"Regulatory Pathway for Registration of ORS with Zinc in Domestic Market and its Comparison with African Countries"

&

"The Regulatory Perspective of Real-World Data in the US, Europe, and the UK"

A Thesis Submitted to

NIRMA UNIVERSITY

in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

REGULATORY AFFAIRS

BY

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Under the guidance of

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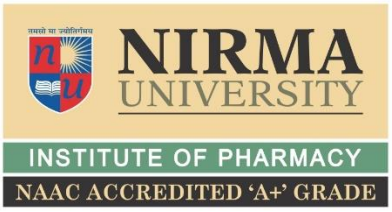

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MAY 2024

CERTIFICATE

This is to certify that the dissertation work entitled "Regulatory Pathway for Registration of ORS with Zinc in Domestic Market and its Comparison with African Countries" & "The Regulatory Perspective of Real-World Data in the US, Europe, and the UK" submitted by Ms. Gargi Vaghela with Regn. No. (22MPH803) in partial fulfillment for the award of Master of Pharmacy in "Regulatory Affairs" is a bonafide research work carried out by the candidate at the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University under my/our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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This is to certify that **Ms. Gargi Vaghela** student of **M. Pharm**(Academic year 2022-2024) from **Institute of Pharmacy, Nirma University.** she has successfully completed her industrial training in Regulatory Affairs Department from 12/06/2023 to 12/12/2023 at Acme Pharmaceuticals.

She was found very sincere and hardworking during the training period.

We wish her a bright and successful career ahead.

With regards,

For Acme Pharmaceuticals.

Tejas Patel
Human Resources

Place: Ahmedabad

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This is to undertake that the dissertation work entitled "Regulatory Pathway for Registration of ORS with Zinc in Domestic Market and its Comparison with African Countries" & "The Regulatory Perspective of Real-World Data in the US, Europe, and the UK" Submitted by Ms. Gargi Vaghela (22MPH803) in partial fulfillment for the award of Master of Pharmacy in "Regulatory Affairs" is a bonafide research work carried out by me at the "Department of Pharmaceutical Analysis", Institute of Pharmacy, Nirma University under the guidance of Dr. Nagja Tripathi, Assistant Professor. I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my knowledge.

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I hereby declare that the dissertation entitled "Regulatory Pathway for Registration of ORS with Zinc in Domestic Market and its Comparison with African Countries" & "The Regulatory Perspective of Real-World Data in the US, Europe, and the UK", is based on the original work carried out by me under the guidance of Dr. Nagja Tripathi, Assistant Professor, under the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Gargi Vaghela

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LIST OF ABBREVIATIONS:

ORS	Oral Rehydration Salt
FDC	Fixed Dose Combination
UNICEF	United Nations Children's Fund
CDSCO	Central Drugs Standard Control Organization
REC	Regional Economic Communities
AMRH	African Medicines Regulatory Harmonization
ORT	Oral Rehydration Treatment
CAGR	Compound Annual Growth Rate
SEC	Subject Expert Committee
DCGI	Drugs Controller General (India)
CTD	Common Technical Document
BP	British Pharmacopoeia
USP	United States Pharmacopoeia
IHS	In-House Specifications
AMA	African Medicines Agency
PPB	Pharmacy & Poison Board
NDA	National Drug Authority
TMDA	Tanzania Drug & Medical Device Authority
MCAZ	Medicine Control Authority of Zimbabwe
BoMRA	Botswana Medicines Regulatory Authority

ZAMRA	Zambia Medicines Regulatory Authority
EFDA	Ethiopian Food and Drug Authority
RWD	Real World Data
RWE	Real World Evidence
USFDA	United States Food and Drug Administration
EU	European Union
UK	United Kingdom
MHRA	Medicines and Healthcare products Regulatory Agency
HHS	Health and Human Services
EMA	European Medicines Agency
DRA	Drug Regulatory Agency
EHR	Electronic Health Record(s)
RCT	Randomised Clinical Trial(s)
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
CDRH	Center for Devices and Radiological Health
CDER	Center for Drugs Evaluation and Research
CBER	Center for Biologics Evaluation and Research
WHO	World Health Organisation
PMS	Post Market Surveillance
HTA	Health Technology Assessment
PRO	Patient- Reported Outcomes
HIPPA	Health Insurance Portability and Accountability Act
CDPA	Consumer Data Protection Act

CCPA	California Consumer Privacy Act
GDPR	General Data Protection Regulation
EEA	European Economic Area
DPIA	Data Protection Impact Assessments
EHDS	European Health Data Space
EHDEN	European Health Data and Evidence Network
ICO	Information Commissioner's Office
DPO	Data Protection Officer

MAJOR

“Regulatory Pathway for Registration of ORS with Zinc in Domestic Market and its Comparison with African Countries”.

