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2024

COMPARATIVE ANALYSIS OF REGULATORY FRAMEWORK FOR PAEDIATRIC AND GERIATRICS ACROSS THE USA, EU AND INDIA

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BACHELOR OF PHARMACY

UNDER THE GUIDANCE OF

DR. CHARMY KOTHARI

INSTITUTE OF PHARMACY
NIRMA UNIVERSITY

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COMPARATIVE ANALYSIS OF REGULATORY FRAMEWORK FOR PAEDIATRIC AND GERIATRICS ACROSS THE US, EU AND INDIA

Thesis submitted to the Institute of Pharmacy, Nirma University,
in partial fulfilment of the requirements for the Degree of

BACHELOR OF PHARMACY

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Semester VIII
(PROJECT WORK BP812PW)

UNDER THE GUIDANCE OF
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DECLARATION BY STUDENT

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This is to undertake that the B. Pharm. Project work (BP812PW) entitled **"COMPARATIVE ANALYSIS OF REGULATORY FRAMEWORK FOR PAEDIATRIC AND GERIATRICS ACROSS THE UAS, EU AND INDIA"** Submitted by **CHANDRABHANSINH CHAVDA (20BPH017), HIMADRI MANDALIA (20BPH042), ISHAVYAS (20BPH047), LABDHI BAVISHI (20BPH058), MAHI SETH (20BPH060)** B. Pharm. Semester VIII is a bonafide research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of **"Dr. Charmy S. Kothari"**. We are aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad.

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List of Abbreviations:

1. USA: United State of America
2. EU: European Union
3. FDA: The Food and Drug Administration
4. PREA: The Paediatric Research Equity Act
5. BPCA: The Best Pharmaceuticals for Children Act
6. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
7. PDCO: The Paediatric Committee
8. PUMA: The Paediatric Use Marketing Authorization
9. PIP: Paediatric Investigation Plan
10. EMA: European Medicines Agency
11. GEG: The Geriatric Expert Group
12. NIMHANS: The National Institute of Mental Health and Neurosciences
13. ICMR: Indian Council of Medical Research
14. NICU: Neonatal Intensive Care Units
15. WHO: World Health Organization
16. COPD: Chronic Obstructive Pulmonary Disease
17. AGS: American Geriatric Society
18. VADT: Veterans Affairs Diabetes Trial
19. ACCORD: Action to Control Cardiovascular Risk in Diabetes
20. ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron-Modified Release Controlled Evaluation
21. ADA: American Diabetes Association
22. AHA: American Heart Association
23. ACC: American College of Cardiology
24. ATS: American Thoracic Society
25. CHEST: The American College of Chest Physicians
26. CVD: Cardiovascular Disorders
27. PSP: Paediatric Study Plan
28. WR: Written Request
29. PPSR: Proposed Paediatric Study Request
30. NDA: New Drug Application
31. BLA: Biologics License Application
32. IPSP: initial Paediatric Study Plan
33. DMF: Drug Master File
34. IPEC: International Pharmaceutical Excipients Council
35. GIP: Geriatric Investigation Plan
36. ADR: Adverse Drug Reaction
37. MA: Marketing Authorization
38. MAA: Marketing Authorization Application
39. LDL: Low-Density Lipoprotein
40. HDL: High-Density Lipoprotein
41. GVP: Good Pharmacovigilance Practices
42. PASS: Post-Authorization Safety Studies
43. AD: Alzheimer Disease

44. EFNS: European Federation of Neurological Societies
45. IDFE: International Diabetes Federation Europe
46. ESC: European Society of Cardiology
47. EASD: European Association for the Study of Diabetes
48. EUGMS: European Union of Geriatric Medicine
49. CHMP: Committee for Medicinal Products for Human Use
50. FPG: Fasting Plasma Glucose
51. CDSCO: The Central Drugs Standard Control Organization
52. DCGI: Drug Controller General of India
53. NHM: National Health Mission
54. VHSNC: The Village Health Sanitation and Nutrition Committee
55. ICDS: Integrated Child Development Service program

Abstract

Understanding the unique pharmacokinetic and pharmacodynamics characteristics of children and the elderly is crucial for tailoring drug effects. Consequently, it's imperative to validate drug efficacy in both demographics. This study delves into dosage and formulation research aligned with national guidelines in the US, EU, and India, focusing on regulatory frameworks for paediatric and geriatric medications. Plans for paediatric clinical studies, incentives, timelines, difficulties, and potential recommendations are covered. The Paediatric Research Equity Act (PREA) of the US Food and Drug Administration (FDA) requires, unless it is waived or postponed, that certain new drug and biologic applications contain a paediatric evaluation. Also Sponsors are encouraged to perform paediatric trials by the Best Pharmaceuticals for Children Act (BPCA), which offers possible 6-month marketing exclusivity or "paediatric exclusivity." Before the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E7 guideline was adopted in 1994, the FDA published a guideline in 1989 for the investigation of drugs anticipated to be used in the elderly (FDA, 1989). The three basic foundations of EU paediatric regulation are the Paediatric Committee (PDCO), the Paediatric Use Marketing Authorization (PUMA), and the Paediatric Investigation Plan (PIP). 2011 saw the release of the Geriatric Medicines Strategy by the European Medicines Agency (EMA), which also established the Geriatric Expert Group (GEG) and followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E7guideline. The Central government of India launched the National Policy for Older Persons in 1999. Organizations like the National Institute of Mental Health and Neurosciences (NIMHANS) are increasingly utilizing tele psychiatry services, especially geriatric tele psychiatry. Clinical studies involving children require adherence to ethical guidelines as specified by the Indian Council of Medical Research, in addition to regulatory guidelines. However, unlike the USA and EU, India lacks precise criteria for the development of paediatric and geriatric medicine.

1. Introduction

Paediatrics and geriatrics, as specialized branches of medicine, are vital for the healthcare needs of two distinct age groups: children and the elderly. Regulation of paediatric and geriatric care is essential to ensure the delivery of high-quality, evidence-based healthcare services tailored to the unique needs of these populations. In the United States, paediatric and geriatric care are regulated by a combination of federal and state laws, as well as professional organizations. The American Academy of Paediatrics (AAP) sets standards and guidelines for paediatric healthcare. Similarly, the American Geriatrics Society (AGS) provides guidance on the care of older adults. Also FDA has established BPCA (Best pharmaceuticals for children Act) and PREA (Paediatric Research Equity Act). In Europe, regulation of paediatric and geriatric care varies among countries due to differences in healthcare systems and cultural norms. However, several European organizations, such as the European Academy of Paediatrics (EAP) and the European Geriatric Medicine Society (EuGMS), play essential roles in setting standards and guidelines for these specialties. In India, paediatric and geriatric care are regulated by various governmental bodies and professional organizations. The Indian Academy of Paediatrics (IAP) sets guidelines for paediatric healthcare. Similarly, the Geriatric Society of India (GSI) plays a crucial role in promoting standards of care for older adults in the country. Government agencies such as the Ministry of Health and Family Welfare oversee healthcare policies, licensure of healthcare providers, and reimbursement mechanisms for paediatric and geriatric services. While there are stringent regulations in US and EU, India lacks such definite guidelines and relies on broader regulations of Schedule Y and ICH guidelines.

2. Regulatory framework in the US

2.1. FDA

The Food and Drug Administration (FDA) protects public health by guaranteeing the safety, efficacy, and security of drugs for humans and animals, along with biological products and medical devices. It also advances public health by promoting technological innovations that enhance the effectiveness, safety, and affordability of medical products, and by offering trustworthy, evidence-based information to assist individuals in using food and medical products to improve their health.

2.2. Regulations Governing the Elderly

Elderly patients, who predominantly use medications, have traditionally been underrepresented in clinical trials, leading to gaps in our knowledge of how drugs affect this varied group. With the global population aging, there's a growing need for safe and effective medications for seniors. Common chronic conditions in the elderly, like cardiovascular diseases, dementia, Parkinson's disease, COPD, depression, diabetes, cancer, and musculoskeletal disorders, often coexist, known as comorbidity. Polypharmacy compounds this complexity as individuals take multiple medications at once (Shenoy and Harugeri 184).

2.2.1. WHO Classification of the Elderly Population

i. Elderly: 60 to 75 years old
ii. Old: 76 to 90 years old
iii. Very old: Above 91 years old

Nonetheless, an increase in the average life expectancy of the Indian populace could indicate a future rise in the retirement age in India (Shenoy and Harugeri 184).

2.2.2. The USA's Geriatric Regulatory Framework: A Look at the Food and Drug Administration (The FDA)

In 1989, the FDA introduced a guideline for studying medications meant for elderly use, which came before the adoption of the ICH E7 guideline in 1994. Following that, in 1997, the FDA created the Geriatric Use section within the Precautions part of labelling for biological products and prescription drugs. This section required the inclusion of pertinent data on the use of these products in the elderly. This requirement applied retroactively, meaning holders of approved medicinal products had to submit a supplement for geriatric labelling (The FDA, 2001).

