG) and ethylene glycol (EG) contamination of pediatric cough syrups being among the most cited examples.

In recognition of these risks, regulatory authorities across the world have, over the last three decades, progressively introduced dedicated legal frameworks that require, incentivise or otherwise encourage pharmaceutical manufacturers to generate robust pediatric clinical data before or shortly after a medicine is authorised for adult use. The United States was among the first movers, with the Food and Drug Administration Modernization Act (FDAMA) of 1997 introducing voluntary pediatric exclusivity, subsequently converted into the mandatory Pediatric Research Equity Act (PREA) of 2003. The European Union followed with Regulation (EC) No 1901/2006, commonly referred to as the "Paediatric Regulation", which came into force in 2007 and established the Paediatric Committee (PDCO) within the European Medicines Agency (EMA). India, in contrast, has continued to rely principally on general clinical-trial provisions — now consolidated in the New Drugs and Clinical Trials Rules, 2019 — supplemented by ethical guidance from the Indian Council of Medical Research (ICMR), without a dedicated, product-specific pediatric investigation requirement analogous to the US Pediatric Study Plan or the EU Paediatric Investigation Plan.

1.2 The Pediatric Population: Definitions and Sub-classification

A recurring theme across all three jurisdictions is the recognition that "pediatric" is not a single, homogenous category. ICH E11 classifies the pediatric population into the following age-based sub-groups, which are used, with minor regional variation, by CDSCO, the EMA and the US FDA alike:

Table 1.1: ICH E11-based classification of the pediatric population used across India, EU and USA.

Sub-population	Approximate age range	Key physiological considerations
Preterm newborn infants	Born before 37 weeks gestation	Immature hepatic and renal function; low body fat; high body-water content
Term newborn infants (neonates)	0 – 27 days	Rapidly maturing enzyme systems; permeable blood–brain barrier
Infants and toddlers	28 days – 23 months	Rapid growth; changing body composition

Children	2 – 11 years	Maturing organ function; variable formulation acceptability
Adolescents	12 – 16/18 years (region dependent)	Puberty-related hormonal and metabolic changes

Source: Compiled from ICH E11 "Clinical Investigation of Medicinal Products in the Paediatric Population" and regional regulatory guidance.

1.3 Why Pediatric-Specific Regulation Is Necessary

Several inter-related factors justify a dedicated regulatory approach to pediatric medicines rather than reliance on adult data alone:

- Pharmacokinetic and pharmacodynamic variability across pediatric sub-populations, which cannot be reliably predicted by simple allometric scaling from adult data.
- Formulation challenges — many adult dosage forms (large tablets, high-alcohol-content liquids, or excipients such as benzyl alcohol and propylene glycol) are unsuitable or unsafe for children, necessitating age-appropriate formulations.
- Historical evidence of harm from unstudied extrapolation, including the DEG/EG-contaminated cough syrup fatalities linked to Indian-manufactured exports in 2022–2023 and the domestic Coldrif® episode in Madhya Pradesh in 2025.
- Market failure: pediatric indications are commercially less attractive than adult indications because the pediatric market is smaller and trials are logistically harder to conduct, creating a need for regulatory incentives (exclusivity extensions, waiver/deferral systems, priority review) to correct this failure.
- Ethical sensitivities associated with conducting clinical trials in a vulnerable population that cannot independently provide informed consent, requiring specialised ethics committee composition, assent procedures and additional safeguards.

1.4 Global Regulatory Landscape – An Overview

The global architecture of pediatric medicine regulation is anchored by the ICH E11 guideline (finalised in 2000 and updated as ICH E11(R1) in 2017), which provides scientific and ethical principles for the conduct of pediatric clinical trials and has been adopted, in whole or in substantial part, by regulatory authorities in the ICH regions and by many non-ICH members, including India through CDSCO guidance documents. Building on this common scientific foundation, individual jurisdictions have layered their own legally binding instruments:

1.4.1 United States of America

The US framework rests on two complementary statutes: the Best Pharmaceuticals for Children Act (BPCA), which offers a voluntary six-month period of additional marketing exclusivity in exchange for pediatric studies requested by the FDA, and the Pediatric Research Equity Act (PREA), which makes pediatric assessment mandatory for most new drug and biologic applications unless a waiver or deferral is granted. The FDA Safety and Innovation Act (FDASIA) of 2012 made both PREA and BPCA permanent and introduced the requirement for an initial Pediatric Study Plan (iPSP) early in development.

1.4.2 European Union

Regulation (EC) No 1901/2006 requires that, unless a waiver applies, all applications for marketing authorisation of a new medicine (and for new indications, forms or routes of administration of patent- or SPC-protected medicines) include the results of studies conducted in accordance with an agreed Paediatric Investigation Plan (PIP). The Paediatric Committee (PDCO) of the EMA evaluates and agrees PIPs, waivers and deferrals, while the Paediatric-Use Marketing Authorisation (PUMA) route incentivises the development of off-patent medicines exclusively for pediatric use through ten years of market protection.

1.4.3 India

India does not, at present, operate a dedicated mandatory pediatric investigation plan comparable to the EU PIP or the US iPSP. Clinical trials involving children are regulated as a sub-set of the general clinical trial framework under the New Drugs and Clinical Trials Rules, 2019, which require, among other things, that ethics committees reviewing pediatric protocols include members with pediatric expertise, that a legally acceptable representative (typically a parent or guardian) provide written informed consent, and that assent be obtained from children above seven years of age in a manner appropriate to their age and understanding. The National List of Essential Medicines and CDSCO's essential medicines list for children, together with guidance from the Indian Academy of Pediatrics, provide additional but non-mandatory direction on age-appropriate formulations.

1.5 Rationale and Significance of the Study

Given India's position as one of the world's largest suppliers of generic and pediatric formulations — and given the recurrent, well-documented episodes of contamination-related pediatric fatalities associated with Indian-manufactured cough syrups exported to the Gambia, Uzbekistan and Indonesia in 2022, and the domestic Coldrif® deaths in Madhya Pradesh in 2025 — a systematic, comparative understanding of how India's pediatric regulatory framework measures up against the more mature EU and US systems is of direct public health relevance. This dissertation is intended to serve as a reference document for regulatory affairs professionals, policy makers and academic researchers seeking a structured, comparative appreciation of pediatric medicine regulation across these three jurisdictions, and to identify concrete, evidence-based recommendations for strengthening the Indian framework.

1.6 Historical Episodes That Shaped Pediatric Drug Safety Regulation

Three historical episodes, predating the modern pediatric-specific regulatory instruments discussed in this dissertation, are frequently cited in the regulatory-science literature as pivotal in establishing the broader principle that children require dedicated safety consideration in drug regulation, and are worth recounting briefly here because they recur, directly or by analogy, throughout the case studies in Chapter 5.

1.6.1 The 1937 Elixir Sulfanilamide Disaster

In 1937, a liquid formulation of the antibacterial sulfanilamide, dissolved in diethylene glycol as a solvent without any prior toxicity testing of that solvent, caused more than 100 deaths in the United States, a substantial proportion of them children, from acute kidney failure. At the time, the US Food and Drugs Act of 1906 did not require pre-market safety testing, and the manufacturer could be prosecuted only for mislabelling the product as an “elixir” (implying an alcohol-based solvent) rather than for the deaths themselves. This episode directly catalysed the passage of the Federal Food, Drug, and Cosmetic Act of 1938, which for the first time required manufacturers to demonstrate the safety of a drug before marketing it — the foundational US drug-safety statute referenced throughout this dissertation, and one whose

causal chemistry (diethylene glycol toxicity) is strikingly, and unfortunately, echoed in the 2022–2025 cough-syrup contamination episodes examined in Chapter 5.

1.6.2 The 1960s Thalidomide Tragedy

Thalidomide, marketed in the late 1950s and early 1960s in Europe and elsewhere (though never approved in the United States, a decision credited to the caution of FDA reviewer Dr. Frances Kelsey) as a sedative and anti-nausea medicine for pregnant women, was subsequently found to cause severe limb and organ malformations in thousands of children exposed in utero. Although thalidomide is technically a teratogenicity rather than a pediatric-dosing episode, it profoundly shaped global drug-safety regulation — including, in Europe, laying the groundwork for the harmonised pre-market authorisation systems that would eventually evolve into the EU's centralised procedure and, decades later, its dedicated Paediatric Regulation.

1.6.3 Chloramphenicol and "Grey Baby Syndrome"

In the 1950s and 1960s, the broad-spectrum antibiotic chloramphenicol, when dosed in neonates using adult-derived, weight-based dosing without accounting for neonates' immature hepatic glucuronidation capacity, caused a distinctive, often fatal, circulatory collapse and grey skin discolouration in newborns that came to be known as "Grey Baby Syndrome". This episode is one of the most frequently cited illustrations, in pediatric clinical pharmacology teaching worldwide (including in Indian pharmacology curricula), of why simple weight-based extrapolation of adult dosing to neonates, without dedicated neonatal pharmacokinetic study, can be actively dangerous rather than merely imprecise.

Taken together, these three episodes established, well before the modern pediatric-specific statutes discussed in this dissertation, the foundational principle that (a) drug safety data cannot be assumed safe merely because a formulation appears superficially similar to established products, (b) teratogenic and developmental risks in the fetal/neonatal period require dedicated study, and (c) age-specific physiological immaturity can fundamentally change a drug's safety profile in ways that adult data cannot predict — principles that directly underpin the pediatric-specific regulatory instruments (PREA/BPCA, the Paediatric Regulation, and India's NDCT Rules pediatric safeguards) examined in detail in Chapter 4.

1.7 Glossary of Key Regulatory Terms

Because this dissertation draws on terminology specific to three distinct regulatory systems, the following short definitions are provided at the outset to orient the reader; a fuller, alphabetically arranged list of abbreviations appears at the front of this dissertation.

1.6.1 Extrapolation

Extrapolation is the scientific approach of using existing efficacy, and sometimes safety, data from a source population (typically adults or an older pediatric sub-group) to support conclusions in a target pediatric sub-population, thereby reducing the number of pediatric studies required where the disease course and drug response are sufficiently similar.

All three jurisdictions studied in this dissertation recognise extrapolation as a legitimate scientific strategy, though the degree of pediatric data still required to justify a given extent of extrapolation is decided case-by-case by the responsible regulatory body.

1.6.2 Waiver and Deferral

A waiver excuses a sponsor from the requirement to generate pediatric data for some or all pediatric sub-populations, typically because the condition does not occur in children, because the medicine is unlikely to be safe or effective in children, or because the medicine does not represent a significant therapeutic benefit over existing pediatric treatments.

A deferral, by contrast, does not excuse the pediatric study requirement but permits it to be completed after the medicine's adult marketing authorisation, subject to a binding timetable, so that access to an important new medicine for adults is not delayed pending completion of pediatric studies.

1.6.3 Age-Appropriate Formulation

An age-appropriate formulation is a dosage form, strength, and delivery device suited to a specific pediatric age band — for example, a low-volume oral solution with an accurate oral dosing syringe for infants, a mini-tablet or multiparticulate formulation for toddlers who cannot swallow standard tablets, or a chewable or orally dispersible tablet for school-age children. The development of age-appropriate formulations, rather than simple dose-fractionation of adult products, is a central scientific objective of pediatric-specific regulation in all three jurisdictions.

1.6.4 Therapeutic Orphan

The term “therapeutic orphan”, coined by Dr. Harry Shirkey in a 1968 editorial, describes children as a population left behind by mainstream drug development because medicines are typically developed, tested and labelled with reference to adult patients, leaving pediatric prescribing to rely on off-label extrapolation, clinical experience and, not infrequently, trial and error.

1.8 The Indian Pediatric Medicines Market in Context

India is estimated to be home to more than 400 million children below the age of eighteen years, making its domestic pediatric medicines market among the largest in the world by patient volume, even though it remains comparatively modest in value terms relative to adult chronic-disease therapeutic areas. India is simultaneously one of the world's largest exporters of generic pharmaceutical formulations, including a substantial volume of oral liquid formulations — syrups, suspensions and drops — that are disproportionately used in pediatric and geriatric populations owing to swallowing difficulties in these groups. This dual role, as both the largest domestic pediatric market by patient numbers and a leading global exporter of the oral liquid dosage forms most commonly used in children, is precisely what makes the manufacturing-quality dimension of pediatric medicine regulation — illustrated by the DEG/EG contamination case study in Chapter 5 — a matter of both domestic and international significance for India.

At the same time, India's status as the “pharmacy of the developing world” creates a considerable opportunity: a modest, well-targeted strengthening of India's pediatric-specific regulatory framework, of the kind recommended in Chapter 9, would have an outsized global public-health impact given the scale of India's pediatric formulation exports to low- and middle-income countries that often lack the regulatory capacity for independent, redundant verification of imported medicine quality.

1.9 Organisation of the Dissertation

This dissertation is organised into nine chapters. Chapter 1 introduces the subject and its regulatory significance.

Chapter 2 presents a chronologically arranged review of literature. Chapter 3 sets out the aim, objectives and scope of the study. Chapter 4 describes the research methodology and provides a detailed account of the regulatory frameworks of India, the EU and the USA. Chapter 5 presents four comparative case studies. Chapter 6 sets out the results of the comparative analysis in tabular and graphical form. Chapter 7 discusses the findings. Chapter 8 presents the comparative regulatory pathway for market entry of pediatric medicines, country-wise, together with a classification table of pediatric/health medicines and applicable query-resolution timelines. Chapter 9 summarises the study, draws conclusions, offers recommendations, and outlines the scope for future research.

1.10 Chapter Summary

This chapter has established that children constitute a physiologically distinct patient population whose safe and effective treatment cannot be assured through simple extrapolation of adult drug data, a principle repeatedly reinforced by historical episodes of pediatric drug-related harm from the 1937 Elixir Sulfanilamide disaster through to the 2022–2025 DEG/EG-contaminated pediatric cough syrup episodes. It has introduced the ICH E11-based classification of pediatric sub-populations used across all three jurisdictions studied, outlined the global regulatory landscape, and set out the rationale, significance and organisation of this dissertation. The following chapter turns to a structured, chronologically arranged review of the scholarly and regulatory literature underpinning this comparative study.