Abstract:

This work examines the regulatory pathway for registration and dossier filing of ORS with Zinc in the domestic market and compares it with various African countries. The study concludes that the regulatory pathway for the registration of ORS with Zinc in India is more streamlined and efficient than that of African countries. This work also examines how the FDC-Fixed Dose Combination registration and approval process takes place in India. Here FDC used is ORS with Zinc. Basically, Zinc with ORS is more effective than ORS alone as this combination helps prevent diarrhoea by restoring immunity in malnourished children, it also reduces the risk of recurrent diarrhoeal episodes. There are certain regulatory provisions and rules governing FDCs in India and a checklist for the data requirements for approval of FDCs that needs to be followed when registering in the SUGAM portal. This work also focuses on the registration process of FDC in various African markets. In Africa, access to water, sanitation, and hygiene is poor and the burden of diarrhoea is countless relative to the rest of the world.

A comparative analysis of the regulatory processes, requirements, and harmonization efforts across these regions can provide valuable insights and identify opportunities for further streamlining and collaboration.

CHAPTER 1:

INTRODUCTION

Chapter 1.: Introduction:

Diarrheal illnesses continue to be a serious public health issue, particularly in resource-limited settings, contributing to a substantial burden of morbidity and mortality, especially among children under five years of age. Oral Rehydration Salts (ORS) have long been recognized as a simple and cost-effective intervention for the prevention and treatment of dehydration caused by diarrhea. However, the addition of zinc to ORS formulations has further enhanced the efficacy of this essential medicine, as zinc has been proven to significantly lessen the frequency and intensity of diarrheal episodes.

The World Health Organization (WHO) and UNICEF have endorsed the use of ORS with zinc as a comprehensive strategy for managing diarrheal diseases, underscoring its importance in child health and survival. Ensuring access to this life-saving intervention requires navigating complex regulatory pathways for the registration of products in various countries and regions.

In the domestic market, the regulatory framework for registering ORS with zinc is governed by the Central Drugs Standard Control Organization (CDSCO) in India. The registration process involves a series of steps, including obtaining a manufacturing license, conducting stability studies, preparing dossiers, submitting applications, undergoing regulatory evaluation, and ultimately obtaining marketing authorization. Specific guidelines and requirements outlined in the Drugs and Cosmetics Act and Rules, as well as other relevant regulations, must be adhered to throughout the process.

On the other hand, the regulatory landscape in African countries is shaped by regional harmonization initiatives, such as the African Medicines Regulatory Harmonization (AMRH) and Regional Economic Communities (RECs). These initiatives aim to streamline regulatory requirements and promote harmonization across participating countries, potentially facilitating the registration and access to essential medicines like ORS with zinc.

However, despite these efforts, variations in national regulatory frameworks and specific requirements may still exist, posing challenges for manufacturers and stakeholders seeking product registration in multiple African countries.

Understanding the regulatory pathways for ORS with zinc registration in both the domestic market (India) and African countries is crucial for ensuring timely access to this essential medicine and supporting public health initiatives aimed at managing diarrheal diseases. A comparative analysis of the regulatory processes, requirements, and harmonization efforts across these regions can provide valuable insights and identify opportunities for further streamlining and collaboration.

This study aims to comprehensively analyze the regulatory pathway for the registration of ORS with zinc in the domestic market of India, while also exploring the regulatory frameworks and harmonization initiatives in African countries. Through a comparative assessment, the research seeks to identify similarities, differences, and areas for potential harmonization, ultimately contributing to informed decision-making and strategies for enhancing regulatory efficiency and improving access to this crucial intervention.

CHAPTER 2:

AIM & OBJECTIVES

CHAPTER 2: AIM & OBJECTIVES

1. To analyze the regulatory pathway for ORS with zinc registration in India
2. To examine the regulatory pathways in African countries
3. To compare and contrast the regulatory requirements and processes

CHAPTER 3:

LITERATURE REVIEW

CHAPTER 3: LITERATURE REVIEW

1. **"Guidelines on Fixed Dose Combinations (FDCs): A Review".**

The article explores the regulatory landscape of Fixed Dose Combinations (FDCs) in pharmaceuticals. It emphasizes the role of regulatory bodies like CDSCO (India) and FDA (US) in establishing guidelines for FDCs. These guidelines ensure patient safety and public health by regulating the development, marketing, and use of FDCs, including those already on the market.