In 2014, the FDA introduced the "FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data," focusing on improving the inclusion of demographic subgroups, such as those over 75, in clinical trials. This initiative prioritizes identifying barriers to their enrolment and implementing strategies to increase their participation. The FDA also collaborates with the industry to ensure that trial enrolment criteria are appropriately applied to avoid excluding older patients (Spiegeleer et al. 23).

2.2.2.1. Treatment of hyperglycaemia in elderly patients with diabetes mellitus

The American Geriatric Society's Guidelines prioritize managing six geriatric syndromes polypharmacy, depression, cognitive impairment, urinary incontinence, injurious falls, and pain over strictly adhering to glycaemic goals. The group recognizes that treating hypertension and dyslipidaemia for two years can decrease cardiovascular disease risk, while aggressive glycaemic control takes eight years to lower the risk of diabetic microvascular complications. Thus, managing cardiovascular risk factors can have a greater impact on reducing morbidity and mortality than stringent glycaemic control (Baruah et al. 75)

Table 2.1: Results of the veteran affairs, diabetes trial based on American geriatric society (Baruah et al. 75).

	American Diabetes Association	Veteran Affairs Department	American Geriatric Society
Glycated Hb target	<7.0 %	7.0% in adults with life expectancy of > 15 years along with good functional status (no major comorbidity). 8.0% if frail or if life expectancy is 5-15 years (in the presence of moderate co-morbidities). 9% if life expectancy is <5 years (major co-morbidities).	< 7.5% in adults who have good functional status. 8% if frail or life expectancy is <5 years.

According to findings from the Veterans Affairs Diabetes Trial (VADT), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Action in Diabetes and Vascular Disease: Preterax and Diamicron-Modified Release Controlled Evaluation (ADVANCE) trials, the American Diabetes Association (ADA), The American Heart Association, and American College of Cardiology have advised that for patients with a history of severe hypoglycaemia, advanced atherosclerosis, advanced age, or frailty, the potential risks of intensive glycaemic control may outweigh the benefits.

2.2.3. The management and epidemiology of respiratory diseases in the elderly

The regulatory framework for treating patients with respiratory disorders in the geriatric population in the USA involves several key steps:

1. Clinical Assessment and Diagnosis: Healthcare providers conduct comprehensive assessments to diagnose respiratory disorders in geriatric patients. This may include medical history, physical examination, lung function tests, imaging studies, and other diagnostic procedures.
2. Evidence-Based Treatment Guidelines: Healthcare providers follow the evidence-based treatment guidelines established by professional medical organizations such as the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST). These guidelines provide

recommendations for the management of specific respiratory disorders in older adults.

3. Medication Management: Healthcare providers prescribe medications according to established guidelines for the treatment of respiratory disorders in geriatric patients. This may include bronchodilators, corticosteroids, antibiotics, and other medications to manage symptoms and improve lung function (Akgün et al. 276).
4. Non-Pharmacological Interventions: In addition to medications, non-pharmacological interventions such as pulmonary rehabilitation, oxygen therapy, smoking cessation programs, and vaccination against respiratory infections are important components of treatment for respiratory disorders in older adults.
5. Monitoring and Follow-Up: Healthcare providers monitor geriatric patients with respiratory disorders closely to assess treatment response, manage medication side effects, and adjust treatment plans as needed. Regular follow-up visits and monitoring of symptoms and lung function are essential for optimizing patient outcomes.
6. Coordination of Care: Effective management of respiratory disorders in geriatric patients often requires multidisciplinary care involving primary care providers, pulmonologists, respiratory therapists, nurses, pharmacists, and other healthcare professionals. Coordination of care among these providers ensures comprehensive and integrated treatment.

Professional medical organizations and government agencies primarily establish regulatory guidelines for the treatment of respiratory diseases in the geriatric population. These guidelines aim to provide evidence-based recommendations for the diagnosis, treatment, and management of respiratory diseases in older adults. (Akgün et al. 291) (Ceci et al. 948)

2.2.4. Treatment of Cardiovascular Disorders in USA

The US regulatory framework for CNS disorders in older adults focuses on drug development, clinical trials, and treatment guidelines. Healthcare providers diagnose cardiovascular conditions through assessments and tests, following evidence-based guidelines for treatment, including medications and lifestyle changes. Monitoring, follow-up, and coordination among healthcare professionals are crucial. Patient

education, empowerment, and adherence to regulations are vital for geriatric cardiovascular care.

1. Specialized Care Programs: Implementing specialized care programs for older adults with cardiovascular disorders, including heart failure clinics, cardiac rehabilitation programs, and multidisciplinary care teams.
2. Healthcare Policy Development**:** Developing healthcare policies that address the unique needs of older adults with cardiovascular disorders, including access to care, insurance coverage, and reimbursement policies.
3. Public Health Initiatives: Implementing public health initiatives aimed at preventing cardiovascular disorders in the geriatric population, such as promoting healthy lifestyles, smoking cessation programs, and vaccination campaigns.
4. Quality Metrics: Establishing quality metrics and performance measures for the management of cardiovascular disorders in older adults to ensure the delivery of high-quality care.
5. Research and Innovation: Supporting research and innovation in the field of cardiovascular disorders in older adults, including clinical trials, biomarker studies, and technology development.

By addressing these additional aspects, the regulatory framework for cardiovascular disorders in the geriatric population in the USA can be further enhanced to improve outcomes and quality of life for older adults with CVD (Arnett et al. 597).

2.2.5. Clinical trials and the moral implications of elder care medications

The Food and Drug Administration (The FDA) and other regulatory bodies primarily govern the regulatory framework for clinical trials involving the geriatric population in the USA. Here is an overview of the key aspects of this framework along with references to relevant regulations and guidelines:

1. Inclusion of Geriatric Participants
2. Ethical Considerations
3. Safety Monitoring
4. Data Analysis
5. Geriatric Pharmacokinetics
6. Post-Marketing Surveillance

2.3. Paediatric regulations in USA

Children's responses to medication differ significantly from adults due to variations in serum protein composition and body water content. Understanding these pharmacokinetic and pharmacodynamics disparities is vital to ensuring safe and effective treatment for paediatric patients. Currently, a significant portion of prescriptions for children involve "off-label" medications, lacking proper safety and efficacy evaluations. This practice puts children at risk of experiencing unforeseen side effects and receiving inappropriate doses, highlighting the urgent need for thorough examination of pharmaceuticals in paediatric populations to optimize their healthcare outcomes. (Field and Boat 34)

2.3.1. The US FDA'S Regulatory Legislation for Paediatric Drug

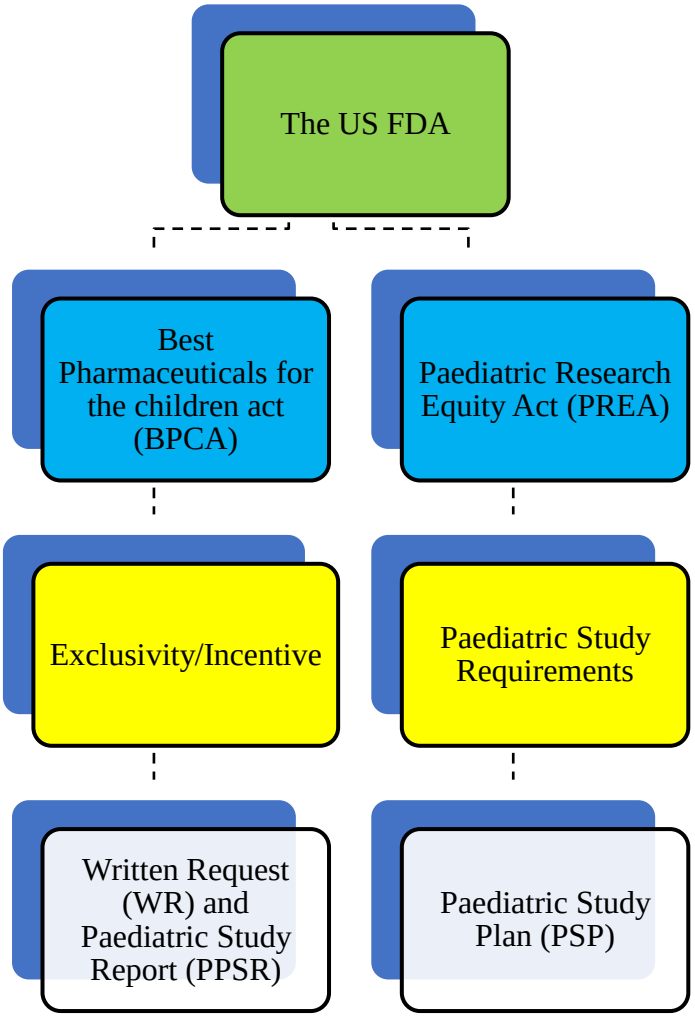


Figure 2.1. Flow Chart for Paediatric Regulations (Parashar 2020).

2.3.2. Regulatory procedure in BPCA

1) Sponsor submits the Proposed Paediatric Study Request (PPSR) to FDA and requests to issue Written Request (WR).
2) FDA issues WR to sponsor without PPSR

Sponsor need to understand all the rule related to exclusivity before submitting the PPSR and should consider if there is sufficient time to complete the requested studies to benefit from the exclusivity. It's up to the FDA to grant exclusivity or not if all the conditions are fulfilled (Parashar 4).