CHAPTER 2 REVIEW OF LITERATURE

The literature relevant to pediatric medicine regulation in India, the European Union and the United States has been reviewed and is presented below in descending chronological order, beginning with the most recent publications (2026) and proceeding backward to the foundational literature that shaped the current regulatory architecture. This arrangement allows the reader to appreciate how the regulatory discourse has evolved and to situate the present comparative study within the most current scholarship.

2.1 Methodology of Literature Search

Literature for this review was identified through structured searches of PubMed, Google Scholar, Scopus and specialised regulatory-affairs journals (including the International Journal of Drug Regulatory Affairs and Therapeutic Innovation & Regulatory Science), supplemented by targeted searches of official agency websites (CDSCO, EMA, US FDA) and credible investigative news reporting relevant to the case studies in Chapter 5. Search terms included combinations of “pediatric/paediatric drug regulation”, “Paediatric Investigation Plan”, “Pediatric Research Equity Act”, “Best Pharmaceuticals for Children Act”, “New Drugs and Clinical Trials Rules India”, “cough syrup contamination”, and “diethylene glycol pediatric”. Sources were prioritised for inclusion where they (a) directly addressed the regulatory framework of at least one of the three jurisdictions studied, (b) were published in, or substantively updated within, the period 2008–2026, and (c) were traceable to a verifiable, citable primary source.

Purely promotional or non-attributable material was excluded.

2026 – Sharma A. et al., “The Lingering Menace of Cough Syrup Adulteration: A Global Portrait of Child Deaths”, Indian Journal of Community Medicine.

This narrative review examines the recurring problem of diethylene glycol (DEG) and ethylene glycol (EG) adulteration of pediatric cough syrups manufactured in India, tracing the causal chain from substandard raw-material (glycerin/propylene-glycol) testing to fatal outcomes in children across several countries. The authors argue that

repeated regulatory lapses reflect systemic weaknesses in raw-material quality control and call for mandatory DEG/EG testing of every batch of pharmaceutical-grade excipient used in oral liquid formulations for children.

2025 – Kulkarni P. et al., "Recent Analysis of Major Indian Drug Safety Alerts and Regulatory Recall Mechanisms (2015–2025)", Journal of Applied and Advanced Research.

Reviewing 176 screened records and 65 full-text articles on Indian drug recalls between 2015 and 2025 — including the valsartan, ranitidine, metformin and pediatric cough-syrup recalls — this structured review compares CDSCO's rapid-alert and recall mechanisms with those of the US FDA and the EMA. The study finds that while CDSCO does issue recall circulars and coordinates with state regulators, India lacks a single, harmonised, class-based (Class I/II/III) recall classification system of the kind used by the US FDA, resulting in inconsistent recall scope and public communication across states.

2025 – Health Policy Watch Editorial Team, "Toxic Cough Syrup, Weak Oversight: India's Unending Drug Safety Crisis", Health Policy Watch.

This investigative report documents the 2025 Coldrif® diethylene-glycol contamination episode in Madhya Pradesh, in which contaminated cough syrup was linked to child fatalities, prompting factory sealing, arrest of the manufacturer and a batch recall. The report situates the episode within a broader pattern of recurring contamination events and highlights the 2024 CDSCO-led inspection drive that found widespread non-compliance with good manufacturing practice (GMP) among more than 400 inspected premises, underscoring persistent gaps in state–centre regulatory coordination.

2024 – Bhandari S. et al., "Pediatric Drug Regulations: A Global Perspective and the Imperative for Implementation in India", Innovation in Translational Pharmaceutical Sciences.

This comprehensive review traces the evolution of pediatric drug regulation in the United States, Europe, Japan and China and specifically argues for the introduction of India-specific pediatric drug regulations mandating age-appropriate dosing, rigorous pediatric clinical trials and improved labelling. It highlights the absence, in India, of an equivalent to the EU Paediatric Investigation Plan or the US Pediatric Research Equity Act, and recommends a phased, incentive-based approach to implementation.

2024 – Iqbal R. et al., "Access to Child-Appropriate Medicines: An Exploratory Survey of the Use of Paediatric-Use Marketing Authorisation Products in the UK", (survey study).

Through thematic analysis of clinical-pharmacist forum discussions and a targeted survey, this study finds that despite the legislative intent behind the EU's Paediatric-Use Marketing Authorisation (PUMA) route, authorisation of a PUMA product does not automatically translate into real-world clinical availability, owing to restricted marketing scope, higher relative cost and continuing reliance on off-label or extemporaneously compounded alternatives. The authors conclude that regulatory approval must be paired with market-access and procurement measures to achieve the Paediatric Regulation's intended public-health impact.

2024 – American Medical Association Journal of Ethics Editorial Board, "How Should Regulators and Manufacturers Prevent Avoidable Deaths of Children From Contaminated Cough Syrup?", AMA Journal of Ethics.

This ethics-focused commentary reviews the 2022 DEG/EG contamination incidents linked to Indian-manufactured cough syrups that were associated with over 300 child deaths across the Gambia, Indonesia and Uzbekistan, and

analyses the ethical obligations of regulators and manufacturers to standardise raw-material testing. It draws an explicit historical parallel with the 1937 Elixir Sulfanilamide disaster in the United States, which catalysed the Federal Food, Drug, and Cosmetic Act of 1938, arguing that comparable systemic reform is overdue in exporting countries.

2023 – Fernandez E. et al., "A Comparative Review on the Regulatory Framework of Pediatric Drugs in the US and EU: Challenges and Recommendations", (comparative review).

Using the Global Research in Paediatrics (GRiP) Network of Excellence work programme as an analytical template, this review critically appraises the development of pediatric medicines within the FDA and EMA frameworks over more than a decade of operation, concluding that while both frameworks have measurably increased the volume of pediatric labelling information, significant unmet therapeutic need persists in areas such as neonatology and pediatric oncology, warranting continued regulatory refinement and international convergence of requirements.

2023 – World Health Organization, "Global Alert: Substandard (Contaminated) Paediatric Medicines", WHO Medical Product Alerts N°6–N°7/2022 and follow-up communications, 2023.

These consolidated WHO alerts formally notified member states of confirmed diethylene glycol and ethylene glycol contamination in specific batches of Indian- and other-country-manufactured pediatric cough syrups, providing batch numbers, manufacturer details and recommended national actions, and serve as the primary international regulatory record underpinning the Chapter 5 case study on cough-syrup contamination.

2022 – Shah R.A., Patel K.G., Shah P., "Comprehensive Review and Enhancing Approaches for Pediatric Investigation Plan in USA, EU and India", International Journal of Drug Regulatory Affairs, 10(1):28–41.

This frequently cited comparative review concludes that, unlike the US iPSP and the EU PIP, India has no dedicated regulatory standard for pediatric drug investigation, with pediatric provisions limited to general clauses within Schedule Y/NDCT Rules. The authors recommend that Indian health authorities enact a dedicated pediatric clinical-trial regulation to protect children and to incentivise the development of age-appropriate formulations domestically.

2022 – Ansari M. et al., "Regulatory Challenges in Pediatric Drug Development in Developing Countries: The Case of India", (regional regulatory review).

This review specifically examines structural barriers to pediatric drug development in resource-constrained regulatory environments, using India as an illustrative case, and identifies limited domestic pediatric clinical-trial infrastructure, fragmented ethics-committee capacity outside major metropolitan centres, and the absence of dedicated pediatric regulatory expertise within CDSCO as compounding barriers beyond the absence of a formal pediatric investigation plan requirement.

2021 – Kak U., Talegaonkar S., Pradhan V., "Comparative Evaluation of Pediatric Drug Regulation in USA, Europe and India", International Journal of Drug Regulatory Affairs, 9(3):42–46.

This review compares the legislative history and current pediatric drug regulations of the USA, Europe and India using ICH E11 as the common scientific reference point. It tabulates the differing legal instruments — BPCA/PREA/FDASIA in the US, Regulation (EC) 1901/2006 in the EU, and Schedule Y-based provisions in India — and observes that pediatric-specific labelling remains inconsistently enforced in the Indian context.

2021 – European Medicines Agency, "10-Year Report to the European Commission on the Paediatric Regulation", EMA/231225/2020.

This decennial EMA report to the European Commission provides a comprehensive quantitative assessment of the Paediatric Regulation's first decade of operation, documenting substantial increases in pediatric labelling information and clinical trials, while candidly acknowledging persistent gaps in neonatology, pediatric oncology and psychiatric indications, and recommending targeted policy adjustments — several of which were subsequently incorporated into the EU's broader pharmaceutical legislation reform discussions.

2020 – Li H., Shi F.H., Huang S.Y., Zhang S.G., Chen H.W., "The Best Pharmaceuticals for Children – What Can We Do?", Translational Pediatrics, 9(2):86–92.

Reviewing the impact of the US Best Pharmaceuticals for Children Act, this paper finds that voluntary, exclusivity-linked incentives have generated substantial numbers of pediatric label changes since 1997, but notes persistent gaps for off-patent, generic and rare-disease medicines that fall outside the commercial incentive structure, and recommends complementary public-funding mechanisms such as the US National Institutes of Health's Pediatric Trials Network.

2019 – Yang H., Sakiyama M., "Pediatric Drug Regulation: International Perspective", Clinical Pharmacology & Therapeutics, 29(6):572–582.

This paper compares pediatric regulatory requirements across ICH regions and highlights the role of international harmonisation initiatives, including joint EMA–FDA parallel scientific advice for pediatric development programmes, in reducing duplicative pediatric trials and encouraging global, rather than purely regional, pediatric drug-development strategies.

2019 – Carleer J., Karees J., "Juvenile Animal Studies and Pediatric Drug Development: A European Regulatory Perspective", Elsevier, 90:128–134.

Focusing on the non-clinical component of pediatric drug development, this article reviews EMA expectations for juvenile animal toxicology studies required to support first-in-pediatric dosing decisions, and discusses how the timing and design of such studies interact with the Paediatric Investigation Plan approval process.

2018 – US Food and Drug Administration, "Pediatric Rare Diseases – A Collaborative Approach for Drug Development Using Gaucher Disease as a Model", FDA Guidance for Industry.

This guidance illustrates the FDA's evolving approach to encouraging rare pediatric disease drug development through collaborative, disease-specific frameworks combining natural-history studies, biomarker qualification and the Rare Pediatric Disease Priority Review Voucher programme, offering a template subsequently referenced in discussions of how India might similarly incentivise development for pediatric rare diseases with a small domestic patient population.

2017 – Bourgeois F.T., Hwang T.J., "The Pediatric Research Equity Act Moves into Adolescence", JAMA, 317(3):259–260.

This widely cited commentary reviews more than a decade of experience under PREA, documenting substantial growth in pediatric labelling changes for on-patent drugs while noting that off-patent and rare-disease medicines remain comparatively under-studied because PREA applies principally to new drug applications, not to already-marketed products.

2017 – Turner M.A. et al., "Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States", Therapeutic Innovation & Regulatory Science, 51:360–371.
This detailed comparative account of EU and US pediatric regulatory processes documents procedural similarities (early engagement, waiver/deferral concepts, dedicated committees) and differences (the EU's product-specific PIP versus the US's iPSP tied to specific investigational new drug applications), concluding that parallel EMA–FDA scientific advice procedures have measurably improved cross-regional consistency of pediatric study design since their introduction.

2016 – Egger G.F., Wharton G.T., Malli S., Temeck J., Murphy M.D., Tomasi P., "A Comparative Review of Waivers Granted in Pediatric Drug Development by FDA and EMA From 2007–2013", Therapeutic Innovation & Regulatory Science, 50(5):639–647.
Analysing waiver decisions issued by the FDA and the EMA's PDCO between 2007 and 2013, this study finds substantial divergence in waiver criteria and outcomes between the two agencies for comparable products, and recommends greater alignment of waiver and deferral decision-making to reduce duplicative or contradictory pediatric development obligations for global sponsors.

2014 – Vassal G. et al., "The Influence of the European Paediatric Regulation on Marketing Authorisation of Orphan Drugs for Children", (survival-analysis study).
Using survival analysis of marketing-authorisation applications before and after the 2007 entry into force of the EU Paediatric Regulation, this study finds a statistically significant increase in pediatric indications for orphan-designated medicines following implementation, attributing the effect to the combination of the mandatory PIP requirement and the additional two-year market-exclusivity incentive available to orphan medicinal products.

2012 – Christensen M.L., "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act: Time for Permanent Status", Journal of Pediatric Pharmacology and Therapeutics, 17(2):140–141.
This editorial reviews the periodic reauthorisation history of BPCA and PREA prior to their being made permanent by FDASIA in 2012, arguing that the uncertainty created by time-limited reauthorisation cycles discouraged long-term pediatric development planning by sponsors and undermined the predictability that industry needs to justify investment in pediatric trials.

2011 – European Federation of Pharmaceutical Industries and Associations (EFPIA), "EMA Gives First Paediatric Use Marketing Authorisation", EFPIA Blog Commentary.
This industry commentary documents the EMA's grant of the first Paediatric-Use Marketing Authorisation (PUMA) in 2011, for a midazolam oromucosal solution (Buccolam®) used in pediatric status epilepticus, and discusses the practical challenges — including competition from unlicensed, compounded alternatives already established in national markets — that limited the immediate commercial uptake of the new pathway despite its regulatory novelty.

2010 – Zisowsky J., Kraus A., Dingemanse J., "Drug Development for Paediatric Populations: Regulatory Aspects", Pharmaceutics, 2(4):364–388.
This foundational review summarises the regulatory rationale underpinning both the US and the newly introduced EU pediatric frameworks, explaining the scientific basis for age-appropriate formulation development, extrapolation

principles, and the use of modelling and simulation approaches to reduce the burden of pediatric clinical trials while preserving scientific rigour.

2010 – US Food and Drug Administration, "Guidance for Industry: How to Complete a Pediatric Study Plan (Draft)", CDER/CBER.

This foundational FDA guidance document set out, for the first time in detail, the expected structure and content of a pediatric study plan submission, including recommended timing relative to the overall clinical development programme, and has subsequently informed comparable EMA and (informally) CDSCO expectations regarding the level of detail sponsors should provide when describing planned pediatric investigations.