2. **Gupta, Y. K., & Ramachandran, S. S. (2016). "Fixed dose drug combinations: Issues and challenges in India."**

This review provides a comprehensive analysis of the issues and challenges surrounding FDCs in India. It underscores the need for a balanced approach that balances therapeutic benefits with safety concerns and regulatory oversight. Moving forward, addressing these challenges requires collaborative efforts from healthcare professionals, policymakers, and regulatory authorities to ensure the rational use of FDCs and optimize patient outcomes.

3. **Chandler S Gautam, Lekha Saha "Fixed dose drug combinations (FDCs): rational or irrational: a view point".**

This article provides valuable insights into the rationality and irrationality surrounding FDCs. Their analysis underscores the need for a balanced approach that maximizes the therapeutic benefits of FDCs while minimizing the risks associated with irrational combinations. Moving forward, concerted efforts from healthcare stakeholders and regulatory bodies are essential to ensure the rational use of FDCs and optimize patient care outcomes.

4. **"The New Drugs and CT Rules 2019"**

The New Drugs and Clinical Trial Rules 2019 herald a new era in the regulation of new drugs and clinical trials in India, aiming to balance innovation with patient safety and welfare. Moving forward, continued vigilance, stakeholder engagement, and periodic revisions will be

essential to ensure the effectiveness and responsiveness of the regulatory framework in promoting public health and fostering biomedical innovation.

5. **Black R. E. (2019). Progress in the use of ORS and zinc for the treatment of childhood diarrhea.**

This article provides exploration of the advancements in the use of Oral Rehydration Solution (ORS) and zinc supplementation for childhood diarrhea treatment offers a comprehensive overview of these life-saving interventions. It underscores the pivotal role of ORS in preventing dehydration and reducing mortality rates, while also highlighting zinc's efficacy in alleviating the severity and duration of diarrhea episodes. By advocating for the integrated approach of ORS and zinc supplementation, it also emphasizes the importance of addressing both fluid-electrolyte imbalances and underlying nutritional deficiencies in combating childhood diarrhea. This work not only reflects the transformative impact of these interventions but also underscores the continued efforts needed to ensure their widespread availability and utilization, thereby contributing to improved child health outcomes globally.

6. **Oral Rehydration Salts and Zinc - Market and Supply Update September 2022**

This update provides information on supply and demand for oral rehydration salts and zinc for 2019-2025. Despite these products being highly effective against diarrhoea and are readily available, demand through UNICEF remains very low. UNICEF advocates for countries to improve access and scale-up their use, as well as to adopt World Health Organization treatment guidelines to use oral rehydration salts and zinc and include products into their national essential medicine lists.

CHAPTER 4:

OVERVIEW AND INTRODUCTION TO ORS AND ITS MARKET

Chapter 4.: Overview and Introduction to ORS and its Markets

4.1. Oral Rehydration Salt:

India is a major player in the worldwide vaccine and pharmaceutical sectors. It is the largest supplier of generic medications worldwide. Approximately 60% of the world's vaccinations are contributed by the nation, that represents 20% of global supply. India is third in terms of volumeand fifteenth in terms of value among all countries. Vaccines, biosimilars, generics, OTC drugs, APIs are the main sectors of the Indian pharmaceutical business.

India is the world leader in vaccine provision, including DPT, BPG, and measles. It also boasts the most amount of plants approved by the US FDA that are not in the country. High quality at a cheap price is the Indian pharmaceutical industry's main USP; as a result, India is sometimes referred to as the "Pharmacy of the World." The industry’s entire yearly turnover in 2021-2013 was US$ 41.68 billion. Access to reasonably priced HIV medications is one of the Indian pharmaceutical industry's biggest achievement. One of the world's biggest suppliers of inexpensive vaccines is India.

India exports biologicals and drug formulations, which account for over 75% of the country's total pharmaceutical exports. To promote exports in this industry, the Indian government established the Pharmaceuticals Export Promotion Council of India (Pharmexcil, 2004).