2.3.3. Conditions for exclusivity

For exclusivity to be granted:

- A written request from the FDA is required. Studies submitted before the request will not qualify.
- The specified timeframe and terms in the request must be met.
- The active moiety must have remaining patent life or exclusivity. There's no financial incentive for sponsors of off-patent products to conduct paediatrics studies.

2.3.4. Sponsor submits the Proposed Paediatric Study Request (PPSR) to the FDA and requests to issue WR

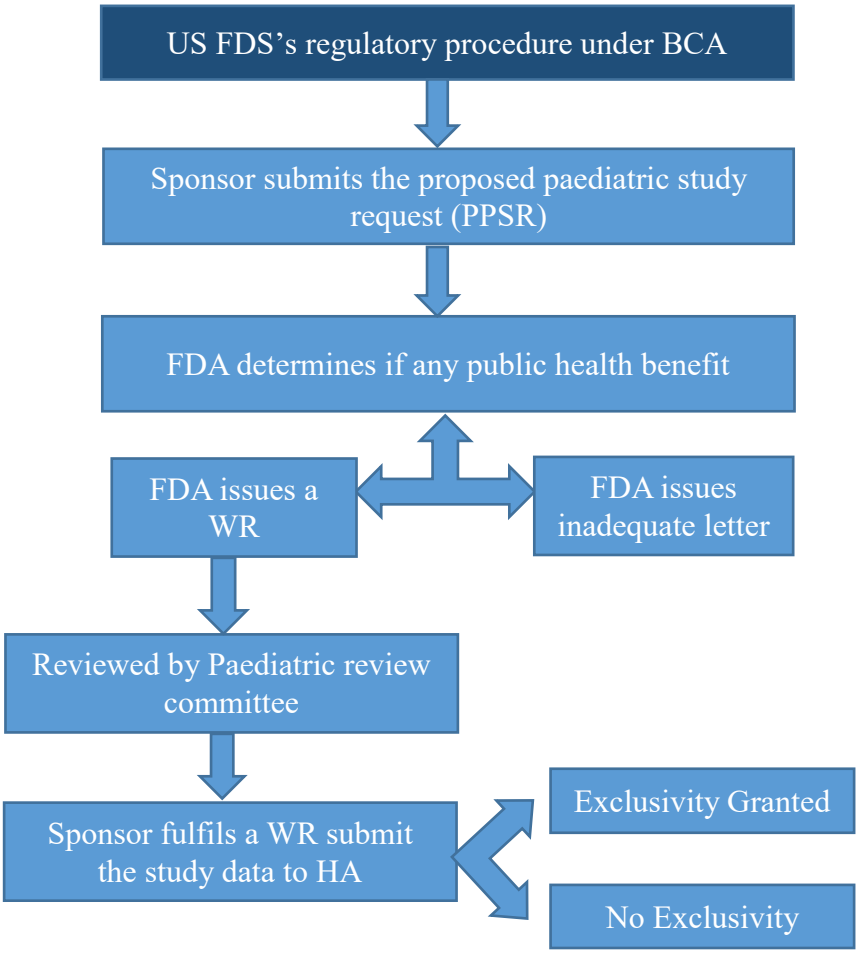


Figure 2.2: Regulatory Procedure with PPSR.(Parashar 2020)

2.3.4.1. FDA issue WR to sponsor without PPSR

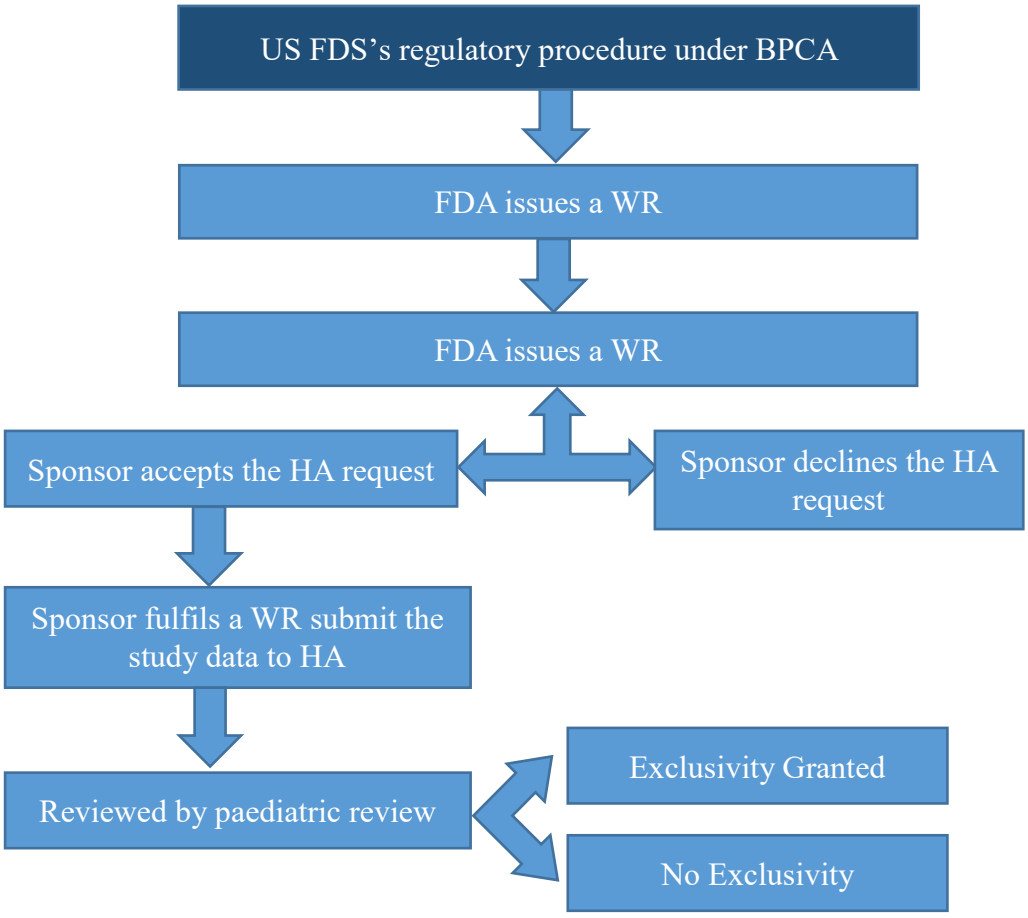


Figure 2.3: Regulatory Procedure without PPSR (Parashar 2020).

2.3.5. Regulatory Procedure to PREA

2.3.5.1. The US FDA'S REGULATORY PROCEDURE UNDER PREA:

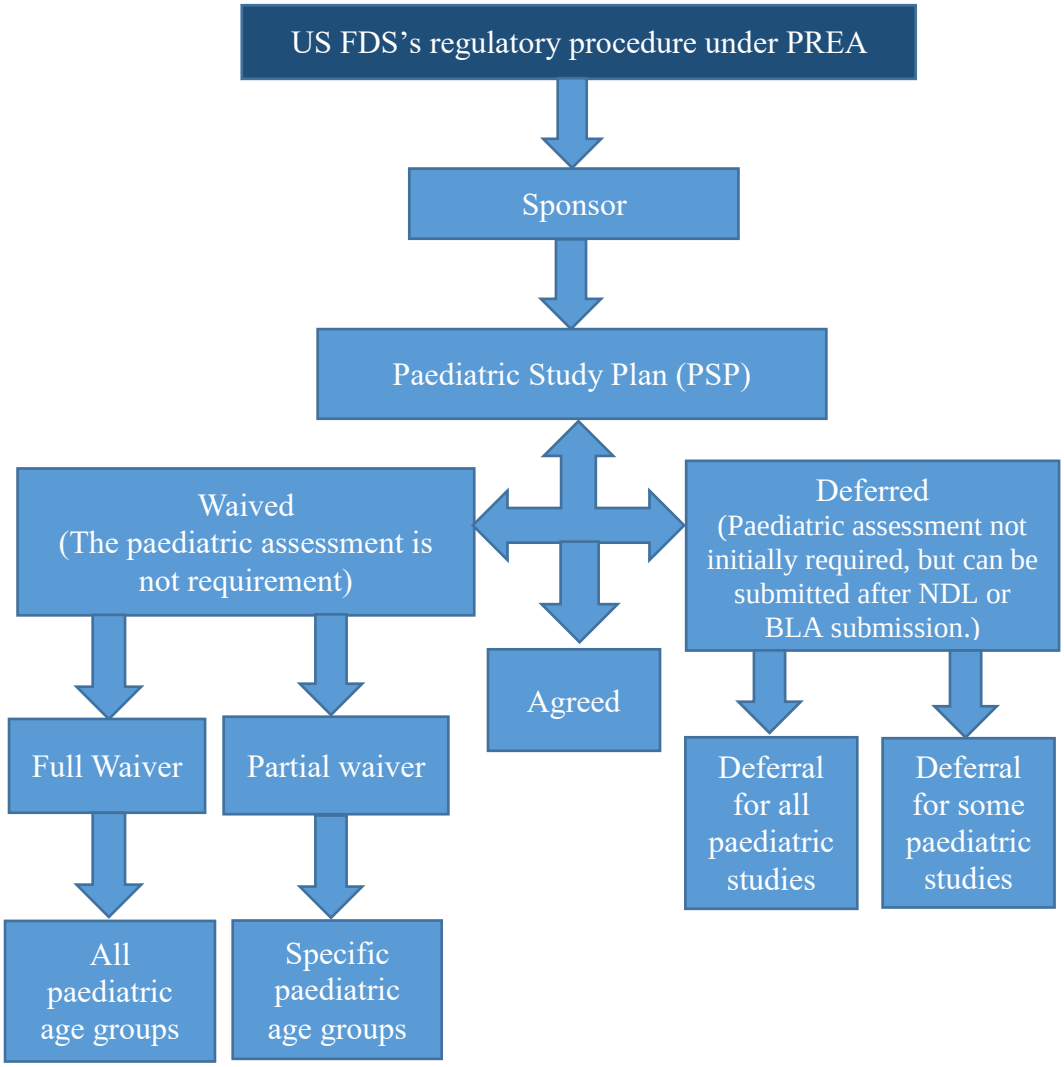


Figure 2.4. Regulatory Procedure under PREA (Parashar 2020).