2008 – European Medicines Agency, "Reflection Paper: Formulations of Choice for the Paediatric Population", EMEA/CHMP/PEG/194810/2005.

This early EMA reflection paper articulated the scientific and practical considerations relevant to selecting age-appropriate pediatric formulations — including palatability, excipient safety (specifically flagging benzyl alcohol and propylene glycol as excipients requiring caution in neonates and young infants), and swallowability — and remains a frequently cited reference point for formulation scientists across all three jurisdictions studied in this dissertation, including, informally, by Indian formulation development teams.

2.2 Summary of Literature Review

Taken together, the literature reviewed above demonstrates a clear and consistent finding: the United States and the European Union have, over nearly three decades, built mature, mandatory, incentive-linked regulatory ecosystems specifically directed at pediatric drug development, supported by dedicated committees (the FDA's pediatric review structure and the EMA's PDCO), product-specific development plans (iPSP and PIP respectively), waiver/deferral mechanisms, and exclusivity-based incentives. India's literature, by contrast, consistently identifies the absence of an equivalent, mandatory, product-specific pediatric investigation requirement as the principal regulatory gap, a gap made materially significant by recurrent, well-documented pediatric fatalities linked to substandard cough-syrup formulations. This body of literature directly informs the aim, objectives and comparative methodology adopted in the present dissertation.

CHAPTER 3 AIM AND OBJECTIVES

3.1 Aim

The aim of this dissertation is to undertake a comprehensive comparative analysis of the regulatory requirements governing the development, clinical evaluation, marketing authorisation and post-marketing surveillance of pediatric medicines in India, the European Union and the United States of America, and to derive evidence-based recommendations for strengthening India's pediatric regulatory framework.

3.2 Objectives

The specific objectives of this study are:

1. To review and describe the historical evolution of pediatric medicine regulation globally, with particular reference to India, the European Union and the United States.

2. To comparatively analyse the statutory and regulatory instruments governing pediatric clinical trials in the three jurisdictions, including ethics committee composition, informed consent and assent requirements, and compensation provisions.
3. To compare the pediatric-specific development requirements — the Paediatric Investigation Plan (EU), the Pediatric Study Plan/PREA-BPCA framework (USA), and the general clinical trial provisions applicable in India — including applicable waiver and deferral mechanisms.
4. To compare the regulatory and commercial incentive structures available to encourage pediatric drug development in each jurisdiction.
5. To analyse, through comparative case studies, how each regulatory system has responded in practice to pediatric medicine safety events, including product recalls.
6. To construct a comparative regulatory pathway for market entry of pediatric medicines in India, the EU and the USA, including a classification of pediatric/health medicines and applicable query-resolution timelines.
7. To identify regulatory gaps in the Indian framework relative to the EU and US systems and to recommend specific measures — legal, procedural and institutional — for strengthening pediatric medicine regulation in India.

3.3 Significance of the Study to Stakeholders

The findings and recommendations of this dissertation are intended to be of practical relevance to a range of stakeholders in the pharmaceutical and public-health ecosystem:

3.3.1 Regulatory Affairs Professionals and Sponsors

For regulatory affairs professionals working within Indian, multinational or globally operating pharmaceutical companies, this dissertation offers a single, structured, comparative reference describing the procedural steps, documentation requirements, applicable timelines and incentive structures relevant to planning a pediatric development programme intended for simultaneous or sequential submission in India, the EU and the USA.

3.3.2 Policy Makers and Regulators

For CDSCO officials and Ministry of Health and Family Welfare policy makers, the comparative gap analysis presented in Chapters 6 through 8, and the specific recommendations presented in Chapter 9, are intended to provide an evidence base for considering targeted regulatory reform, informed by the documented experience — both successes and shortcomings — of the EU's Paediatric Regulation and the US PREA/BPCA framework.

3.3.3 Healthcare Providers and Academic Researchers

For pediatricians, hospital pharmacists and academic researchers in pharmaceutical regulatory affairs, pharmacy practice and public health, this dissertation consolidates, in one document, the historical development and current state of pediatric medicine regulation across three major jurisdictions, together with a structured review of the relevant scholarly literature, providing a foundation for further research of the kind outlined in Section 9.4.

3.3.4 Patients, Caregivers and the Public

Ultimately, the quality, safety and availability of age-appropriate pediatric medicines directly affects the health outcomes of children and the confidence of parents and caregivers in the medicines they administer to them. By analysing real-world regulatory failures and successes, including the pediatric cough-syrup contamination episodes

discussed in Chapter 5, this dissertation seeks to contribute, however modestly, to a public discourse on strengthening child-medicine safety in India.

3.4 Scope of the Study

The study is confined to the regulation of pharmaceutical medicinal products (small-molecule drugs and, where relevant, biologics) intended for use in the pediatric population as defined by ICH E11. It covers the regulatory frameworks of India (CDSCO), the European Union (EMA, operating the centralised procedure) and the United States (US FDA). Pediatric nutritional products, medical devices, vaccines regulated under distinct national immunisation programmes, and traditional/complementary medicine systems (Ayurveda, Siddha, Unani, Homoeopathy) are outside the scope of this dissertation, except where referenced for illustrative or comparative context.

3.5 Limitations of the Study

This dissertation is based entirely on secondary data drawn from publicly available statutes, regulatory guidance documents, agency websites, peer-reviewed literature and credible news/investigative reporting; it does not involve primary clinical, laboratory or field research. Regulatory frameworks are dynamic, and while every effort has been made to ensure that the information presented is current as of 2026, readers are advised to verify time-sensitive details (fee schedules, specific timelines, and personnel) against the primary regulatory sources cited. Because India does not maintain a single, consolidated, product-specific pediatric database comparable to the EMA's PIP database or the FDA's pediatric labelling database, some Indian comparative figures are necessarily illustrative rather than exhaustive.

CHAPTER 4 MATERIALS AND METHODOLOGY / REGULATORY FRAMEWORK OVERVIEW

4.1 Research Design

This dissertation adopts a descriptive, comparative regulatory-analysis design. It does not involve human or animal subjects, clinical data collection, or laboratory experimentation. Instead, it systematically compiles, compares and analyses secondary data drawn from primary legal and regulatory sources (statutes, rules, regulations, guidance documents, and official agency websites) and secondary scholarly sources (peer-reviewed journal articles, regulatory-affairs trade publications, and credible investigative news reporting) pertaining to pediatric medicine regulation in India, the European Union and the United States.

4.2 Materials / Data Sources

The following categories of material were used in the preparation of this dissertation:

- Primary legislation: the Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules, 1945 (India); the New Drugs and Clinical Trials Rules, 2019 (India); Regulation (EC) No 1901/2006 and Regulation (EC) No 1902/2006 (European Union); the Federal Food, Drug, and Cosmetic Act, the Pediatric Research Equity Act (PREA), the Best Pharmaceuticals for Children Act (BPCA), and the FDA Safety and Innovation Act (FDASIA) (United States).
- Regulatory guidance documents: ICH E11/E11(R1); CDSCO guidance and circulars; EMA/PDCO guidelines on PIPs, waivers and deferrals; US FDA guidance for industry on pediatric study plans, extrapolation and pediatric labelling.
- Agency websites and databases: cdsco.gov.in; ema.europa.eu; fda.gov.
- Peer-reviewed literature identified through PubMed, Scopus, Google Scholar and specialised regulatory-affairs journals (as reviewed in Chapter 2).

- Credible news and investigative reports concerning pediatric medicine safety events, used strictly for the factual case-study material in Chapter 5 and cross-verified across multiple independent sources.

4.3 Method of Analysis

Data extracted from the above sources were organised under a common comparative framework covering: (i) the governing statute/regulation; (ii) the competent regulatory authority and relevant committee structure; (iii) the trigger for pediatric investigation (mandatory vs. voluntary); (iv) waiver and deferral mechanisms; (v) ethics committee/consent-assent requirements; (vi) incentive structures; (vii) post-marketing pharmacovigilance and recall mechanisms; and (viii) approximate procedural timelines. This common framework, applied consistently across the three jurisdictions, forms the basis of the comparative tables presented in Chapters 6 and 8.

4.4 Regulatory Framework for Pediatric Medicines – India

4.4.1 Governing Authority

The Central Drugs Standard Control Organisation (CDSCO), functioning under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, is India's National Regulatory Authority (NRA) for pharmaceuticals. CDSCO is headed by the Drugs Controller General of India (DCGI) and operates through zonal, sub-zonal and port offices in addition to its head office in New Delhi. State drug-control departments exercise concurrent jurisdiction over manufacturing licensing, sale and distribution.

4.4.2 Governing Statute and Rules

The primary legislation is the Drugs and Cosmetics Act, 1940, supplemented by the Drugs and Cosmetics Rules, 1945.

Clinical trial and new-drug approval provisions, formerly contained in Part XA and Schedule Y of the 1945 Rules, were consolidated and substantially revised through the New Drugs and Clinical Trials Rules, 2019 (“NDCT Rules, 2019”), notified on 19 March 2019. The NDCT Rules, 2019 comprise thirteen chapters and eight schedules and govern the approval of new drugs, conduct of clinical trials and bioavailability/bioequivalence studies, and the constitution and functioning of ethics committees.

4.4.3 Pediatric-Specific Provisions

Unlike the EU and the USA, India does not operate a dedicated, product-specific, mandatory pediatric investigation plan. Pediatric clinical trials are instead regulated as a sub-set of the general NDCT Rules, 2019 framework, with the following pediatric-relevant safeguards:

- Ethics committees reviewing protocols involving children must include at least one member with recognised pediatric expertise; for vaccine trials, the quorum must additionally include a pediatrician and an immunologist.
- Written informed consent must be obtained from a parent or legally acceptable representative; assent must additionally be obtained from children capable of understanding the nature of the research (generally above seven years of age), documented in a manner appropriate to the child's age and comprehension.
- The National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, issued by the Indian Council of Medical Research (ICMR), provide additional ethical safeguards specific to pediatric and other vulnerable populations, including restrictions on more-than-minimal-risk research without direct benefit to the child participant.

- Serious adverse events and injuries must be reported to the Drugs Controller General of India and the concerned ethics committee within fourteen days, with compensation calculated under the formula in the Seventh Schedule to the NDCT Rules, 2019.

India's essential medicines policy is supplemented by the National List of Essential Medicines (NLEM), which identifies a subset of pediatric-relevant formulations, and by guidance from the Indian Academy of Pediatrics (IAP) on rational pediatric prescribing; however, neither instrument creates a binding, product-specific pediatric development obligation on sponsors equivalent to the EU PIP or the US iPSP.

4.4.4 New Drug Approval Pathway

An application to manufacture and market a new drug in India is made in Form CT-04/Form 44 (as applicable) under the NDCT Rules, 2019, accompanied by a dossier compiled per the Second Schedule and the prescribed fee.

Applications are evaluated by CDSCO with the assistance of Subject Expert Committees (SECs), which may include pediatric specialists where the application concerns a pediatric indication or formulation. Following satisfactory evaluation, permission is granted in Form 45/Form CT-19; import registration follows a parallel process.

4.4.5 Pharmacovigilance and Recall Mechanism

Post-marketing surveillance is coordinated through the Pharmacovigilance Programme of India (PvPI), housed at the Indian Pharmacopoeia Commission (IPC), and the Materiovigilance Programme of India (MvPI) for medical devices.

CDSCO authorises drug recalls and issues rapid alerts/circulars (for example, in connection with metformin and pantoprazole nitrosamine-impurity findings), implements PvPI/IPC recommendations such as label or package-insert changes, and coordinates recall execution with state drug-control authorities. Unlike the US FDA, India does not operate a single, harmonised, publicly searchable, class-based (Class I/II/III) recall database, a gap discussed further in Chapters 5 and 7.

4.5 Regulatory Framework for Pediatric Medicines – European Union

4.5.1 Governing Authority

The European Medicines Agency (EMA), based in Amsterdam, coordinates the scientific evaluation of medicines authorised through the EU's centralised procedure. Pediatric-specific evaluation is the responsibility of the Paediatric Committee (PDCO), a dedicated scientific committee established under the Paediatric Regulation, working alongside the Committee for Medicinal Products for Human Use (CHMP) and national competent authorities of EU member states.

4.5.2 Governing Statute

Regulation (EC) No 1901/2006 of the European Parliament and of the Council, on medicinal products for paediatric use, entered into force in January 2007 and amended earlier instruments including Directive 2001/20/EC and Directive 2001/83/EC. It was accompanied by the consequential amending Regulation (EC) No 1902/2006. Together, these instruments require that, unless exempted by a waiver, all applications for marketing authorisation of a new medicinal product — and applications for a new indication, pharmaceutical form or route of administration of an already-authorised, patent- or supplementary-protection-certificate (SPC)-protected medicine — include the results of studies conducted in accordance with an EMA-agreed Paediatric Investigation Plan (PIP).

4.5.3 The Paediatric Investigation Plan (PIP)

A PIP is a binding development plan, agreed with the PDCO, describing the studies and measures needed to support the eventual authorisation of a medicine in children, encompassing all pediatric sub-populations that may benefit from the medicine. A PIP application generally comprises a covering letter, letter of authorisation (where applicable), Application Form (Part A), a Scientific Document (Parts B–F) describing the background, development rationale and study proposals, and supporting annexes. The PDCO may grant a full or partial waiver where the medicine is unlikely to be safe or effective in children, where the disease does not occur in the pediatric population, or where the medicine offers no significant therapeutic benefit over existing pediatric treatments; deferrals allow pediatric studies to be conducted after adult authorisation where scientifically or ethically justified, subject to a binding completion timetable.

4.5.4 Incentives

The EU framework links regulatory compliance directly to commercial incentives:

- A six-month extension of the Supplementary Protection Certificate (SPC) where the results of an agreed PIP are included in the product information, applicable to new, on-patent medicines (Article 7/8 route).
- An additional two years of market exclusivity for orphan-designated medicinal products that comply with an agreed PIP.
- The Paediatric-Use Marketing Authorisation (PUMA): a dedicated authorisation route for off-patent medicines developed exclusively for pediatric use, granting eight years of data protection and ten years of market protection upon grant.
- Free-of-charge scientific advice and protocol assistance from the EMA in relation to pediatric development plans.