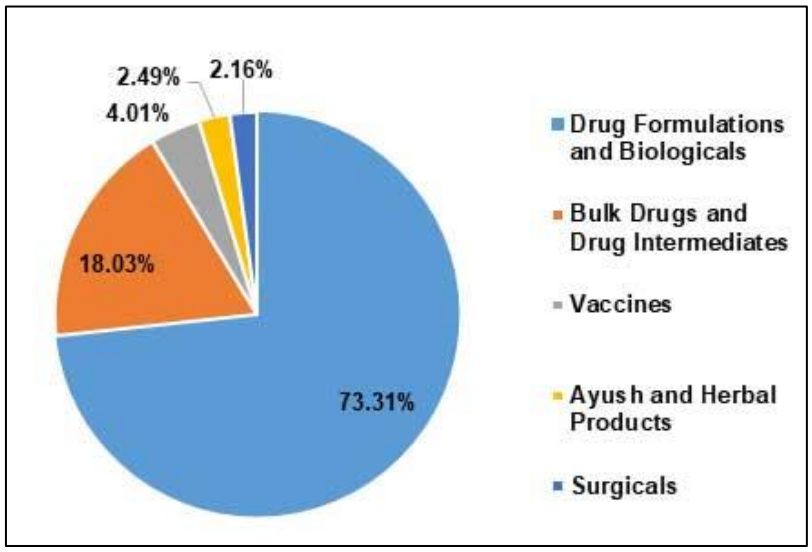

Figure 1 'India's Category wise export share (2021-22') Source: Pharmaceutical Export Promotion Council

In Generic Sector

In the world, the pharmaceutical sector in India is the third largest producer of medicines by volume. The pharmaceutical industry makes the nation one of the most valuable in the world. In terms of worth, it is ranked 14th out of all. Over the coming years, there will likely be a steady and substantial expansion in the market for generic medications. Over the next ten years, generic demand is expected to generate billions of dollars at a compound annual growth rate of 10%. India is the world's leading producer of inexpensive generic pharmaceuticals as of 2021, which is beneficial for exporting medications to other nations. Consequently, 20% of all pharmaceutical exports worldwide are made up of pharmaceuticals, specifically in the generic pharmaceutical industry.

With the aid of a talent pool, it might offer a leadership position to keep flourishing. This can be accomplished by fostering and encouraging high standards in pharmaceutical education for formulation research domestically.

Global diarrheal diseases programme:

With ORS as its core, the WHO started a global initiative to combat diarrheal illness. Despite a 70% rise in the global population, the 4·6 million yearly deaths from diarrhoea in children under five that were estimated in 1980 have decreased to slightly under 365 000 deaths by 2019. As of 2007, it was projected that oral rehydration therapy (ORT) alone averted 54 million diarrheal fatalities, despite the fact that several causes contributed to this reduction. Furthermore, ORT lessens the negative nutritional effects of diarrhoea. But even as late as 2022, critically impacted nations continue to underutilize ORT. To stop the deaths from cholera and other acute watery diarrheal diseases, funding should be provided for programmes that encourage its usage. In high-income nations, ORT is likewise underutilised and ought to be encouraged to cut expenses.

A balanced glucose–electrolyte mixture is known by the non-proprietary term Oral Rehydration Salts (ORS) with zinc. It is a medication that is authorised, suggested, and sold all over the world to treat clinical dehydration. Anhydrous dextrose, anhydrous zinc sulphate, sodium citrate, potassium chloride, and sodium chloride are all present.

In many underdeveloped nations, acute diarrheal illnesses are one of the main causes of baby and early childhood mortality. Dehydration is the primary cause of mortality in most cases. Diarrhoea can be treated easily, affordably, and effectively in all age groups and except the most severe instances by giving patients an appropriate oral glucose-electrolyte solution. Dehydration from diarrhoea can be avoided by supplying extra fluids at home. Oral rehydration treatment is the term for this technique of giving fluids to treat or prevent dehydration (ORT). The WHO Department of Child and Adolescent Health and Development (CAH) recommends ORT as the primary method to reduce child malnutrition and diarrhea-related mortality in conjunction with guidelines on proper feeding practices.

The CAH Department is working with WHO Member States to design, carry out, and assess national diarrheal disease control initiatives in order to meet both the short- and long-term goals of reducing diarrhoea morbidity. By encouraging ORT and supplying copious amounts of oral rehydration salts (ORS), a balanced combination of glucose and electrolytes suggested

by both organisations for the treatment of dehydration, the United Nations Children's Fund (UNICEF) actively promotes these efforts. It has been designed to help national authorities become self-sufficient in addressing the needs of their national diarrheal disease control efforts by helping them establish the local manufacture of a pharmaceutical-quality product.

Oral rehydration treatment (ORT) is very well adapted to the primary health care strategy since it may be administered by village health professionals and administered at home by moms with some training. Furthermore, it has been discovered that ORT improves weight gain and lessens the negative effects of diarrhoea on nutritional status when it is administered in conjunction with guidance on appropriate feeding techniques. In order to prevent dehydration, ORT should start at home with readily available "home fluids" or a homemade "sugar and salt" solution administered early in the diarrhoea episode. When a kid starts to get dehydrated, a complete and balanced standard mixture of salts and glucose (ORS) should be given as ORT.