2.3.5. PREA

The Paediatric Research Equity Act (PREA) mandates paediatric assessments for new drug applications, unless waived. An initial Paediatric Study Plan (iPSP) must be submitted within 60 days after an end-of-phase 2 meeting, or earlier for life-threatening conditions. Agreement on the iPSP is required before submitting a New Drug Application (NDA) or Biologics License Application (BLA).

2.3.6. BPCA

The Best Pharmaceuticals for Children Act (BPCA) offers sponsors a 6-month marketing exclusivity, termed "paediatric exclusivity," as an incentive for conducting paediatric studies. Unlike PREA, BPCA allows studies for any indication benefiting public health, not just those in the New Drug Application (NDA) or Biologics License Application (BLA). Sponsors must meet FDA study requirements outlined in a Written Request (WR) to qualify (Field and Boat 34).

2.3.7. Challenges

The majority of FDA excipient guidelines are based on IPEC recommendations, which provide safety tests for new excipients. Testing for excipients is case-by-case, referencing ICH Safety Testing Guidelines. DMF systems for excipients are available, with the IPEC-Americas Master File Guide offering a format for submissions. Excipients, colorants, etc., are classified as Type IV DMFs. DMFs can support new drug applications. FDA discusses testing strategies for short-, intermediate-, and long-term usage and considers a "family approach" for related excipients. However, its applicability to paediatric products is unclear. Juvenile toxicity studies are required for paediatric products, including excipients, but there's no separate approval process for them (Saito et al. 11).

3. Regulatory framework in EU

The European Medicines Agency (EMA) is a decentralized agency of the EU responsible for evaluating, supervising, and monitoring the safety of medicines. It safeguards public and animal health in the EU Member States and the European Economic Area by ensuring that all medicines on the EU market are safe, effective, and of high quality. The EMA collaborates with national regulatory authorities in the EU Member States through the European medicines' regulatory network. The agency consists of the Secretariat (about 600 staff members), a management board, seven scientific committees, and several scientific working parties.

3.1. EMA

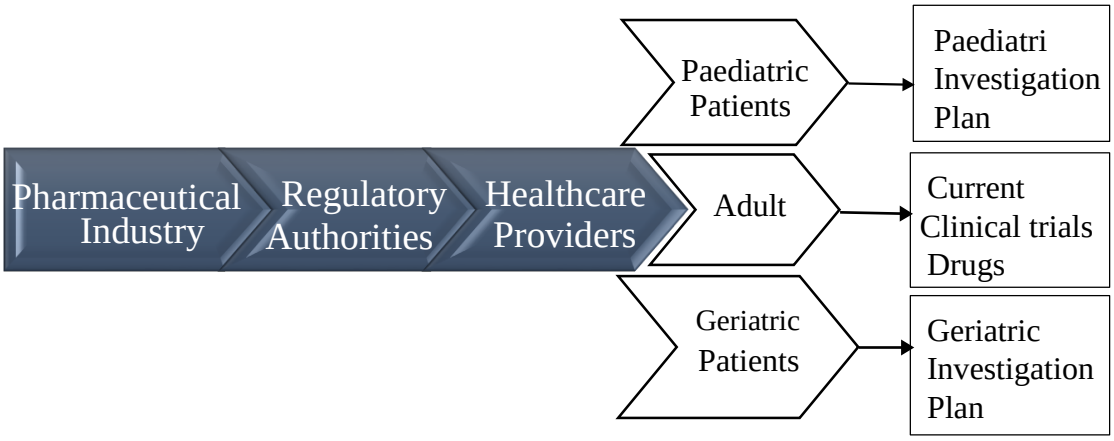


Figure 3.1: A Graphical overview of the regulatory pathway for paediatrics and geriatrics.

3.2. The Regulatory framework for paediatrics

The European Union considers the paediatrics population as individuals aged 0 to 18 years. Paediatric research is crucial for creating safe and effective treatments for children. The current regulatory framework, called the "Paediatric Regulation" (Regulation EC No 1901/2006), became effective on January 26, 2007(Sowmya et al. 2023). It establishes three main components: the Paediatric Committee (PDCO), Paediatric Use Marketing Authorization (PUMA), and Paediatric Investigation Plan (PIP) (Chinmayi et al. 3067).

- The Paediatric Committee (PDCO) in the EU, similar to the US Perc, is composed of specialists and is responsible for evaluating Paediatric Investigation Plans (PIPs) to ensure compliance with EU paediatric regulations.
- In the EU, a Paediatric Investigation Plan (PIP) is required for all new pharmaceutical products, unless waived or deferred. It is a critical document submitted early in development, often after Phase I, and contains information on pharmacokinetics, safety, and efficacy in paediatric patients. The PIP is limited to 40 pages and includes product data, treatment benefits, waiver requests if applicable, and proposed paediatric development plans.
- Evaluation and timeline procedures for PIP: Upon submission of an "intent to file," the PDCO appoints a rapporteur and peer reviewer to evaluate the initial PIP. The evaluation process, which lasts 120 days, includes a pause on Day 60 for the PDCO to interview the applicant. The PDCO then reviews the results from the rapporteur and peer reviewer to ensure high-quality evaluation.
- Paediatric Use Marketing Authorisation (PUMA): The EMA grants PUMAs for drugs intended solely for use in children, valid throughout the European Economic Area like standard EMA approvals. PUMA applicants must adhere to PDCO-approved PIPs. Partial fee waivers are available, and data for PUMA-approved drugs are protected for ten years.

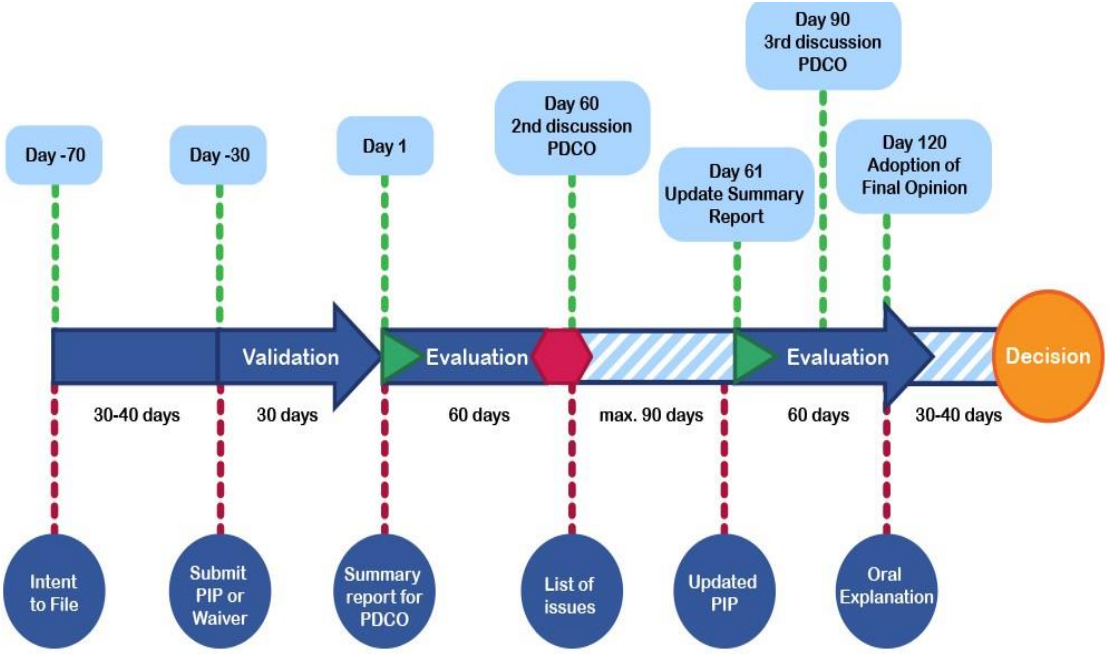


Figure 3.2: Paediatric Investigation Plan Assessment Procedure (Chinmayi et al. 2023).