4.5.5 Governance and Networks

The European Network of Paediatric Research at the EMA (Enpr-EMA) connects national and European networks, investigators and centres with recognised expertise in pediatric drug research, facilitating multi-centre pediatric trial conduct across member states. Joint procedural mechanisms exist between the EMA and the US FDA, allowing sponsors to obtain parallel scientific advice on a PIP and a corresponding iPSP, thereby reducing duplicative or conflicting pediatric-study obligations for globally developed medicines.

4.5.6 Pharmacovigilance and Recall Mechanism

Post-authorisation safety monitoring in the EU is coordinated through EudraVigilance and the Pharmacovigilance Risk Assessment Committee (PRAC), with recalls executed at member-state level by national competent authorities under a harmonised EU Rapid Alert System, ensuring coordinated, simultaneous market withdrawal across all member states when a safety signal is confirmed.

4.6 Regulatory Framework for Pediatric Medicines – United States of America

4.6.1 Governing Authority

The United States Food and Drug Administration (US FDA), specifically its Office of Pediatric Therapeutics and the pediatric review staff embedded within the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), administers the pediatric regulatory framework in the United States.

4.6.2 Governing Statutes

Two complementary statutes form the core of the US framework. The Best Pharmaceuticals for Children Act (BPCA) — originating from voluntary pediatric-exclusivity provisions in the Food and Drug Administration Modernization Act of 1997 and subsequently codified as BPCA in 2002 — offers sponsors an additional six months of marketing exclusivity in exchange for conducting pediatric studies requested by the FDA in a Written Request. The Pediatric Research Equity Act (PREA) of 2003 makes pediatric assessment mandatory for most applications for a new active ingredient, indication, dosage form, dosing regimen or route of administration, unless a waiver or deferral is obtained.

The FDA Safety and Innovation Act (FDASIA), enacted in 2012, made both BPCA and PREA permanent (removing the earlier periodic sunset/reauthorisation requirement) and introduced the requirement for sponsors to submit an initial Pediatric Study Plan (iPSP).

4.6.3 The Initial Pediatric Study Plan (iPSP)

Under PREA/FDASIA, sponsors of covered applications must submit an iPSP early in development (generally by the end of Phase 2 clinical development for drugs), outlining planned pediatric studies, timelines, and any request for partial or full waiver or deferral. The FDA's internal Pediatric Review Committee (PeRC) evaluates iPSPs and pediatric assessments, coordinating review across relevant disciplines. Waivers may be granted where the disease does not occur in children, where studies are impossible or highly impracticable, or where the drug is unlikely to be effective/safe in the pediatric sub-population; deferrals allow post-approval completion of pediatric studies with FDA-agreed timelines.

4.6.4 Incentives and Priority Programmes

- Pediatric exclusivity under BPCA: an additional six months of marketing exclusivity attached to all existing exclusivities and patents listed for the product, granted in exchange for completing FDA-requested pediatric studies.
- Rare Pediatric Disease Priority Review Voucher programme, incentivising development of medicines for rare pediatric diseases through a transferable priority-review voucher.
- Humanitarian Device Exemption and orphan-drug incentives, applicable where a pediatric medicine also qualifies for orphan designation.

4.6.5 Pharmacovigilance and Recall Mechanism

The US FDA operates a well-established, publicly searchable recall classification system (Class I – reasonable probability of serious adverse health consequences or death; Class II – temporary or medically reversible adverse consequences; Class III – unlikely to cause adverse health consequences), with recalls listed on the FDA's public Recalls, Market Withdrawals & Safety Alerts database and adverse events monitored through the FDA Adverse Event Reporting System (FAERS) and the Sentinel Initiative for active surveillance.

4.7 ICH E11/E11(R1) as a Harmonising Framework

The ICH E11 guideline, “Clinical Investigation of Medicinal Products in the Paediatric Population”, finalised in 2000 and revised as ICH E11(R1) in 2017, provides the common scientific and ethical foundation upon which the region-specific legal frameworks of the EU and USA are built, and which CDSCO references in its own guidance. ICH E11(R1) addresses extrapolation of efficacy data from adults or older pediatric sub-populations, age-appropriate formulation development, pediatric-specific pharmacokinetic/pharmacodynamic modelling, and the ethical conduct of

pediatric trials, and represents the principal vehicle for international scientific convergence in this field, notwithstanding continuing divergence in the binding legal instruments of individual jurisdictions.

4.8 Comparative Data Exclusivity and Patent-Term Provisions

Because pediatric-specific incentives in the EU and USA operate by extending or supplementing existing data-exclusivity and patent-term protections, it is useful to briefly compare the underlying (non-pediatric) data-exclusivity and patent-term regimes of the three jurisdictions, summarised in Table 4.1, before layering the pediatric-specific extensions described in Sections 4.5.4 and 4.6.4 on top of them.

Table 4.1: Comparative underlying patent-term and data-exclusivity regimes, before pediatric-specific extensions.

Feature	India	European Union	United States
Standard patent term	20 years from filing (Patents Act, 1970, as amended)	20 years from filing; Supplementary Protection Certificate (SPC) available for up to 5 additional years	20 years from filing; Patent Term Extension available for regulatory delay (up to 5 years)
Regulatory data exclusivity (non-pediatric)	No statutory data-exclusivity regime specific to pharmaceuticals	8 years data exclusivity + 2 years market protection ("8+2(+1)" formula)	5 years for new chemical entities; 3 years for new clinical data supporting a new indication/use
Orphan-drug exclusivity	Limited orphan-drug policy provisions	10 years market exclusivity for orphan-designated medicines	7 years market exclusivity for orphan-designated medicines
Pediatric-specific extension	None	+6 months SPC extension; +2 years for orphan medicines (PIP-linked)	+6 months exclusivity attached to existing exclusivities/patents (BPCA-linked)

Source: Compiled from the Patents Act, 1970 (India); Regulation (EC) No 726/2004 and Directive 2001/83/EC (EU); and the Hatch-Waxman Act and Orphan Drug Act (USA).

This comparison clarifies that India's absence of a pediatric-specific incentive is compounded by the broader absence of a general pharmaceutical data-exclusivity regime, meaning that any future Indian pediatric incentive mechanism would need to be designed largely from first principles, rather than simply grafted onto an existing exclusivity structure as was done in the EU and USA — a design consideration explicitly reflected in the phased recommendations of Chapter 9.

4.9 Comparative Snapshot of the Three Regulatory Frameworks

Table 4.2: Comparative snapshot of the pediatric medicine regulatory frameworks of India, the EU and the USA.

Parameter	India (CDSCO)	European Union (EMA)	United States (US FDA)
Governing pediatric instrument	NDCT Rules, 2019 (general provisions; no dedicated pediatric regulation)	Regulation (EC) No 1901/2006 ("Paediatric Regulation")	PREA (2003) + BPCA (2002) + FDASIA (2012)
Dedicated pediatric committee	No dedicated committee; SECs may include pediatric experts	Paediatric Committee (PDCO)	Pediatric Review Committee (PeRC) / Office of Pediatric Therapeutics
Product-specific development plan	Not mandatory	Paediatric Investigation Plan (PIP) – mandatory unless waived	Initial Pediatric Study Plan (iPSP) – mandatory unless waived
Trigger mechanism	General NDCT clinical-trial provisions	Mandatory at marketing-authorisation application stage	Mandatory (PREA) with voluntary exclusivity add-on

			(BPCA)
Key incentive	None specific to pediatric development	SPC +6 months; orphan +2 years; PUMA (8+10 years)	+6 months exclusivity (BPCA); Rare Pediatric Disease PRV
Off-patent product pathway	Not applicable	PUMA	Not applicable (BPCA/PREA apply mainly to patent-protected/NDA products)

Source: Compiled by the author from CDSCO, EMA and US FDA primary legal instruments and guidance documents cited in Chapters 2 and 4.

4.10 Regulatory Fee Structures

Application fees represent a further, often-overlooked, point of comparison between the three jurisdictions, with material implications for smaller sponsors and academic developers of pediatric formulations. In India, an application for permission to manufacture and market a new drug under the NDCT Rules, 2019 attracts a prescribed fee (for example, a fee in the region of Rs. 3,00,000 for a Form 44 application, subject to periodic revision), while clinical trial applications and ethics committee registration attract separate, generally lower, fee schedules. In the European Union, PIP applications benefit from complete fee waivers for scientific advice and protocol assistance directly related to pediatric development, reflecting a deliberate policy choice to remove cost as a barrier to pediatric study planning; centralised marketing-authorisation fees are payable at the time of the full MAA submission, with a fee reduction available to PUMA applicants. In the United States, fees for New Drug Applications are set under the Prescription Drug User Fee Act (PDUFA) and are substantial for standard NDAs, though products developed exclusively under a Written Request pursuant to BPCA, or qualifying for orphan-drug designation, may benefit from specific fee waivers.

4.11 Role of International and Multilateral Organisations

Beyond the three national/regional regulators that are the primary focus of this dissertation, several international bodies materially influence pediatric medicine regulation and availability:

4.11.1 World Health Organization (WHO)

The WHO maintains the WHO Model List of Essential Medicines for Children, updated periodically, which many national essential-medicines lists (including India's NLEM) reference in whole or in part. The WHO also issues Medical Product Alerts — as it did repeatedly during the 2022–2023 DEG/EG contamination episodes discussed in Chapter 5 — and operates a Prequalification Programme that assesses the quality, safety and efficacy of medicines (including pediatric formulations) intended for procurement by United Nations agencies and other international purchasers, a mechanism of particular relevance to Indian manufacturers exporting to WHO-prequalification-dependent markets.

4.11.2 UNICEF

UNICEF, as one of the largest global procurers of pediatric vaccines and essential medicines for humanitarian and development programming, exerts substantial influence over pediatric formulation standards through its supplier-qualification and quality-assurance requirements, which frequently reference WHO prequalification or stringent regulatory authority (SRA) approval — a category that includes the US FDA and, for centrally authorised products, the EMA, but does not, at present, include CDSCO.

4.11.3 International Council for Harmonisation (ICH)

As discussed in Section 4.7, the ICH provides the shared scientific foundation (principally through ICH E11/E11(R1)) referenced by all three jurisdictions. India's Central Drugs Standard Control Organisation participates in ICH as a regulatory member, a status that offers a structural opportunity for closer future alignment of India's pediatric-specific requirements with ICH-harmonised scientific principles, as recommended in Chapter 9.

4.12 Comparative Ethics Committee Composition for Pediatric Trials

Given the centrality of ethics committee oversight to the pediatric clinical-trial safeguards described in Sections 4.4 through 4.6, Table 4.3 below compares the composition and specific pediatric-competence requirements of ethics committees / institutional review boards across the three jurisdictions in greater detail.

Table 4.3: Comparative ethics committee / IRB composition requirements relevant to pediatric clinical trials

Feature	India	European Union	United States
Minimum committee size	Minimum 7 members (per NDCT Rules, 2019 Ethics Committee registration requirements)	Varies by member state; generally a multidisciplinary committee of at least 5–15 members	IRB: minimum 5 members under 21 CFR 56
Mandatory pediatric expertise	At least one member with pediatric expertise; pediatrician + immunologist required for vaccine-trial quorum	Required where the protocol involves children, per national implementing law and ICH E11(R1) principles	IRB must include, or regularly consult, individuals knowledgeable about pediatric welfare when reviewing pediatric research
Lay/community member requirement	At least one lay person from outside the institution/profession	Generally required, varies by member state	At least one non-scientist member required
Registration with national authority	Mandatory registration with DHR/CLA under Form CT-01	Varies; many member states require national ethics-committee accreditation	IRB registration with the US Office for Human Research Protections (OHRP) generally required for federally funded research

Source: Compiled from the NDCT Rules, 2019, ICH E11(R1), and 21 CFR Parts 50/56.

4.13 Comparative Document Content – PIP versus iPSP

Although the EU's Paediatric Investigation Plan and the US's initial Pediatric Study Plan serve an analogous regulatory function — requiring the sponsor to set out, upfront, its proposed approach to generating pediatric data — the two documents differ in structure and binding effect, as summarised in Table 4.4.

Table 4.4: Comparative content and legal effect of the EU Paediatric Investigation Plan and the US initial Pediatric Study Plan.

Feature	EU Paediatric Investigation Plan (PIP)	US initial Pediatric Study Plan (iPSP)
Legal status once agreed	Binding; non-compliance (absent waiver/deferral) invalidates the marketing authorisation application	Agreed with FDA but subject to iterative refinement; non-compliance may result in refusal to file or other regulatory consequences under PREA
Timing of submission	No later than completion of adult Phase 2 studies (in practice, often earlier)	Generally within 60 days of an End-of-Phase-2 meeting, per FDASIA
Scope	Covers all pediatric sub-populations that may benefit from the medicine, across all relevant indications	Covers pediatric sub-populations relevant to the indication(s) under the specific application
Review body	Paediatric Committee (PDCO)	Pediatric Review Committee (PeRC), coordinating with relevant CDER/CBER

		review divisions
Amendment process	Formal PIP modification procedure, itself subject to PDCO review	iPSP updates discussed at subsequent milestone meetings with FDA

Source: Compiled from Regulation (EC) No 1901/2006, EMA PIP procedural guidance, and US FDA guidance on pediatric study plans under FDASIA.

India's absence of any equivalent, named document — whether binding like the PIP or iteratively agreed like the iPSP — is precisely the structural gap identified across the literature reviewed in Chapter 2 and is the central justification for the phased introduction of an Indian pediatric development plan requirement recommended in Chapter 9.

4.14 Synthesis

The detailed regulatory framework description in this chapter establishes the factual and legal foundation for the comparative analysis that follows in Chapters 5 through 8. Three points warrant particular emphasis before proceeding.

First, all three jurisdictions share a common scientific vocabulary, rooted in ICH E11(R1), regarding extrapolation, age-appropriate formulation, and pediatric sub-population classification, notwithstanding differences in binding legal instruments. Second, the EU and USA both combine a mandatory development trigger with a structured, product-specific development plan (PIP/iPSP) evaluated by a dedicated committee, whereas India relies on general clinical-trial ethics oversight without an equivalent product-specific instrument. Third, incentive design differs materially in target: the EU's PUMA specifically targets off-patent medicines, the US's BPCA and PREA are oriented primarily toward on-patent/new applications, and India currently offers no pediatric-specific incentive of either kind. These three observations directly frame the comparative case studies presented in Chapter 5 and the recommendations developed in Chapter 9.

CHAPTER 5 CASE STUDIES: A COMPARATIVE PERSPECTIVE

This chapter presents three comparative case studies chosen to illustrate, in concrete regulatory practice, how India, the European Union and the United States respond to real-world challenges in pediatric medicine safety, development and access. Each case study is presented in a comparative, country-wise format.

5.1 Case Study 1 – Diethylene Glycol / Ethylene Glycol Contamination of Pediatric Cough Syrups (2022–2025)

Between 2022 and 2025, several countries reported clusters of acute kidney injury and death among children who had consumed diethylene glycol (DEG) and/or ethylene glycol (EG) contaminated oral liquid cough and cold preparations.

The World Health Organization issued multiple global medical-product alerts. Contaminated cough syrups manufactured in India were linked to over 300 child deaths in the Gambia, Indonesia and Uzbekistan in 2022–2023. A further, domestic episode occurred in 2025, when a contaminated cough syrup (Coldrif®) was linked to child deaths in Madhya Pradesh, India, prompting the arrest of the manufacturer, sealing of the factory, and an immediate recall of implicated batches. DEG/EG contamination typically arises when pharmaceutical-grade glycerin or propylene glycol — solvents used in liquid formulations — is adulterated or substituted with industrial-grade material contaminated with these toxic glycols, a mechanism with historical precedent in the 1937 Elixir Sulfanilamide disaster in the United States, which itself catalysed the passage of the Federal Food, Drug, and Cosmetic Act of 1938.

Table 5.1: Comparative regulatory response to DEG/EG-contaminated pediatric cough syrup episodes, 2022–2025, including product-recall mechanisms.

Parameter	India	European Union	United States
Direct exposure	Domestic fatalities (Madhya Pradesh, 2025); manufacturing origin of exported contaminated syrups (2022–2023)	No confirmed domestic fatalities; monitored as an imported-product risk	No confirmed domestic fatalities; FDA confirmed implicated products were not shipped to the US
Regulatory response	CDSCO/state drug controllers ordered recalls, sealed the implicated factory, and conducted a nationwide 2024 GMP inspection drive covering 400+ premises	EMA/national authorities monitored WHO alerts and reinforced import-testing vigilance for glycerin-containing excipients	FDA issued a 2023 guidance document, "Testing of Glycerin for Diethylene Glycol", and contacted manufacturers to reinforce GMP/testing obligations; publicly listed recalled products
Underlying regulatory gap identified	Inconsistent raw-material (glycerin/propylene glycol) batch-testing enforcement across manufacturing units; fragmented state–centre recall coordination	Reliance on third-country manufacturing oversight for imported excipients/finished products	Reliance on import-alert and manufacturer self-certification for foreign-manufactured products not intended for the US market
Recall classification used	No formal Class I/II/III system; ad hoc circulars and press notices	EU Rapid Alert System; simultaneous member-state withdrawal	Formal Class I recall (life-threatening) with public FDA recall database entry

Source: Compiled from WHO medical product alerts, US FDA public communications, and Indian regulatory/press reporting cited in Chapter 2.

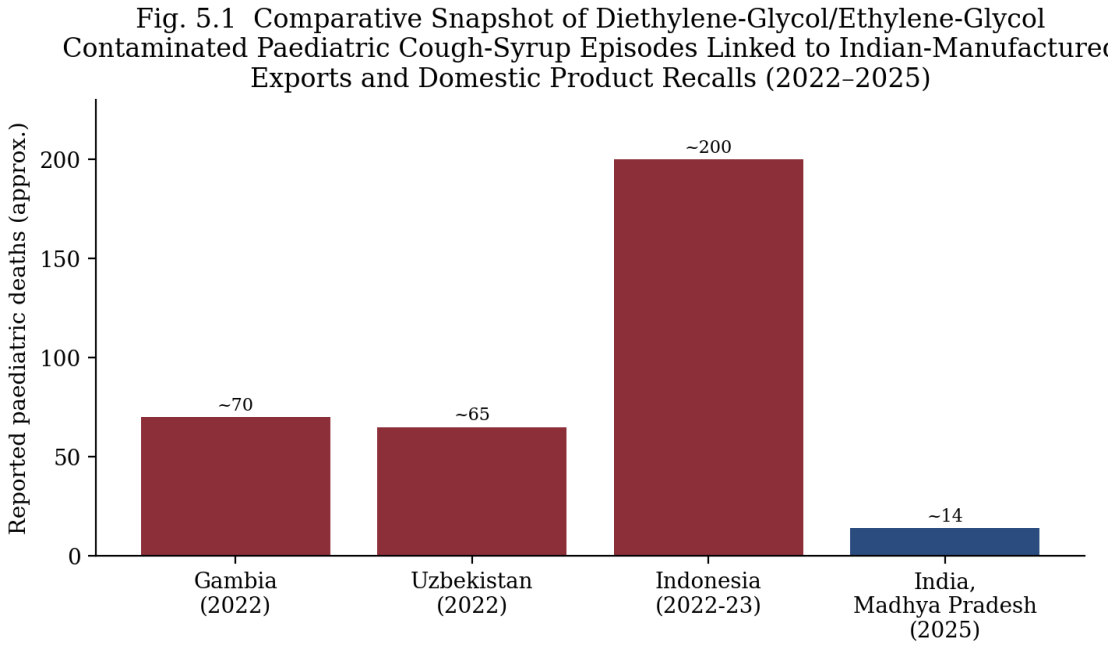

Figure 5.1: Comparative snapshot of DEG/EG-contaminated pediatric cough-syrup episodes and associated product recalls (2022–2025)

Source: Author's compilation from WHO, US FDA and Indian regulatory/press sources; figures are approximate and drawn from publicly reported data.

This case illustrates that while the US and EU systems possess formal, harmonised, class-based recall mechanisms with rapid public communication, India's recall process — though capable of decisive action, as seen in the 2025 factory sealing and arrest — remains less standardised, reinforcing the recommendation (Chapter 9) for a harmonised, class-based national recall classification system in India.

5.2 Case Study 2 – The First Paediatric-Use Marketing Authorisation: Midazolam Oromucosal Solution (Buccolam®)

In September 2011, the European Medicines Agency granted the first-ever Paediatric-Use Marketing Authorisation (PUMA) to a midazolam oromucosal solution (marketed as Buccolam®), indicated for the treatment of prolonged, acute convulsive seizures in infants, toddlers, children and adolescents. Midazolam had long been used off-label or as an unlicensed, pharmacy-compounded product for pediatric status epilepticus in many countries prior to this authorisation. The PUMA route was designed specifically to formalise and incentivise the development of dedicated, age-appropriate formulations of established, off-patent active substances.

Table 5.2: Comparative regulatory pathway and market outcome for pediatric midazolam oromucosal solution.

Parameter	India	European Union	United States
Pathway used for pediatric midazolam	No dedicated pediatric formulation pathway; pediatric use largely via off-label prescribing of injectable/adult formulations or hospital-compounded preparations	Paediatric-Use Marketing Authorisation (PUMA) granted 2011; 8 years data protection + 10 years market protection	Approved via standard NDA/pediatric-exclusivity mechanisms for related benzodiazepine formulations; oromucosal pediatric formulation authorised under a distinct NDA pathway
Formulation innovation incentivised	Limited; reliance on extemporaneous hospital compounding	Directly incentivised via the PUMA's market-protection period	Indirectly incentivised via pediatric exclusivity and orphan-type provisions where applicable
Practical uptake / access	Access dependent on hospital-level compounding capability and importation	Documented uptake challenges — competition from established, cheaper, nationally compounded alternatives limited immediate commercial success despite regulatory approval	Generally available through standard pharmacy distribution once approved

Source: Compiled from EMA press communications, EFPIA commentary (2011) and subsequent PUMA-access literature (Iqbal et al., 2024) cited in Chapter 2.

This case demonstrates that a well-designed dedicated regulatory pathway (the EU's PUMA) can successfully formalise a previously unlicensed pediatric practice, but also that regulatory approval alone does not guarantee market uptake where compounding alternatives remain entrenched — a lesson directly relevant to India, where hospital-level compounding of pediatric formulations remains the default practice in the absence of an equivalent dedicated pathway.

5.3 Case Study 3 – Off-Label and Unlicensed Use of Medicines in Pediatric Practice

Off-label prescribing — use of an authorised medicine outside the terms of its marketing authorisation (e.g., in an unapproved age group, dose or indication) — and unlicensed use — use of a medicine without any marketing

authorisation for the relevant population, often via extemporaneous compounding — remain pervasive in pediatric practice worldwide, notwithstanding three decades of regulatory reform.

Table 5.3: Comparative extent and regulatory response to off-label and unlicensed pediatric medicine use.

Parameter	India	European Union	United States
Reported extent of off-label/unlicensed pediatric use	Very high; national pediatric essential-medicines coverage remains incomplete for many age-appropriate formulations	Documented range of 13–69% (hospital) and 2–100% (outpatient) of pediatric prescriptions across studies in multiple member states, despite the Paediatric Regulation	Lower but still material; PREA/BPCA have generated substantial pediatric labelling for on-patent drugs, but off-patent, generic and rare-disease medicines remain comparatively under-labelled
Primary regulatory lever	None specific; reliance on National List of Essential Medicines and IAP clinical guidance	PIP requirement (new/on-patent medicines) + PUMA (off-patent medicines), though PUMA uptake has been limited	PREA (on-patent/new applications) + BPCA (exclusivity-linked, primarily benefits on-patent products); off-patent gap only partly addressed by NIH-funded pediatric trials networks
Identified structural gap	Absence of a mandatory, product-specific pediatric development trigger equivalent to PIP/iPSP	Incentive structure favours on-patent development; off-patent PUMA route commercially under-utilised	Similar bias toward on-patent, commercially attractive indications; off-patent/generic pediatric formulation gap persists

Source: Compiled from EUPATI Open Classroom materials, Iqbal et al. (2024), Li et al. (2020) and Shah et al. (2022), cited in Chapter 2.

Across all three jurisdictions, this case study reveals a common structural weakness: regulatory incentive structures are more effective at generating pediatric data for new, on-patent medicines than for the older, off-patent generics that in practice constitute the bulk of everyday pediatric prescribing — a finding with direct relevance to India, where the pediatric medicines market is overwhelmingly generic.

5.4 Case Study 4 – Generic Pediatric Essential Medicines: Amoxicillin Dispersible Tablets

Amoxicillin dispersible tablets — a WHO-recommended, age-appropriate, generic first-line antibiotic formulation for treating pediatric pneumonia and other common bacterial infections — provide a useful contrast to Case Studies 1–3 because they involve a well-established, off-patent, generic essential medicine rather than an innovative new chemical entity, and therefore test how each regulatory system handles the far larger, everyday universe of generic pediatric prescribing.

Table 5.4: Comparative regulatory treatment of a generic pediatric essential medicine (amoxicillin dispersible tablets)

Parameter	India	European Union	United States
Regulatory classification	Generic new drug application under NDCT Rules, 2019; included in NLEM	Generic marketing authorisation via national or decentralised procedure; WHO-prequalified	ANDA (Abbreviated New Drug Application) under Hatch-Waxman

		versions widely used for international procurement	framework
Pediatric-specific formulation requirement	No mandatory dispersible-tablet requirement; manufacturers voluntarily produce dispersible formulations largely driven by NLEM/international tender demand	Encouraged via national essential-medicines policy and WHO-aligned procurement; no EU-specific mandatory dispersible requirement beyond general PIP applicability to new products	Dispersible/chewable pediatric formulations generally developed voluntarily by generic manufacturers responding to market and procurement demand
Quality assurance pathway relevant to export	WHO Prequalification Programme assessment (voluntary, additional to CDSCO approval) required for UN-agency procurement eligibility	EU GMP certification; centrally authorised or mutually recognised	US FDA ANDA approval implies compliance with US GMP; separate WHO PQ assessment if exporting to UN-procurement markets
Illustrative regulatory takeaway	Domestic approval alone does not guarantee international procurement eligibility; WHO PQ (or an SRA-equivalent designation for CDSCO) remains a a separate, additional quality hurdle	Mature GMP and pharmacovigilance infrastructure generally satisfies most international procurement quality benchmarks without further assessment	FDA approval is broadly recognised internationally as a stringent regulatory authority (SRA) benchmark, easing international procurement acceptance

Source: Compiled from WHO Model List of Essential Medicines for Children, WHO Prequalification Programme documentation, and national generic-approval procedures.

This case study highlights that CDSCO approval, unlike US FDA approval, is not yet uniformly recognised internationally as a stringent-regulatory-authority benchmark, meaning that Indian-manufactured generic pediatric medicines intended for export to UN-procurement-dependent markets typically require a separate WHO Prequalification assessment — an additional administrative and cost burden not faced by equivalent US-approved products, and a further, structural argument for strengthening India's regulatory framework, including its manufacturing-quality oversight, to a level that could eventually support SRA-equivalent recognition.

5.6 Consolidated Case Study Comparison

Table 5.5 below consolidates the four case studies examined in this chapter into a single comparative summary, highlighting the principal regulatory lesson drawn from each for India, the EU and the USA respectively.

Table 5.5: Consolidated comparison of principal regulatory lessons drawn from the four case studies.