3.2.1. Clinical Safety and Pharmacovigilance before authorization of a Paediatric Indication

In 2020, 11% of clinical trials in the European Clinical Trials database involved experimental medical products for children. In Europe, individuals aged 14 to 18 can independently consent to participate in clinical research. EudraCT, created by the EMA, is an EU database that enhances transparency in clinical trials. EnprEMA promotes high-quality, ethical paediatric medical research. The EU Risk Management Plan for paediatric medications should address specific concerns like drug errors and "off-label" use. Directive 2001/20/EC, Article 4, laid the groundwork for integrating paediatric trials into adult drug development. The ICH Guidance 11 requires pharmaceutical companies to conduct clinical trials in children, following a Paediatric Investigational Plan, in exchange for six-month patent protection. Parents must provide informed consent for their children to participate in clinical studies (Lepola et al. 582).

3.2.2. Post authorisation safety studies

These can be categorized into three main types:

I. Trials aimed at proving safety by studying large patient groups to expand safety data.

II. Trials meant to identify new safety concerns (hazard detection).

III. Trials intended to assess known safety concerns, such as those identified before authorization.

Screening for adverse reaction in Eudravigilance:

What properties define an effective signal detection system?

- Sensitivity: Probability that a known ADR would be detected.
- Positive predictive value (PPV or precision): Probability that a DEC highlighted for review identified an ADR
- Time to detection of known ADRs.

Steps for designing a statistical signal detection system include:

- selecting a method for disproportionality,
- setting thresholds for statistically significant drug-event associations,
- Conducting stratification and subgroup analysis.

The proportionality statistic compares the observed proportion of adverse events with a medication to the expected proportion without any correlation. In the EV signal detection system (eRMR) for paediatrics populations, within-group disproportionality is used, calculated as Relative Paediatric ROR = RORPaed/RORRes.

3.2.3. Impact of European paediatric Regulation (EC) N◦ 1901/2006 with respect to satisfying the paediatric therapeutic needs

Between January 26, 2007, and December 2019, the European Paediatric Regulation (EC) No. 1901/2006 became effective, mandating the development of Paediatric Investigational Plans (PIPs) and establishing the European Medicines Agency-Paediatric Committee (EMA-PDCO) (Toma et al. 4). A study examined paediatric medications approved by the EMA during this period, analysing various factors such as approval year, active ingredient, authorization basis, medication type, and orphan drug status, indication for paediatric use, and quantity and type of paediatric studies conducted. Results were compared with data from 1996 to 2006. The analysis revealed that although the ratio of paediatric to total medicinal products remained stable before and after the implementation of the Paediatric Regulation, there was a decline in the ratio of paediatric to total active substances. Following PIP submission, a significant portion of paediatric medicinal products (p-MPs) were accepted per Paediatric Regulation guidelines, while others were approved without a PIP per Directive 2001/83/EC (Toma et al. 4). One notable difference between PIP and non-PIP group medications was the number of paediatric studies conducted per product, with the PIP group having a higher studies-to-product ratio. The majority of non-PIP group medications were off-patent drugs repurposed for paediatric use, extending therapeutic indications to untreated juvenile ages. This suggests that repurposing older pharmaceuticals for paediatric use could reduce off-label use of adult medications in children with various serious conditions. (Toma et al. 8)

Table 3.1: Number of p-MPs and p-ASs and after the Paediatric Regulation.(Toma et al. 3)

	1996-2006	2007-2019	Total
Total MPs	314	876	1190
Total p-MPs	109	296	405
p-MPs/MPs ratio	35%	34%	34%
Total ASs	238	605	843
Total p-ASs	106	216	322
p-ASs/ASs ratio	45%	36%	38%

Table 3.2: Paediatric studies by study type (Nici et al. 1390; Toma et al. 7).

Study type	Studies in the PIP group	Studies in no -PIP group
PK/PD	161	18
Efficacy/safety	178	21
PK/PD/Efficacy/Safety	89	27
Observational/Met analysis	10	5
Extrapolation/Modelling /simulation	18	5
total	456	76

Table 3.3: The EU paediatric regulation (Ceci et al. 949).

	Obligation	**Incentive***	
New medicine	Mandatory PIP or waiver	6 months extension of patent	Necessary for validation of MAA
Approved and on patent medicine	Mandatory PIP or waiver	6 months extension of patent	When new indication, new route ,new formulation Necessary for validation
Orphan medicine	PIP or waiver	2 years of market exclusivity	In addition to 10 years for any orphan drug
Off patent medicine	Voluntary PIP	10 years of data protection	Commission funds paediatric use MA (PUMA)

*once, if compliance with PIP + Product information

3.2.4: Guidelines for treatment of hypertension in paediatrics

Although it is not a prevalent issue in children, hypertension is considered a serious cardiovascular risk factor with potential health consequences. When measured repeatedly, systolic and/or diastolic blood pressure in children and adolescents should be at or above the 95th percentile. This condition is known as hypertension. Emergent consequences in severe childhood hypertension can also include cerebrovascular accidents, encephalopathy, seizures, stroke, abrupt heart failure, and pulmonary oedema (Redon et al. 9).

Human Pharmacology studies:

It is necessary to give PK data for all pertinent paediatric age groups. Measures (such as study methodology, such as less invasive sample techniques, sparse sampling, and population PK) to reduce discomfort and anguish resulting from blood sampling in studies must be anticipated and described. The applicant must address potential

variations in pharmacology, metabolism, and the dose-response slope and PK/PD relationship based on Age (Redon et al. 9).

3.2.5: Guidelines for treatment of lipid disorders in paediatrics

In children with inherited lipid abnormalities, also known as primary lipid disorders, the atherosclerotic process starts in childhood and progresses through known risk factors. The diagnosis and classification of primary lipid diseases in children should be based on LDL cholesterol levels, family history, and, if necessary (e.g., homozygous hypercholesterolemia), genetic study. Secondary lipid diseases will be diagnosed and classified based on the kind of dyslipidaemia and its related cardiovascular risk (Redon et al. 9).

Strategy – Design**:**

Human Pharmacology Studies: When appropriate, the creation of unique paediatric formulations is recommended. In this context, the size of the tablet or capsule may matter. It is necessary to supply pharmacokinetic data for the specified age group.

Safety Aspects:

Instructions for reducing the dosage of the medication in the case of an adverse event have to be included in studies. Drugs belonging to a new class of agents should be followed up with for at least two years. Post-marketing follow-up cohorts will yield more information, such as cardiovascular outcome data. It is important to monitor any changes in steroid hormone profiles and their biological effects while on HDL-cholesterol increasing medication (Redon et al. 10).

3.3. Regulatory framework for geriatrics

To address the specific needs of elderly patients in drug development and access, the European Medicines Agency (EMA) introduced the Geriatric Medicines Strategy in 2011. Its aims include ensuring high-quality medications, filling knowledge gaps, and improving information availability for informed prescribing. Key actions include consultations, forming a Geriatric Expert Group (GEG), and following the ICH E7 guideline. In 2013, the benefits of including geriatric data in new drug information became evident. However, challenges with guideline compliance led to

recommendations for more geriatric expertise in guideline development. Through inclusive collaboration, the EMA is working on a reflection paper on the quality of geriatric medicines to enhance industry and regulatory standards. These ongoing efforts demonstrate a commitment to developing improved drugs for older citizens (Spiegeleer et al. 23).

3.3.1. Geriatrics clinical trials - GCP- regulatory consideration

The Clinical Trials Regulation 2014/536 enforces strict safety and transparency standards for pharmaceutical research in the EU. Member States and EEA nations oversee trial evaluation, authorization, and supervision, streamlining the process with a single electronic submission. The European Medicines Agency is emphasizing a geriatric medication strategy, with half of recent dossiers focusing on patients aged 65 and older. However, there are concerns about the lack of clear evidence on new pharmaceuticals for the elderly, as aging significantly affects drug reactions. Understanding these age-related changes is crucial for adjusting prescriptions and minimizing side effects in older patients. The ICH recommends including at least 100 older participants in phase III trials, particularly for age-related diseases, to ensure thorough testing (Shenoy and Harugeri, 184; Marum 2).

3.3.2. Geriatric Pharmacovigilance

Pharmacovigilance, as defined by the World Health Organization, involves post-authorization actions to identify, evaluate, understand, and prevent adverse drug events and other drug-related issues. Research indicates that inappropriate drug use, especially among seniors, often leads to adverse drug reactions. This includes off-label use, drug interactions, incorrect dosage or duration, and contraindicated situations. Age-related changes in medication dynamics and comorbidities, along with polypharmacy, increase the elderly population's risk.

In 2012, the EU implemented Good Pharmacovigilance Practices (GVP) laws, but these lack specific guidance for pharmacovigilance in the elderly, unlike for paediatrics. The EMA's Geriatric Medicines Strategy highlights the need for tailored approaches. However, current GVP modules and FDA recommendations offer

limited direction for older adults. Pharmacovigilance in the elderly is challenging due to age-related assumptions that may underestimate adverse effects, along with the complexities of polypharmacy and comorbidities. It is crucial to include representative senior populations in pre-authorization clinical studies. Risk Management Plans should address benefit/risk gaps and include post-authorization studies in the EU if older groups are excluded. When the EMA requests these post-authorization safety studies (PASS), they become legally binding (Baruah et al. 75).