Case study	Principal India-relevant lesson	Principal EU-relevant lesson	Principal USA-relevant lesson
1. DEG/EG cough-syrup contamination	Urgent need for mandatory raw-material testing and a harmonised, class-based national recall system	Reinforces the value of import-vigilance and WHO-alert monitoring for externally manufactured products	Confirms the effectiveness of formal Class I recall processes and proactive guidance (2023 glycerin-testing guidance)
2. Midazolam PUMA (Buccolam®)	Illustrates the potential value, and the access-design challenges, of a dedicated off-patent pediatric formulation pathway	Demonstrates that a well-designed pathway (PUMA) does not guarantee market uptake without complementary access measures	Shows how established NDA/exclusivity pathways can achieve pediatric formulation availability without a dedicated off-patent route

3. Off-label/unlicensed pediatric prescribing	Highlights the scale of the off-label prescribing gap in the absence of a mandatory development trigger	Shows that even a mature PIP framework leaves a residual off-label/off-patent gap	Shows that PREA/BPCA incentives are more effective for on-patent than off-patent medicines
4. Generic pediatric essential medicine (amoxicillin)	Domestic approval alone does not confer international procurement recognition absent WHO PQ or SRA status	Mature GMP/pharmacovigilance infrastructure generally satisfies international procurement benchmarks	FDA approval is broadly recognised as an SRA benchmark, easing international acceptance of US-approved generics

5.7 Cross-Case Synthesis

Read together, the three case studies indicate that regulatory maturity (as reflected in dedicated committees, mandatory development plans and structured incentives) correlates with more formalised, though not necessarily complete, protection of pediatric patients. India's principal vulnerability, illustrated most starkly by the recurrent DEG/EG contamination episodes, lies less in the sophistication of its clinical-trial ethics framework — which does incorporate pediatric-specific safeguards — and more in manufacturing-quality assurance, raw-material testing enforcement, and the absence of a harmonised, class-based recall and public-alert mechanism, gaps that are directly addressed in the recommendations of Chapter 9.

CHAPTER 6 RESULTS AND COMPARATIVE ANALYSIS

This chapter presents, in structured tabular and graphical form, the results of the comparative analysis of pediatric medicine regulation in India, the European Union and the United States, drawing on the regulatory framework description in Chapter 4 and the case-study findings in Chapter 5.

6.1 Legislative and Institutional Timeline.

Table 6.1: Comparative legislative and institutional timeline for pediatric medicine regulation

Year	India	European Union	United States
1938	–	–	Federal Food, Drug, and Cosmetic Act enacted (post Elixir Sulfanilamide disaster)
1940 / 1945	Drugs and Cosmetics Act (1940) / Rules (1945) enacted	–	–
1997	–	–	FDA Modernization Act – voluntary pediatric exclusivity introduced
2000	–	–	ICH E11 finalised (globally applicable)
2002–2003	–	–	BPCA codified (2002); PREA enacted (2003, mandatory pediatric assessment)
2006–2007	–	Regulation (EC) No 1901/2006 adopted; entered into force January 2007; PDCO established	–
2011	–	First PUMA granted (midazolam oromucosal solution)	–
2012	–	–	FDASIA – PREA and BPCA made permanent; iPSP requirement introduced
2017	–	ICH E11(R1) addendum adopted	ICH E11(R1)

			addendum adopted
2019	New Drugs and Clinical Trials Rules, 2019 notified, consolidating clinical-trial and new-drug provisions	–	–
2022–2025	DEG/EG cough-syrup contamination episodes (export-linked 2022–23; domestic Coldrif® 2025); nationwide GMP inspection drive (2024)	WHO alerts monitored; import vigilance reinforced	2023 FDA guidance on glycerin/DEG testing issued

Source: Compiled by the author from the primary legal instruments and literature discussed in Chapters 2 and 4.

6.2 Clinical Trial Requirements for Children

Table 6.2: Comparative clinical trial requirements for pediatric research participants.

Requirement	India	European Union	United States
Ethics committee pediatric expertise	Mandatory member with pediatric expertise; pediatrician + immunologist for vaccine trials	National ethics committee requirements vary by member state, generally requiring relevant pediatric expertise	Institutional Review Board (IRB) must include, or consult, members with pediatric expertise for pediatric protocols
Parental/guardian consent	Written informed consent from legally acceptable representative	Written informed consent from parent(s)/legal representative(s) per national law	Written permission from parent(s)/guardian(s) per 21 CFR Part 50 Subpart D
Child assent	Required from children generally above 7 years, age-appropriate format	Required where the child is capable of forming an opinion, per national implementation	Required where FDA/IRB determines the child is capable of assent
Serious adverse event reporting	Report to DCGI/EC within 14 days; compensation per Seventh Schedule formula	Reported via EudraVigilance; PRAC oversight	Reported via FAERS; IND safety reporting requirements

6.3 Incentive Structures for Pediatric Drug Development.

Table 6.3: Comparative incentive structures for pediatric drug development.

Incentive type	India	European Union	United States
Market/data exclusivity extension	Not available	SPC +6 months (on-patent); PUMA 8+10 years (off-patent)	+6 months market exclusivity (BPCA)
Orphan-disease specific bonus	Limited orphan-drug policy; no pediatric-specific bonus	+2 years market exclusivity for orphan medicines complying with PIP	Orphan drug tax credit + 7-year exclusivity (general orphan provisions; not pediatric-specific)
Priority review	Not specific to pediatric applications	Accelerated assessment possible for medicines of major public-health interest	Rare Pediatric Disease Priority Review Voucher
Free regulatory advice	General pre-submission meetings available	Free PIP-related scientific advice/protocol assistance	Free Type B/C meetings under PDUFA; iPSP-related advice

6.4 Comparative Approval / Review Timelines

Published statutory and practical review benchmarks indicate meaningful differences in the pace of new-drug evaluation across the three jurisdictions, summarised in Figure 6.1. These figures represent published regulatory benchmarks (standard vs. priority/expedited review clocks) and are illustrative; actual timelines vary by application complexity, quality of dossier, and the extent of queries raised by the regulator.

Fig. 6.1 Comparative Approval / Review Timelines for New Drug Applications Involving Paediatric Data – India, USA and EU

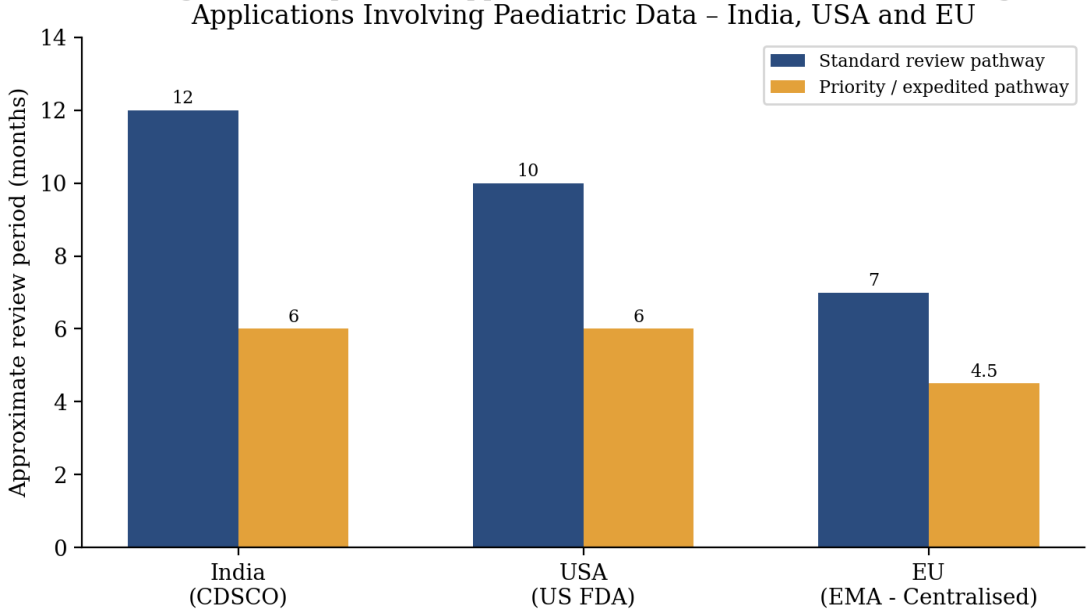

Figure 6.1: Comparative approval/review timelines for new drug applications involving pediatric data – India, USA and EU.

Source: Author's compilation from CDSCO procedural timelines, US FDA PDUFA goals, and EMA centralised-procedure timelines (published regulatory benchmarks).

6.5 Post-Marketing Surveillance and Recall Mechanisms.

Table 6.4: Comparative post-marketing surveillance and recall mechanisms.

Feature	India	European Union	United States
Adverse event database	PvPI (Pharmacovigilance Programme of India), coordinated by IPC	EudraVigilance	FAERS (FDA Adverse Event Reporting System); Sentinel Initiative
Recall classification	No formal class-based system; circular/press-notice based	EU Rapid Alert System; simultaneous member-state action	Formal Class I / II / III system, publicly searchable
Public recall transparency	Limited centralised public database	Centralised EU rapid-alert communications	Publicly searchable FDA recall database, updated regularly

6.6 Comparative Availability of Age-Appropriate Formulation Types

A further useful lens for comparison is the range of age-appropriate pediatric dosage forms actively encouraged or incentivised by each regulatory system, summarised in Table 6.5.

Table 6.5: Comparative availability and regulatory encouragement of age-appropriate pediatric dosage forms.

Dosage form	India	European Union	United States
Oral liquid (syrup/suspension/drops)	Widely manufactured; primary format for pediatric prescribing; principal source of DEG/EG contamination risk	Available; subject to PIP-driven formulation development for new medicines	Available; subject to iPSP-driven formulation development for new medicines
Dispersible / orally disintegrating tablet	Growing availability, largely NLEM/export-tender driven	Actively encouraged under PIP formulation requirements	Actively encouraged under PREA/iPSP formulation requirements
Mini-tablets / multiparticulates	Limited domestic availability	Emerging, EMA-supported formulation science initiatives (e.g., collaborative EU-funded formulation research consortia)	Emerging; FDA has issued specific guidance encouraging age-appropriate multiparticulate development
Fixed-dose combination pediatric products	Common, subject to additional FDC Committee scrutiny	Evaluated as new combination products under standard procedures	Evaluated as combination products under standard NDA procedures

6.7 Cost Implications of Pediatric Drug Development

The cost of generating dedicated pediatric data varies considerably across the three jurisdictions, driven less by direct regulatory fees (addressed in Section 4.9) than by the scale and complexity of the pediatric studies themselves.

Pediatric pharmacokinetic and efficacy studies are frequently smaller in absolute enrolment than adult pivotal trials, but per-patient costs are often higher, owing to the need for specialised pediatric clinical-trial sites, age-appropriate formulation manufacturing for investigational supplies, more intensive safety monitoring, and, in many settings, higher screening-failure and dropout rates. In the United States and the European Union, these costs are at least partly offset by the exclusivity-based incentives described in Sections 4.5.4 and 4.6.4, which can be worth substantially more in commercial terms than the direct cost of the required pediatric studies for a successful, high-revenue medicine — a calculus that is markedly less favourable for lower-revenue, off-patent or purely domestic Indian generic products, helping to explain why voluntary pediatric formulation development in India has historically been concentrated among internationally export-oriented manufacturers responding to WHO Prequalification or international tender requirements rather than purely domestic regulatory drivers.

This cost asymmetry reinforces the case, developed further in Chapter 9, for any future Indian pediatric-development requirement to be accompanied by proportionate, calibrated incentives — rather than an unfunded mandate — if it is to avoid unintended consequences for the availability of affordable, off-patent pediatric medicines that currently form the backbone of pediatric therapy in India's public health system.

6.8 Quantitative Trends in Pediatric Regulatory Activity

Although a full bibliometric or regulatory-database analysis is outside the scope of this secondary-data dissertation, the published literature reviewed in Chapter 2 permits a qualitative account of the broad quantitative trends in pediatric regulatory activity across the three jurisdictions over the past decade.

EMA data reported in its decennial report to the European Commission (2021) indicate that several hundred Paediatric Investigation Plans were agreed in the first decade after the Paediatric Regulation's entry into force, generating a substantial, cumulative increase in pediatric-specific labelling information across multiple therapeutic areas, most heavily in infectious disease, endocrinology and, to a lesser extent, oncology. Similarly, US FDA pediatric labelling

change data, as discussed by Bourgeois and Hwang (2017), show several hundred pediatric labelling changes attributable to PREA and BPCA in the fifteen years following PREA's enactment, with the pace of labelling change roughly proportional to the number of iPSPs agreed each year. India does not maintain an equivalent, centralised, publicly reported database of pediatric-specific approvals, labelling changes, or formulation developments, making a directly comparable quantitative trend analysis for India difficult to construct from public sources — itself a notable data-transparency gap identified in this dissertation and a further, practical argument for the introduction of a dedicated pediatric database or registry as part of the reforms recommended in Chapter 9.

6.9 Emerging Regulatory Science Trends Relevant to Pediatric Medicines

Beyond the comparative structural analysis presented above, several emerging regulatory science trends are likely to shape the future practice of pediatric medicine regulation across all three jurisdictions, and are briefly noted here for completeness.

6.8.1 Model-Informed Drug Development (MIDD)

Both the EMA and the US FDA increasingly encourage the use of physiologically based pharmacokinetic (PBPK) modelling and population pharmacokinetic/pharmacodynamic modelling to support pediatric dose selection with a reduced burden of pediatric clinical sampling, particularly in younger age bands where blood sampling volume is ethically and practically constrained. CDSCO guidance has not yet formally incorporated MIDD principles for pediatric applications to the same extent, representing a further area where closer alignment with ICH E11(R1) principles, as recommended in Chapter 9, could bring practical benefit.

6.8.2 Real-World Evidence and Registries

Pediatric disease registries and real-world evidence frameworks are increasingly used, particularly in the EU and USA, to supplement traditional randomised controlled trial data for rare pediatric diseases where recruitment of adequately powered trial cohorts is not feasible. India's relatively nascent pediatric disease registry infrastructure represents both a current gap and a future opportunity, particularly given the country's large pediatric patient population, which could in principle support well-designed pediatric registries of considerable scientific and regulatory value.

6.8.3 Global Pediatric Trial Networks

Multi-national pediatric trial networks — including Enpr-EMA in Europe and the NIH-funded Pediatric Trials Network in the United States — pool investigator expertise and trial infrastructure across multiple sites and, increasingly, across national borders, to make otherwise commercially unattractive pediatric trials feasible. India's clinical-trial capacity and large patient population position it as a potentially valuable partner in such global networks, provided that the regulatory, ethical and data-sharing framework is sufficiently aligned with international partners — a further, practical argument for the harmonisation measures discussed throughout this dissertation.

6.10 Summary of Results

The comparative results presented in this chapter consistently show that the European Union and the United States operate more procedurally mature, mandatory and incentive-linked pediatric regulatory systems than India across almost every parameter examined — legislative history, dedicated committee structures, product-specific development plans, market-exclusivity incentives, and formal recall classification. India's principal comparative strengths lie in its detailed, ethics-committee-level pediatric safeguards (assent, compensation) introduced by the NDCT Rules, 2019,

which are broadly comparable in spirit to EU/US requirements; its principal comparative weaknesses lie in the absence of a mandatory, product-specific pediatric development trigger and a harmonised recall classification system, both of which are directly implicated in the case studies of Chapter 5.

CHAPTER 7 DISCUSSION

7.1 Interpreting India's Regulatory Position

The comparative results in Chapter 6 and the case studies in Chapter 5 together indicate that India's pediatric regulatory framework has made genuine, substantive progress — particularly through the NDCT Rules, 2019, which introduced explicit pediatric-expertise, assent and compensation requirements at the level of clinical-trial ethics oversight.

However, India's framework remains oriented toward general clinical-trial governance rather than pediatric-specific drug development. The absence of a mandatory, product-specific instrument equivalent to the EU's PIP or the US's iPSP means that sponsors marketing a new medicine in India face no binding domestic obligation to generate pediatric data, dosing information or age-appropriate formulations as a condition of approval, even where the medicine will foreseeably be prescribed to children off-label after adult authorisation.

This gap is not merely theoretical. As the DEG/EG contamination case study demonstrates, the practical burden of inadequate pediatric-formulation oversight falls disproportionately on children, and manifests not only as a development-stage data gap but as a manufacturing-quality and post-market-surveillance gap. The Coldrif® episode in 2025 and the earlier export-linked deaths in 2022–2023 both originated in quality-assurance failures at the raw-material and finished-product testing stage — a domain distinct from, but related to, the pediatric clinical-development gap identified in the literature.

7.2 Strengths and Gaps – European Union Framework

The EU's Paediatric Regulation represents arguably the most structurally complete pediatric framework among the three jurisdictions studied, combining a mandatory development trigger (the PIP), a dedicated scientific committee (the PDCO), and a layered incentive system addressing both on-patent (SPC extension, orphan bonus) and off-patent (PUMA) medicines. Its principal documented weakness, evident in Case Study 2 and corroborated by Iqbal et al. (2024), is that regulatory approval through the PUMA route does not automatically translate into clinical availability or affordability, particularly where established compounding practices or generic alternatives already meet clinical need at lower cost. This suggests that development-stage incentives, however well designed, must be complemented by post-authorisation market-access and procurement measures to achieve their intended public-health effect.

7.3 Strengths and Gaps – United States Framework

The US framework's principal strength lies in the combination of a mandatory obligation (PREA) with a voluntary, exclusivity-linked incentive (BPCA), made permanent by FDASIA in 2012 — a structure that Bourgeois and Hwang (2017) and Christensen (2012) both credit with generating substantial, sustained pediatric labelling improvements for on-patent medicines over more than two decades. Its documented weakness, shared with the EU, is that PREA applies principally to new applications, leaving a large stock of older, off-patent, generic pediatric medicines — which constitute the bulk of everyday pediatric prescribing — comparatively under-studied, a gap only partially addressed by publicly funded initiatives such as the NIH-funded pediatric trials networks referenced by Li et al. (2020).

7.4 Harmonisation Prospects

ICH E11(R1) provides a genuinely shared scientific foundation across all three jurisdictions, and the existence of parallel EMA–FDA scientific advice procedures for pediatric development plans (as documented by Turner et al., 2017) demonstrates that cross-regional procedural convergence is achievable even where the underlying legal instruments differ. India's continued, active engagement with ICH as an associate/observer member and its adoption of ICH-aligned guidance documents suggest a plausible pathway toward closer future alignment, particularly if a dedicated Indian pediatric development instrument is introduced that explicitly references ICH E11(R1) principles, as recommended in Chapter 9.

7.5 Public Health Implications

Given India's role as a major global manufacturer and exporter of generic and pediatric formulations, weaknesses in India's pediatric regulatory and manufacturing-quality framework carry public-health consequences that extend well beyond its own borders, as starkly illustrated by the 2022–2023 export-linked fatalities in the Gambia, Indonesia and Uzbekistan. Strengthening India's framework is therefore not only a matter of domestic child-health policy but also one of international public-health significance and pharmaceutical-trade credibility, reinforcing the urgency of the recommendations developed in Chapter 9.

7.6 Stakeholder Perspectives

The discussion above can usefully be read through the lens of the different stakeholders identified in Section 3.3. From a sponsor/industry perspective, a more codified, predictable Indian pediatric development and review pathway — of the kind that PDUFA/GDUFA goal letters provide in the USA — would reduce planning uncertainty and could, over time, make India a more attractive location for pediatric-specific clinical research, provided that any new mandatory requirement is phased in with adequate transition time and proportionate to company size. From a regulator's perspective, the introduction of a dedicated pediatric committee within CDSCO would need to be resourced with appropriately trained personnel, a non-trivial institutional investment, but one that both the EU and the US experience suggests pays clear long-term public-health dividends. From a healthcare-provider perspective, clearer, pediatric-specific labelling driven by a mandatory development requirement would reduce reliance on informal, experience-based off-label dosing practices, particularly in resource-constrained public-hospital settings. From a patient/caregiver perspective, the most immediate and tangible benefit of regulatory reform would likely be improved manufacturing-quality assurance for oral liquid formulations, directly addressing the root cause of the case studies examined in Chapter 5.

7.7 Balancing Regulatory Burden and Access

Any recommendation to introduce a more stringent, mandatory pediatric development framework in India must be balanced against the risk of inadvertently discouraging the development or continued domestic manufacture of affordable generic pediatric medicines, which remain the backbone of pediatric therapy in India's public health system.

The EU and US experience offers a relevant lesson here: both jurisdictions apply their most stringent mandatory requirements (PIP/iPSP) primarily to new, on-patent medicines, while using lighter-touch, incentive-based mechanisms (PUMA, and publicly funded pediatric trials networks) to address the generic, off-patent segment of the market. A calibrated Indian reform, differentiating between new chemical entities and established generics along similar lines,

would be more likely to achieve the intended safety and formulation-availability benefits without unduly restricting access to low-cost, essential pediatric medicines.

7.8 An Illustrative Regulatory Maturity Index

To synthesise the multi-parameter comparison developed across Chapters 4 and 6 into a single, illustrative summary, Table 7.1 scores each jurisdiction (on an indicative 1–5 scale, where 5 represents the most structurally complete provision observed among the three jurisdictions studied) across six dimensions of pediatric regulatory maturity. This index is presented as an interpretive, qualitative synthesis device for the purposes of this dissertation, and not as a validated, externally benchmarked scoring instrument.

Table 7.1: Illustrative regulatory maturity index across six dimensions of pediatric medicine regulation (indicative scale 1–5).

Dimension	India	European Union	United States
Dedicated pediatric committee/structure	2	5	4
Mandatory product-specific development trigger	1	5	5
Waiver/deferral mechanism clarity	2	5	4
Commercial incentive linkage	1	5	4
Ethics/consent/assent safeguards	4	4	4
Recall/pharmacovigilance transparency	2	4	5

Source: Author's qualitative synthesis based on the comparative analysis in Chapters 4 and 6; scores are illustrative and intended for interpretive discussion rather than as a validated metric.

This illustrative index reinforces the discussion above: India's principal comparative strength lies in ethics-committee-level safeguards, which are broadly comparable to the EU and US position, while its principal comparative weaknesses lie in the absence of a dedicated committee structure, a mandatory development trigger, and a linked incentive system — precisely the three gaps that the recommendations in Chapter 9 are designed to address.

CHAPTER 8 COMPARATIVE REGULATORY PATHWAY FOR MARKET ENTRY OF PEDIATRIC MEDICINES

This chapter presents Figure 8.1, a generalised comparative regulatory pathway for market entry of pediatric medicines, set out country-wise in tabular form on separate pages for India, the United States and the European Union, followed by Table 8.1, a classification of pediatric/health medicines that consolidates, for each jurisdiction, the applicable query-resolution / response timelines.

8.1 Figure 8.1 (A) – Regulatory Pathway for Market Entry of Pediatric Medicines in India

The Indian pathway to market entry for a medicine intended (wholly or partly) for pediatric use follows the general new-drug approval process under the NDCT Rules, 2019, since India does not operate a separately branded, product-specific pediatric development pathway. Pediatric considerations are addressed at the ethics-committee and Subject Expert Committee review stages, rather than through a dedicated, upfront pediatric development plan of the kind used in the EU and USA. The seven-step generalised pathway is set out in tabular form below.

Step	Stage	Description / Requirement	Responsible Authority
1	Pre-submission	Sponsor compiles non-clinical, clinical and CMC (chemistry, manufacturing & controls) dossier per the Second Schedule of the NDCT Rules, 2019; pediatric data included where available or extrapolation justified	Sponsor / Applicant
2	Application filing	Application for permission to conduct clinical trial (Form CT-04) or to manufacture/market a new drug (Form CT-04/Form 44) filed with fee challan	CDSCO (Central Licensing Authority)
3	Ethics Committee review	Registered Ethics Committee (Form CT-01 registration) reviews protocol; must include pediatric-expert member for pediatric trials; informed consent + child assent requirements verified	Institutional/Independent Ethics Committee
4	Subject Expert Committee (SEC) evaluation	CDSCO constitutes/consults relevant SEC (with pediatric expertise where applicable) for scientific and technical evaluation of the dossier	CDSCO / SEC
5	Query resolution	Deficiency letter issued; sponsor responds with additional data/clarifications within the prescribed period (see Table 8.1)	CDSCO ↔ Sponsor
6	Grant of permission	Permission to conduct clinical trial (Form CT-06) or manufacture/market (Form 45/CT-19) granted upon satisfactory review	DCGI / CDSCO
7	Post-marketing surveillance	Pharmacovigilance Programme of India (PvPI) monitoring; periodic safety update reports; recall coordination with state authorities if required	IPC (PvPI) / CDSCO / State Drug Control

Source: Compiled from the New Drugs and Clinical Trials Rules, 2019 and CDSCO procedural guidance.

8.2 Figure 8.1 (B) – Regulatory Pathway for Market Entry of Pediatric Medicines in the United States of America

The US pathway is anchored by the mandatory iPSP requirement under PREA, agreed early in development with the FDA's Pediatric Review Committee, and is further shaped by the voluntary, exclusivity-linked BPCA mechanism that can attach an additional six months of marketing exclusivity where the FDA specifically requests pediatric studies through a Written Request. The eight-step generalised pathway is set out in tabular form below.

The US pathway is distinguished by the early, mandatory integration of pediatric planning into the overall clinical development programme through the initial Pediatric Study Plan, which must generally be submitted well before the New Drug Application itself, allowing the FDA's Pediatric Review Committee to weigh in on pediatric study design while adult development is still underway. This early-engagement model is intended to prevent pediatric considerations from becoming an afterthought bolted onto a near-complete adult development programme. The seven-step generalised pathway is set out in tabular form below.

Step	Stage	Description / Requirement	Responsible Authority
1	Pre-IND / early development	Sponsor plans pediatric strategy; where PREA applies, an initial Pediatric Study Plan (iPSP) must generally be submitted by the end of Phase 2 (or as agreed)	Sponsor / Applicant
2	iPSP review	FDA's Pediatric Review Committee (PeRC) evaluates the iPSP; agrees, requests modification, or evaluates waiver/deferral request	US FDA (PeRC / Office of Pediatric Therapeutics)
3	IND / pediatric study conduct	Pediatric clinical studies conducted per agreed iPSP under an Investigational New Drug (IND) application, with IRB oversight including pediatric expertise, parental permission and child assent	Sponsor / IRB
4	NDA / BLA submission	New Drug Application / Biologics License Application submitted including pediatric assessment (PREA) and,	Sponsor → US FDA (CDER/CBER)

		where sought, pediatric-exclusivity study reports (BPCA)	
5	Query resolution	FDA information requests / deficiency communications issued during review; sponsor responds within FDA-specified timeframes (see Table 8.1)	US FDA ↔ Sponsor
6	Approval / exclusivity determination	NDA/BLA approved with pediatric labelling; BPCA pediatric exclusivity (additional 6 months) granted where applicable; Rare Pediatric Disease Priority Review Voucher issued where applicable	US FDA
7	Post-marketing surveillance	FAERS adverse-event monitoring; Sentinel Initiative active surveillance; Class I/II/III recall mechanism as required	US FDA

Source: Compiled from PREA, BPCA, FDASIA statutory text and US FDA guidance for industry.

8.3 Figure 8.1 (C) – Regulatory Pathway for Market Entry of Pediatric Medicines in the European Union

The EU pathway is distinguished by its mandatory, binding Paediatric Investigation Plan requirement, agreed with the PDCO before an application for marketing authorisation can be validated (unless a waiver applies), and by the availability of a dedicated Paediatric-Use Marketing Authorisation route for off-patent medicines. The eight-step generalised pathway is set out in tabular form below.

The EU pathway is distinguished by the binding nature of the agreed Paediatric Investigation Plan, which, once agreed by the PDCO, becomes a mandatory component of the eventual marketing authorisation application — failure to comply (absent an agreed waiver or deferral) results in the application being deemed invalid by the EMA. This creates a stronger upstream enforcement mechanism than either the Indian or, arguably, the US pathway, at the cost of additional upfront procedural complexity for sponsors. The eight-step generalised pathway is set out in tabular form below.