3.3.3. Polypharmacy management

This study examines the impact of polypharmacy on adverse drug reactions (ADRs). Of the 61 adverse responses observed, 34.4% of patients were prescribed 11–15 medications, while 54% were administered 6–10 drugs. Only 6.5% of the population took 0–5 medications, and 4.9% were prescribed 16–20 drugs. Polypharmacy, defined as the use of five or more medications, is often associated with excessive or inappropriate medication use for a clinical issue. People taking many medications as they age are more likely to experience ADRs due to either a synergistic effect or changes in drug effects through interactions. There is a direct correlation between the number of drugs taken and the increased risk associated with multiple medication therapy. Statistical analysis using Spearson's rho showed a significant correlation between age and polypharmacy ($p=0.000$). Studies indicate that most patients take six to ten medications, although one survey in Nigeria found that 51.8% of patients had prescriptions for three to four medicines. Another study found an ADR incidence of 10.5% and a polypharmacy prevalence of 70% in the study population (Sreekala et al. 7).

3.3.4. Challenges

The main issue is changed organ functioning, which show themselves in different ways in the elderly population. As an example, the aging process affects the immune system, skin physiology, gut microbiota composition, blood–brain barrier, and stem cells.

1. Elderly face organ function changes, impacting communication, activity, finances, comfort, and health.
2. Combat communication challenges with tech education and regular contact.
3. Promote physical activity with accessible resources and tech tools.
4. Address financial literacy and fraud concerns through education and services.
5. Enhance comfort and fulfilment with social support and healthcare access.
6. Support seniors in managing chronic health conditions with accessible healthcare and treatment options (Stuck and Masud 4).

3.3.5. Regulations for Alzheimer's disease (AD) and other dementia disorders

In Western Europe, Alzheimer's disease and related dementias present significant challenges to individuals' physical, social, and mental well-being, along with caregiver stress. Annual healthcare costs for dementia exceed 55 billion euros in Europe, primarily due to institutional care. Despite the benefits of early detection, treatment, and support highlighted by research, diagnosis and treatment rates vary across Europe. Neurologists and interdisciplinary teams collaborate with general practitioners to diagnose and treat dementia. A task group formed in 2003 updated the EFNS dementia guideline, providing evidence-based recommendations focusing on diagnostic evaluation and therapy for Alzheimer's disease and other dementias. Recommendations are tailored to patient characteristics and resource availability, offering flexibility while maintaining minimal practice standards based on clinical presentation and resources (Waldemar et al. 14).

Management of Alzheimer's disease (AD) and other dementia disorders:

Specialist physicians should collaborate with dementia care specialists to address the complex needs of patients and caregivers. Regular follow-up visits are essential to: (1) assess symptoms and functional status, (2) evaluate treatment effectiveness, (3) manage concomitant conditions, (4) assess caregiver burden, (5) identify sources of support, (6) provide counselling on various issues, and (7) implement necessary interventions. Ideally, caregivers should accompany patients to appointments. This guideline focuses on pharmaceutical treatments and excludes aspects like living arrangements and end-of-life concerns. Only clinically studied medications for dementia, not cognitive illness, are considered, including negative outcomes if

published. Recommendations are based on data's affect size and therapeutic relevance, not just the type of evidence (Waldemar et al. 14).

3.3.6. Regulations for Cardiovascular disease

In Europe, cardiovascular disease (CVD) is the leading cause of premature death and disability, leading to high medical costs. Several organizations, including the AHA, ACC, and ESC, have issued numerous guidelines accessible through National Societies' websites. However, the proliferation of guidelines risks reducing their credibility. To tackle this, the ESC and others advocate for clearer guideline development and dissemination processes. The Third Joint Task Force has released updated European recommendations, incorporating new data (De Backer et al. 10). The Task Force now includes the International Diabetes Federation Europe and the European Association for the Study of Diabetes, leading to substantial revisions to previous recommendations:

1. Focus on CVD Prevention: Guidelines now emphasize preventing all cardiovascular diseases, not just coronary heart disease, due to shared causes and risks.
2. Improved Risk Assessment: Use risk charts and the SCORE model to evaluate 10-year risk of fatal cardiovascular events, adjusting for national variations.
3. Clinical Priorities and Imaging: Prioritize high-risk cardiovascular disease patients and use new imaging techniques to identify subclinical atherosclerosis.
4. Incorporating Recent Knowledge: Guidelines include latest research on dietary changes, effective risk management, and medications, even for elderly and those with low cholesterol.

The recommendations aim to be adaptable to different situations and call for national guidelines on preventing cardiovascular disease. Collaboration among various professional groups is essential, considering social, political, economic, and medical factors. The guidelines propose inclusive solutions for all communities to tackle the significant burden of cardiovascular disease in Europe focusing on high-risk individuals (Backer et al. 1603).

3.4. Comparison between regulations of Paediatrics and Geriatrics in EU

Table 3.4: Comparison between regulations of Paediatrics and Geriatrics in EU.

Paediatrics	Geriatrics
PIP - the foundational document for the creation and approval of a paediatric medicinal product, must be filed early in the development of a new chemical.	GIP - This plan outlines how pharmaceutical firms will study their products' effects on older patients to ensure safety and efficacy in clinical trials.
The Paediatric Committee (PDCO): At EMA, it was founded. A new kind of marketing was created with the Paediatric Use Marketing Authorization (PUMA).	European Union of Geriatric Medicine: All of the geriatric medicine professionals' national societies in the European Union and its member states make up the EUGMS.
EMA created EudraCT, an EU clinical trial database listing paediatric and pharmaceutical needs by therapeutic sectors for greater openness and accessibility.	The EMA and CHMP will review adding geriatric safety and efficacy requirements for papers, particularly for conditions affecting a significant geriatric population.

4. Regulatory framework in India

The Central government established the National Policy for Older Persons in 1999 to enhance the health and welfare of senior citizens. In 2017, India had a total of 9,909,501 fatalities, with an estimated 59% of them belonging to the older population. The primary causes of death among seniors are cancer, chronic respiratory disorders, stroke, and cardiovascular diseases, which align with data from the Sample Registration System (2010–2013). (Malik et al. 72)

4.1 Regulatory Framework for diseases in elderly in India

4.1.1. Respiratory Disorders

Over 90% of tuberculosis cases among the elderly originate from within the body, and the disease is increasingly common in this age group. Among seniors, the mortality rate from tuberculosis is 20%, compared to 3% in younger individuals. COPD is one of the leading causes of death and illness among the elderly. Due to having two or more other health conditions and limitations in daily living activities, COPD patients often experience poor health status and quality of life. Asthma affects people of all ages, including the elderly. Physician-diagnosed asthma prevalence ranges from 6% to 10% in older individuals. In a cohort study, nearly a quarter of 1485 older asthmatics recruited by chest physicians were diagnosed after the age of 65. This suggests that additional factors contribute to the higher rates of uncontrolled asthma in older individuals, leading to increased morbidity and mortality (Paul and Asirvatham 242).

4.1.2. Treatment of hyperglycaemia in elderly patients with diabetes mellitus in India

As individuals age, the way diabetes manifests changes. Most diabetes patients have fasting plasma glucose (FPG) levels of 125 mg/dL or lower, but their postprandial values are often higher than 200 mg/dL, increasing their risk of cardiovascular issues.

Older patients experience a decline in glycaemic control, which can affect their cognitive function. While hypertension affects over 60% of diabetic patients aged 75 and older, treating hypertension, along with managing other risk factors like high cholesterol, is crucial. This underscores the importance of non-glycaemic therapy in this population, although there are concerns about the effectiveness of such therapies in elderly diabetic patients. For example, metformin therapy has been associated with higher mortality rates, especially when combined with sulfonylureas (SUs) in older patients (Baruah et al. 75).

Guidelines for treatment plan of an older diabetic patient:

- Calculate approximately the patient's life expectancy compared with the median for individuals of that age-sex cohort by taking into account the presence or absence of unusually good or poor health and function.
- Set up the patient’s healthcare targets and choices for the treatment.
- Assess and manage the geriatric syndromes reliable with the patient’s goals and the impact that these may have on the management of other co morbidities.
- Assist the patient to prioritize treatment options for diabetes mellitus and other medical conditions consistent with the patient's goals and treatment preferences and the magnitude and time to benefit in the context of the patient's overall health.
- Remember that for older adults with diabetes and an absence of significant medical illness or disability, intensive management of blood pressure and lipid levels and use of aspirin therapy have the greatest chance of benefit within 2-3 years.
- Consider intensive glycaemic targets for older adults with a life expectancy of longer than 8 years and a low risk of hypoglycaemia, and for those who have existing microvascular complications, who may benefit from intensive glycaemic management in a shorter time frame.

Delicate older adults having multiple co-morbidities, difficulty adhering to therapy, significant risks from intensive management of macrovascular and microvascular risks, or a short life expectancy are more likely to benefit from symptom management and strategies to improve the quality of life (Baruah et al. 75).

4.1.3. Psychiatry and elders in India

Tele psychiatry and telemedicine have been attempted for many years, but their effects have been little. Institutions such as the National Institute of Mental Health and Neurosciences (NIMHANS) are using tele psychiatry services, notably geriatric tele psychiatry, more frequently. Patients and caregivers, outpatients at district hospitals, and convicts receiving institutional care in places like jails and impoverished homes were all directly served by tele psychiatry services. Recent research have shown that tele psychiatry services are feasible, useful, and acceptable. (Kumar et al. 45)

Special Issues in Geriatric Tele psychiatry:

1. Sensory Deficit
2. Cognitive Deficit
3. Seniors Residing in Institutions
4. Technology-Assisted Asynchronous Caregiver Intervention for Dementia
5. Non-pharmacological Tele-Assisted Interventions

4.2. The Government's Proposal for Elderly Care

The government has launched several programs to enhance the independence, health, and well-being of the elderly nationwide. In 1999, the United Nations General Assembly declared it the International Year for Older People. The Indian government introduced the National Policy on Older People in the same year, aiming to ensure the elderly are respected and their well-being prioritized in society. The policy highlights states' efforts to meet the needs of the elderly in areas such as welfare, financial security, healthcare, housing, and protection against exploitation and abuse (Paul and Asirvatham 242). The highlights of the policy were as follows:

- A special emphasis on protecting senior women from becoming victims of their age, gender, or widowhood.
- Rather from being a time of dependency, 60+ is a time of opportunity, choices, and innovation.
- Age-integrated society to improve the relationship between youth and seniors.

Highlights how important it is to increase the availability of social and community services for senior citizens, especially women (Paul and Asirvatham 242).

4.3. Drug Regulation in India

The Central Drugs Standard Control Organization (CDSCO) in India, under the leadership of the Drug Controller General of India (DCGI), regulates drugs and cosmetics. It ensures safety, efficacy, and quality through functions like regulatory approvals, quality control, and pharmacovigilance. Despite its efforts, challenges such as delays in paediatrics drug approvals persist, leading to off-label prescriptions for children. Addressing these challenges requires continuous regulatory efforts and stakeholder collaboration to prioritize paediatrics drug development and ensure child health safety.

4.3.1. Clinical Trials in India

In contrast to the established departments for paediatrics drug development in the US and Europe, India lacks specific regulatory requirements for paediatrics clinical trials. Clinical practice often relies on data from other countries or extrapolates from adult dosing. Drug import, manufacturing, and sales, including traditional medicine systems, are governed by the Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetic Rules, 1945(Nunn and Williams, 32). Schedule Y of the Rules outlines policies for paediatrics trials, dictating study timing based on disease type, data needs, inclusion criteria, and requirements for bioequivalence and pharmacokinetic studies. Ethical guidelines mandate informed consent, assent from competent children, and proxy consent from guardians, participant compensation, and additional care provision if needed. These regulations aim to ensure paediatrics drug safety and efficacy while maintaining ethical research standards. (Zisowsky et al. 364)

4.3.2. Vaccines and Biological Medicines

Biological medications and vaccines require modified safety monitoring protocols, especially when given to healthy children, such as during nationwide immunization

campaigns. A significant portion of the population in many countries receives the same vaccine, representing an entire birth cohort. People have high safety expectations and may be unwilling to accept even minimal risks. Concerns, whether real or perceived, about vaccine safety can erode confidence in immunization programs as a whole.(Powell et al. 673)

4.3.3 Regulation of diarrhoea in paediatrics patients

In India, diarrhoea is the third leading cause of death among children under five, accounting for 13% of all deaths in this age group annually. Information on diarrheal diseases in India was collected, condensed, and analysed. The authors independently extracted and tabulated data on the study population, location, sample size, study design, and effect measurements. The study provides information on the scope of future actions to control diarrheal diseases in children under five in India, including the burden of the problem, determinants, management and intervention strategies, preventive initiatives, and the role of public health. (Lakshminarayanan and Jayalakshmy 24)

4.3.4 Regulation of pneumonia in paediatrics patients

Pneumonia is a leading cause of child mortality worldwide, with India bearing a significant burden, experiencing the highest rate of childhood pneumonia globally. A recent study by Brian Wahl and team in The Lancet Child & Adolescent Health provides the first comprehensive analysis of pneumonia incidence in Indian children by state, using a risk factor-based model.(Pandey and Galvani 643)

To combat this, various Indian government initiatives, such as the National Health Mission, the Village Health Sanitation and Nutrition Committee, and the Integrated Child Development Service program, are pivotal in reducing pneumonia cases. Additionally, the Pradhan Mantri Ujjwala Yojana aims to replace unclean cooking fuel in rural households with liquid petroleum gas, reducing indoor pollution, a major pneumonia risk factor. (Pandey and Galvani 643)

5. Comparative analysis

In the US, paediatric drug development is governed by PREA and BPCA, incentivizing studies. While no specific regulations exist for geriatrics, the FDA encourages their inclusion. In the EU, the EMA mandates PIPs for paediatrics and has guidelines for geriatrics, emphasizing elderly patient representation. In India, CDSCO regulates paediatric drugs via Schedule Y, with no specific geriatric regulations, though elderly-targeted drugs must meet general standards.

Table 5.1. Comparison of paediatric and geriatric across the USA, EU and India

Aspects	USA	EU	INDIA
Paediatric Regulation	Paediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA)	Paediatric Regulation Paediatric Committee (PDCO), Paediatric Use Marketing Authorization (PUMA)	Central Drugs Standard Control Organization (CDSCO) and Schedule Y guidelines
Geriatric Regulation	No specific regulations, but FDA encourages inclusion of elderly patients in trials	Guidelines for geriatric clinical investigation	No specific regulations, but must meet general regulatory requirements for drugs intended for the elderly.
Requirements	Paediatric assessments required for certain new	Paediatric investigation plans (PIPs)	Guidelines outlined in Schedule Y for

	drugs, with incentives for studies	mandated for new drugs	paediatric drug development

Overall, the US and EU have established frameworks for both paediatric and geriatric drug development, while India's regulations are still developing, with a stronger focus on paediatrics than on geriatrics.

6. Discussion

This comparative analysis of paediatric and geriatric regulatory frameworks across the US, EU, and India reveals significant variations and commonalities. In the US, the FDA mandates stringent paediatric drug testing through legislations such as the Paediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). Similarly, the EU's Paediatric Regulation (EC) No 1901/2006 enforces rigorous requirements for paediatric medicine authorization, emphasizing the Paediatric Investigation Plan (PIP). Both regions show strong regulatory support, ensuring drug safety and efficacy for children.

For geriatric populations, the US lacks a dedicated regulatory framework, relying instead on general guidelines and advisories from the FDA's Office of Generic Drugs and the Geriatrics and Extended Care program. The EU similarly does not have a specific geriatric framework, but EMA guidelines encourage consideration of older adults in clinical trials.

In contrast, India's regulatory environment for both paediatric and geriatric populations is less mature. While the Drugs Controller General of India (DCGI) has issued some paediatric guidelines, there is a notable absence of comprehensive regulatory policies for geriatric drugs. These findings suggest that while the US and EU have robust paediatric regulatory systems, there is a universal need for more targeted geriatric frameworks, particularly in India, to address the unique pharmacological needs of older adults. Enhanced international cooperation and harmonization of regulations could further improve drug safety and efficacy across all age groups.

7. Conclusion

In conclusion to the comparative analysis of geriatrics and paediatrics in USA, Europe and India, we have carried out the comparison for geriatric guidelines based on clinical trial inclusion, pharmacovigilance, labelling requirements, risk-benefit assessment, implementation challenges, post-approval monitoring, and informed prescribing practices. However, there is not much regulatory guidelines for geriatric population in India as compared to USA and Europe. Discussing about paediatric guidelines, the comparison has been carried out on the basis of clinical trial inclusion, pharmacovigilance, labelling requirements, paediatric formulations, research ethics and incentives for paediatric drugs, collaborative networks across USA, Europe and India. Every country has its own regulatory base according to its demand and need for the regulations depending on the prevalence of disease and availability of resources or medications and professionals.