8.4 Table 8.1 – Classification of Pediatric / Health Medicines and Query-Resolution Timelines.

Step	Stage	Description / Requirement	Responsible Authority
1	PIP / waiver application	Sponsor submits a Paediatric Investigation Plan (or waiver/deferral request) generally after completion of adult human pharmacokinetic studies and no later than completion of Phase 2 adult studies	Sponsor / Applicant
2	PDCO scientific evaluation	Paediatric Committee (PDCO) evaluates the PIP application; may request modification ("negative opinion" / clock-stop for additional information)	EMA – Paediatric Committee (PDCO)
3	PIP decision	PDCO issues a decision agreeing the PIP (with any waivers/deferrals); binding on the sponsor for all subsequent studies and the marketing authorisation application	PDCO
4	Pediatric study conduct	Studies conducted per agreed PIP, involving Enpr-EMA network sites where relevant; national ethics committee approval, parental consent and child assent obtained per member-state law	Sponsor / National Ethics Committees
5	Marketing Authorisation Application (MAA)	Centralised procedure MAA submitted to EMA including PIP compliance statement and study results (or PUMA application for off-patent medicines)	Sponsor → EMA (CHMP)
6	Query resolution	List of Questions / Points to Consider issued during the (typically 210 active-day) assessment; sponsor responds within EMA-specified clock-stop periods (see Table 8.1)	EMA (CHMP/PDCO) ↔ Sponsor
7	Authorisation & incentive award	European Commission grants marketing authorisation (valid across all member states); SPC +6-month	European Commission / EMA

		extension, orphan +2-year exclusivity, or PUMA 8+10-year protection awarded as applicable	
8	Post-marketing surveillance	EudraVigilance adverse-event monitoring; PRAC oversight; EU Rapid Alert System for recalls	EMA / National Competent Authorities

Source: Compiled from Regulation (EC) No 1901/2006, EMA procedural guidance and PDCO working documents.

Table 8.1 below classifies pediatric/health medicines by regulatory category and sets out, for each jurisdiction, the standard evaluation/response timeline together with the specific time period allowed for the sponsor to resolve regulatory queries (deficiency responses / clock-stop periods) in each country.

Table 8.1: Classification of pediatric / health medicines with standard evaluation and query-resolution (deficiency-response) timelines – India, EU and USA.

Classification of medicine	India (CDSCO) – standard timeline / query-resolution period	European Union (EMA) – standard timeline / query-resolution period	United States (US FDA) – standard timeline / query-resolution period
New Chemical Entity (NCE) / New Active Substance with pediatric indication	Evaluation ~ 12–18 months; query response period generally 90 days (extendable once)	Centralised procedure: 210 active days (clock stops during query response; sponsor typically given up to 3–6 months to respond to Day 120/180 questions)	Standard review 10 months (PDUFA goal); major-deficiency (Complete Response) resubmission generally within 12 months of CRL, with FDA response to sponsor queries via Type A/B meetings scheduled within 30–75 days of request
Priority / expedited pediatric medicine (serious/rare pediatric disease)	Priority evaluation ~ 6–9 months where applicable; query response ~ 60 days	Accelerated assessment: 150 active days; expedited query turnaround	Priority review 6 months (PDUFA goal); Rare Pediatric Disease Priority Review Voucher track
Generic pediatric formulation (ANDA-equivalent)	Evaluation ~ 9–12 months; query response ~ 90 days	Decentralised/Mutual Recognition Procedure: 210 days; national query-response clock-stops of 3 months typical	ANDA standard goal ~10 months under GDUFA; deficiency response typically within the sponsor's discretion but subject to GDUFA program metrics
Fixed-Dose Combination (FDC) pediatric product	Additional Subject Expert Committee (FDC Committee) review; ~ 12–24 months; query response 90 days	Evaluated as a new combination medicinal product; 210 active days; standard clock-stop periods apply	Evaluated as a combination product; standard NDA timelines apply; query response per Type A/B meeting timelines
Paediatric-Use Marketing Authorisation (PUMA) [EU-specific] / off-patent pediatric reformulation	No dedicated pathway; treated as new formulation application, ~12–18 months	PUMA procedure: 210 active days from validation; query response clock-stops as per centralised procedure	No PUMA-equivalent; evaluated under standard NDA (505(b)(2)) pathway, ~10 months
Orphan pediatric medicine	Evaluated under general new-drug pathway; no dedicated orphan query timeline	210 active days + orphan designation review (~90 days upstream); 2-year exclusivity bonus on PIP compliance	Standard/priority review per above; orphan designation review ~90 days; 7-year orphan exclusivity (general, not pediatric-specific) plus BPCA 6-month add-on where applicable

Source: Compiled by the author from CDSCO procedural circulars, EMA centralised-procedure timetables, and US FDA PDUFA/GDUFA goal letters. Timelines are indicative, published regulatory benchmarks and may vary by application; sponsors should verify current timelines against the primary regulatory source at the time of submission.

8.5 Interpretation

The comparative pathway diagrams and Table 8.1 together show that all three jurisdictions embed a formal, time-bound query-resolution mechanism within their review process, but differ in the degree to which that mechanism is codified in enforceable, publicly published statutory goals. The US PDUFA/GDUFA goal-letter framework and the EU's centralised-procedure clock-stop system are both codified with published, negotiated performance metrics, whereas India's timelines, while broadly similar in practice, are less consistently codified in a single, publicly available goal-setting document, an observation that is developed further into a specific recommendation in Chapter 9.

8.6 Limitations of the Pathway Comparison

The generalised pathways presented in Figure 8.1 (A)–(C) necessarily simplify what are, in practice, more variable and case-specific procedures. Actual timelines depend heavily on dossier quality, the number and complexity of regulatory queries raised, whether expedited/priority pathways apply, and, in the EU's case, the specific national rapporteur and co-rapporteur assigned to a given centralised-procedure application. Similarly, the query-resolution timelines in Table 8.1 represent published, standard benchmarks rather than guaranteed outcomes; delays arising from major deficiencies, additional data requests, or inspection findings can and do extend actual timelines beyond these published goals in all three jurisdictions. Readers should therefore treat Figure 8.1 and Table 8.1 as a structured, comparative orientation to the three pathways rather than as a precise procedural guarantee for any individual product.

8.6 Limitations of the Pathway Comparison

The generalised pathways presented in Figure 8.1 (A)–(C) necessarily simplify what are, in practice, more variable and iterative procedures; actual timelines and the exact sequence of steps can differ based on product complexity, the quality and completeness of the initial dossier, whether expedited/priority pathways apply, and the number of rounds of regulatory queries required. The timelines in Table 8.1 are drawn from published regulatory benchmarks and should be treated as indicative reference points for academic and planning purposes rather than as guaranteed processing times for any specific application; sponsors should always confirm current timelines directly with CDSCO, the EMA or the US FDA, as applicable, at the time of planning a submission.

CHAPTER 9 SUMMARY, CONCLUSION AND FUTURE SCOPE

9.1 Summary

This dissertation undertook a comparative regulatory analysis of pediatric medicine regulation in India, the European Union and the United States. Chapter 1 established the scientific and historical rationale for pediatric-specific regulation, rooted in the recognition that children are pharmacokinetically and pharmacodynamically distinct from adults. Chapter 2 reviewed the relevant literature in descending chronological order from 2026 back to 2010, tracing the evolution of the field. Chapter 3 set out the aim, objectives, scope and limitations of the study. Chapter 4 provided a detailed, structured account of the governing statutes, institutions, procedures and incentive mechanisms of CDSCO (India), the EMA/PDCO (European Union) and the US FDA. Chapter 5 examined three comparative case studies — the DEG/EG-contaminated pediatric cough syrup episodes, the first EU Paediatric-Use Marketing Authorisation for midazolam, and the persistence of off-label pediatric prescribing — to test the theoretical framework against real regulatory practice. Chapter 6 consolidated the comparative results in tabular and graphical form. Chapter 7 discussed the findings and their public-health implications. Chapter 8 presented a generalised comparative regulatory pathway for

market entry of pediatric medicines, set out separately for India, the USA and the EU, together with a classification of pediatric/health medicines and their associated query-resolution timelines.

9.2 CONCLUSION

The comparative analysis demonstrates that the European Union and the United States operate more procedurally mature, legally mandatory and incentive-linked pediatric medicine regulatory frameworks than India, anchored respectively in the Paediatric Investigation Plan and the PREA/BPCA/iPSP structure. India's framework, while it has made genuine progress through the New Drugs and Clinical Trials Rules, 2019 — particularly in ethics-committee-level pediatric safeguards, informed consent, child assent and compensation provisions — continues to lack a dedicated, mandatory, product-specific pediatric development trigger equivalent to the PIP or iPSP, and lacks a harmonised, class-based recall and public-alert mechanism comparable to those of the EU and the USA.

The recurrent, well-documented DEG/EG contamination episodes associated with Indian-manufactured pediatric cough syrups between 2022 and 2025 illustrate that this regulatory gap has had material, indeed fatal, real-world consequences, both domestically and internationally, and that its resolution is a matter of urgent public-health significance extending beyond India's borders given the country's position as a major global exporter of pediatric formulations.

9.3 Recommendations

Based on the comparative findings of this dissertation, the following recommendations are made to strengthen India's pediatric medicine regulatory framework:

1. Introduce a dedicated, mandatory Pediatric Study Plan (or equivalent Paediatric Investigation Plan-style instrument) within the NDCT Rules, requiring sponsors of new drug applications reasonably likely to be used in children to submit a pediatric development plan, subject to a structured waiver/deferral mechanism, at an early stage of development.
2. Establish a dedicated Pediatric Expert/Review Committee within CDSCO, analogous to the EMA's PDCO or the FDA's PeRC, to provide consistent, specialised scientific evaluation of pediatric development plans and formulation-appropriateness questions.
3. Introduce incentive mechanisms — such as a limited period of additional data exclusivity or a dedicated fast-track review — for sponsors that voluntarily generate robust pediatric data or develop dedicated age-appropriate, off-patent pediatric formulations, drawing on lessons from both the EU PUMA and US BPCA experience regarding the importance of pairing incentives with market-access support.
4. Mandate batch-wise diethylene glycol/ethylene glycol testing of all pharmaceutical-grade glycerin, propylene glycol, sorbitol and other liquid-formulation excipients used in oral pediatric preparations, with results recorded in the batch manufacturing record and subject to third-party verification for high-risk suppliers.
5. Develop a harmonised, publicly searchable, class-based (Class I/II/III) national drug-recall database and rapid-alert communication system, integrating central (CDSCO) and state drug-control authority action, modelled on the EU Rapid Alert System and the US FDA public recall database.
6. Publish a consolidated, statutorily codified goal-letter document (analogous to PDUFA/GDUFA goal letters) specifying standard and priority review timelines, and query-resolution/deficiency-response periods, for different

classes of new drug and pediatric applications, to improve predictability for sponsors and transparency for the public.

7. Strengthen post-marketing pediatric pharmacovigilance by mandating pediatric-specific adverse-event signal review within the Pharmacovigilance Programme of India, with periodic public reporting.
8. Encourage India's continued and deepened engagement with ICH E11(R1) and pursue parallel scientific-advice arrangements with the EMA and US FDA for pediatric development programmes, to reduce duplicative trial burden on sponsors developing medicines for global pediatric markets.

9.4 Suggested Implementation Roadmap

The recommendations in Section 9.3 are, by design, of varying complexity and institutional cost. Table 9.1 below suggests an indicative, phased implementation roadmap, sequencing the recommendations from those that are lower-cost and can be actioned relatively quickly (raw-material testing mandates, recall-database harmonisation) toward those that require more substantial institutional investment and stakeholder consultation (a dedicated pediatric committee, a mandatory pediatric development plan).

Table 9.1: Suggested phased implementation roadmap for strengthening India's pediatric medicine regulatory framework

Phase	Indicative timeframe	Key actions
Phase 1 – Immediate	0–6 months	Mandate batch-wise DEG/EG testing of glycerin/propylene glycol and other high-risk liquid excipients; issue interim CDSCO circular strengthening raw-material certification requirements
Phase 2 – Short-term	6–18 months	Design and pilot a harmonised, class-based (Class I/II/III) national recall classification system and public recall database, integrated with state drug-control authorities
Phase 3 – Medium-term	18–36 months	Publish a consolidated, codified goal-letter document specifying standard/priority review and query-resolution timelines for major application categories, modelled on PDUFA/GDUFA
Phase 4 – Medium-to-long-term	3–5 years	Establish a dedicated Pediatric Expert/Review Committee within CDSCO; pilot a voluntary, incentive-linked pediatric development/formulation pathway for selected off-patent essential medicines
Phase 5 – Long-term	5+ years	Introduce a mandatory, product-specific pediatric development plan requirement (PIP/iPSP-equivalent) for new chemical entities reasonably likely to be used in children, with calibrated waiver/deferral and incentive mechanisms

9.5 Future Scope

This dissertation, being based on secondary, publicly available regulatory and scholarly literature, points toward several avenues for future research:

9. Empirical, primary-data research quantifying the actual extent of off-label and unlicensed pediatric prescribing across Indian hospital and outpatient settings, to establish a robust baseline against which future regulatory reform can be measured.
10. A detailed cost-benefit and health-economic analysis of introducing a mandatory Pediatric Study Plan requirement in India, examining its likely impact on drug-development timelines, cost of pediatric medicines, and domestic pharmaceutical industry competitiveness.

11. A prospective, comparative pharmacovigilance study tracking pediatric adverse-event signal detection and recall response times across India, the EU and the USA following the implementation of any future harmonised Indian recall classification system.
12. Further comparative research examining additional jurisdictions — including Japan, China and the WHO's prequalification framework — to build a more globally representative comparative regulatory model for pediatric medicines.
13. A qualitative study of the root causes of persistent raw-material adulteration in the Indian pharmaceutical supply chain, informing supply-chain-specific, rather than purely clinical-development-specific, regulatory reform.
14. An evaluation, once implemented, of the real-world clinical uptake and market availability of any future India-specific pediatric formulation incentive pathway, drawing lessons from the EU PUMA experience regarding the gap between regulatory approval and practical accessibility.

9.6 Concluding Remark

Pediatric medicine regulation sits at the intersection of pharmaceutical science, public-health policy and child-protection law. As this dissertation has shown through detailed comparative analysis of India, the European Union and the United States, no single regulatory model is without gaps, but the EU and US experience demonstrates that a mandatory, dedicated, incentive-linked pediatric development framework measurably improves the availability of age-appropriate, evidence-based pediatric medicines. India stands at an important juncture: its substantial manufacturing capacity and pharmaceutical expertise position it to become not merely the world's pharmacy for adult generics, but a global leader in age-appropriate pediatric formulation science — provided the identified regulatory gaps are addressed with the same urgency that recent pediatric safety events have demonstrated is warranted.

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