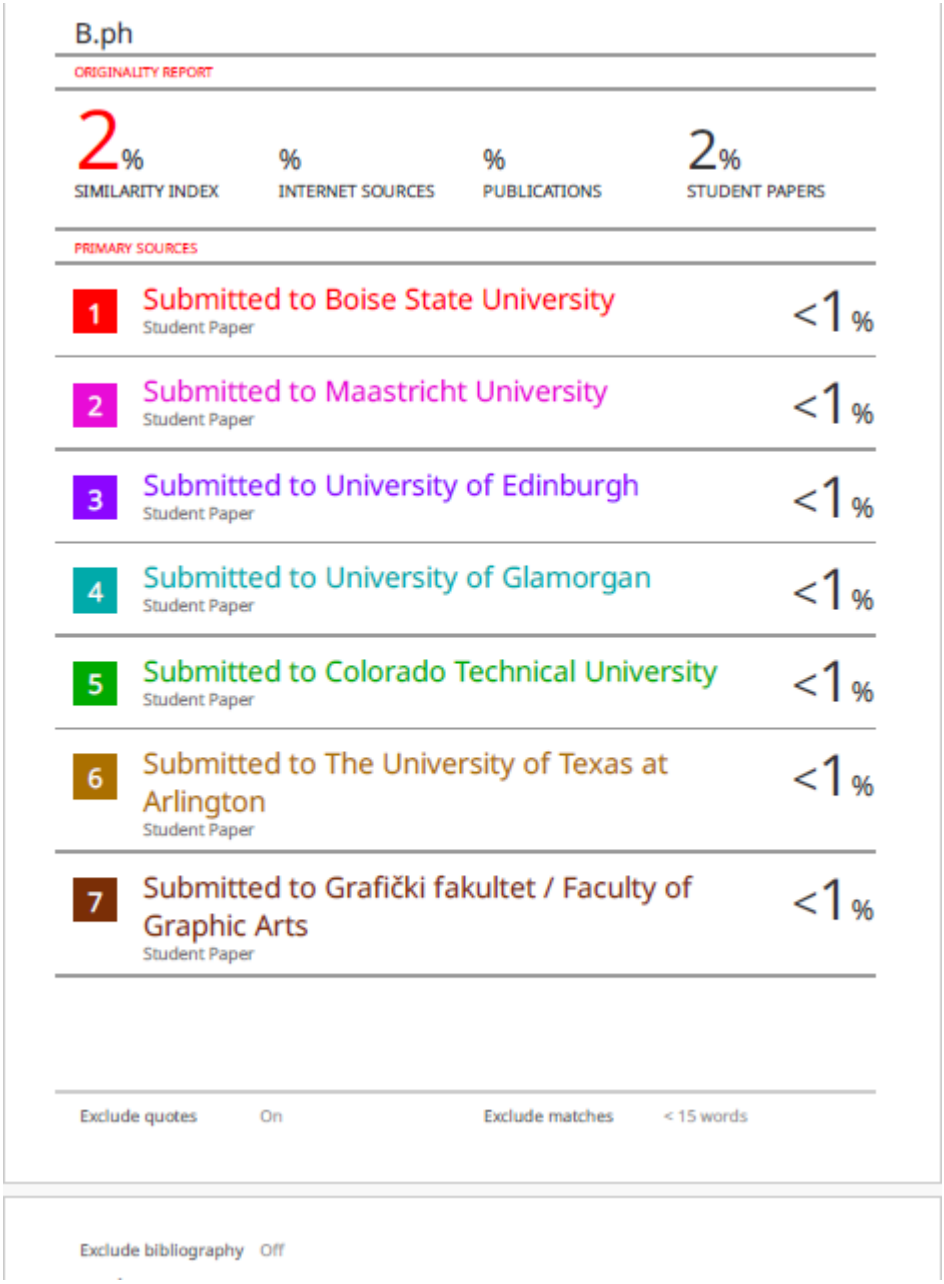
8. References:

1. Ceci, A., et al. “Medicines for Children Licensed by the European Medicines Agency (EMEA): The Balance after 10 Years.” *Springer Link*, vol. 62, 2006, pp. 947–952.
2. Akgün, K. M., K. Crothers, and M. Pisani. “Epidemiology and Management of Common Pulmonary Diseases in Older Persons.” *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, vol. 67A, no. 3, 2012, pp. 276–291.
3. Arnett, D. K., et al. “2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.” Circulation, vol. 140, no. 11, 2019, pp. 596–646.
4. De Spiegeleer, Bart, et al. “Regulatory Development of Geriatric Medicines: To GIP or Not to GIP?” Science Direct, vol. 27, May 2016, pp. 23-36.
5. Baruah, M., et al. “Management of Hyperglycaemia in Geriatric Patients with Diabetes Mellitus: South Asian Consensus Guidelines.” *Indian Journal of Endocrinology and Metabolism*, vol. 15, no. 2, 2011, pp. 75.
6. Chinmayi, C. S., et al. “An Overview and Comparison of Regulatory Pathways and Guidelines for Paediatric Study Plans in the US and EU.” Journal of Medicinal and Chemical Sciences, vol. 6, no. 12, 2023, pp. 3057–3071.
7. De Backer, G., et al. “European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice.” *European Heart Journal*, vol. 24, no. 17, 2003, pp. 1601–1610
8. Field, Marilyn J., and Thomas F. Boat. *Safe and Effective Medicines for Children: Paediatric Studies Conducted under the Best Pharmaceuticals for Children Act and the Paediatric Research Equity Act*. Board on Health Sciences Policy; Institute of Medicine, National Academies Press (US), 2012, pp. 34
9. Redon, Josep, et al. “Narrative Update of Clinical Trials with Antihypertensive Drugs in Children and Adolescents.” *Frontiers in Cardiovascular Medicine*, vol. 9, 21 Nov. 2022, pp. 9, 10.

10. Lepola, P., et al. “Informed Consent and Assent Guide for Paediatric Clinical Trials in Europe.” *Archives of Disease in Childhood*, vol. 107, no. 6, 2022, pp. 582.
11. Malik, C., et al. “Geriatric Population in India: Demography, Vulnerabilities, and Healthcare Challenges.” *Journal of Family Medicine and Primary Care*, vol. 10, no. 1, 2021, pp. 72.
12. European Medicines Agency. The European Regulatory System for Medicines. www.ema.europa.eu/en/human-regulatory/ (Accessed on March 2024).
13. Parashar, Neha. “Step-wise Regulatory Approach for the Paediatric Drug Development.” LinkedIn, 31 Dec. 2020, pp. 4-7, https://www.linkedin.com/pulse/step-wise-regulatory-approach-paediatric-drug-neha/ (Accessed on April 2024).
14. Nici, L., et al. “American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation.” *American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. 12, 2006, pp. 1390–1413.
15. Nunn, T., and J. Williams. “Formulation of Medicines for Children.” *British Journal of Clinical Pharmacology*, vol. 59, no. 6, 2005, pp. 674–676.
16. Paul, Ns. S., and M. Asirvatham. “Geriatric Health Policy in India: The Need for Scaling-Up Implementation.” *Journal of Family Medicine and Primary Care*, vol. 5, no. 2, 2016, pp. 242.
17. Saito, J., et al. “The Current States, Challenges, Ongoing Efforts, and Future Perspectives of Pharmaceutical Excipients in Paediatric Patients in Each Country and Region.” *Children*, vol. 9, no. 4, 2022, pp. 11.
18. “Screening for Adverse Reactions in EudraVigilance.” European Medicines Agency, www.ema.europa.eu/contact. (Assessed on April 2024)
19. Shenoy, P., and A. Harugeri. “Elderly Patients’ Participation in Clinical Trials.” *Perspectives in Clinical Research*, vol. 6, no. 4, 2015, pp. 184.
20. Sivakumar, Palanimuthu Thangaraju, et al. “Geriatric Telepsychiatry: Promoting Access to Geriatric Mental Health Care beyond the Physical Barriers.” *Indian Journal of Psychological Medicine*, vol. 42, 2020, pp. 45.
21. Sowmya, V. S., et al. “A Comparative Review on the Regulatory Framework of Paediatric Drugs in the US and EU: Challenges and Recommendations.”

International Journal of Drug Regulatory Affairs, vol. 11, no. 4, 2023, pp. 74–86.

22. Athira, S. R., et al. “Effect of Polypharmacy in Geriatrics Populations - A Pharmacovigilance Study.” *British Journal of Medical and Health Research*, vol. 5, no. 10, 2018, pp. 1–15.
23. Stuck, A. E., and T. Masud. “Health Care for Older Adults in Europe: How Has It Evolved and What Are the Challenges?” *Age and Ageing*, vol. 51, no. 12, 2022, pp. 2-4.
24. Toma, M., et al. “Paediatric Medicines in Europe: The Paediatric Regulation-Is It Time for Reform?” *Frontiers in Medicine*, vol. 8, 2021, pp. 3,4,7,8.
25. Van Marum, R. J. “Underrepresentation of the Elderly in Clinical Trials, Time for Action.” *British Journal of Clinical Pharmacology*, vol. 86, no. 10, 2020, pp. 2014–2016, pp.1-2.
26. Lakshminarayanan, Subitha, and Ramakrishnan Jayalakshmy. “Diarrheal Diseases among Children in India: Current Scenario and Future Perspectives.” *Journal of Natural Science, Biology and Medicine*, vol. 6, no. 1, 2015, pp. 24.
27. Pandey, Abhishek, and Alison P. Galvani. “The Burden of Childhood Pneumonia in India and Prospects for Control.” *The Lancet Child & Adolescent Health*, vol. 4, no. 9, Sept. 2020, pp. 643.
28. Powell-Jackson, P. R., et al. “Hepatotoxicity to Sodium Valproate: A Review.” *Gut*, vol. 25, no. 6, June 1984, pp. 673.
29. Aldemar, G., et al. “Recommendations for the Diagnosis and Management of Alzheimer’s disease and Other Disorders Associated with Dementia: EFNS Guideline.” *European Journal of Neurology*, vol. 14, no. 1, 2007, pp. 14.
30. Zisowsky, J., A. Krause, and J. Dingemanse. “Drug Development for Paediatric Populations: Regulatory Aspects.” *Pharmaceutics*, vol. 2, no. 4, 2010, pp. 364.



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