Not only is there information on the scientific foundation of ORS and studies of its clinical efficacy and safety available, but there are also comprehensive guidelines for treating acute diarrhoea.

4.2. Oral Rehydration Therapy

In many underdeveloped nations, acute diarrheal illnesses rank among the top causes of newborn and early child mortality. Dehydration is the primary cause of mortality in most cases. Diarrhoea can be treated easily, affordably, and effectively in all age groups and except the most extreme cases by providing patients an appropriate glucose-electrolyte solution orally. Dehydration from diarrhoea can be avoided by giving extra fluids at home. Oral rehydration treatment (ORT) is the term for this method of administering fluids to treat or prevent dehydration. The WHO Department of Child and Adolescent Health and Development (CAH) recommends ORT as the primary method to reduce child malnutrition and diarrhea-related mortality in conjunction with guidelines on proper feeding practices.

The CAH Department is working with WHO Member States in the planning, execution, and assessment of national diarrheal disease control initiatives in order to meet both the short-term goal of decreased diarrhoea morbidity and the longer-term goal of decreased diarrhoea

morbidity. By encouraging ORT and supplying substantial amounts of oral rehydration salts (ORS), the balanced combination of glucose and electrolytes suggested by both organisations for the treatment of dehydration, the United Nations Children's Fund (UNICEF) is actively supporting these initiatives. It has been designed to support national authorities in setting up local production of pharmaceutical-quality products, enabling them to become self-sufficient in supplying the demands of their national efforts to control diarrheal illness.

Oral rehydration treatment (ORT) is a technology that is very well adapted to the primary healthcare approach since it can be administered by village health professionals and used at home by moms with some training. Furthermore, it has been discovered that ORT improves weight gain and lessens the negative effects of diarrhoea on nutritional status when it is administered in conjunction with guidance on appropriate feeding techniques. In order to prevent dehydration, ORT should start at home with readily available "home fluids" or a "sugar and salt" solution made at home and administered early in the diarrhoea episode.

However, ORT should be given in the form of a complete and balanced standard mixture of glucose and salts (ORS) if a kid gets dehydrated. Comprehensive protocols for managing sudden diarrhoea are accessible, along with details regarding the scientific underpinnings of ORS and studies examining its safety and clinical effectiveness.

4.3. **Oral Rehydration Solution (ORS) Market Introduction**

Glucose, NaCl, Sodium citrate, KCl and glucose-salt solution are the ingredients of oral rehydration solution (ORS). Electrolyte pills, liquid, and powder are among the forms of electrolyte that are used to treat or prevent diarrhea-related dehydration. The ORS is affordable, simple to take, and enables treatment to be provided outside of hospitals and homes. This aids in restoring a person's regular energy levels once they have become dehydrated. UNICEF, the United Nations Children's Education Fund, has demonstrated that an individual lacking medical expertise may make and administer the life-saving ORS packet for as little as US$ 0.05 per packet.

Since mothers or other carers can now treat their children, the strain on healthcare professionals (HCPs) has been greatly reduced. In 1978, the World Health Organisation (WHO) decided to

use ORS as its main treatment for diarrhoea. It has been shown that ORS can prevent 93% of diarrhea-related deaths. Supplementing with Zinc can cut the number of deaths from diarrhoea by 23%. Over the past 20 years, a great deal of research has been done to create better ORS. The objective was to present a safe and efficient product for the management of dehydration caused by diarrhoea of any kind.

Combining zinc therapy with oral rehydration salts (ORS) is an inexpensive and efficient way to treat diarrhoea in children since it reduces the length and intensity of the symptoms of an episode as well as stops it from happening again. Every year, there are around 1.7 billion episodes of diarrheal illness in children worldwide. There is a straightforward therapy for the illness, yet an estimated 525,000 children under five may away from it every year. It is estimated that 93% of children do not receive zinc and 56% of children with diarrhoea do not receive therapy with ORS. Compliance and adherence are difficult for patients receiving zinc and ORS treatment.

Manufacturers co-packaged zinc and ORS according to World Health Organisation (WHO) treatment protocol recommendations to increase patient adherence to the prescribed course of treatment.
UNICEF is still encouraging governments in promote the use of zinc and ORS by locating and promoting high-quality co-packaged zinc and ORS, as well as by facilitating access in nations where a reliable, secure, and consistent supply is necessary. To enable faster delivery timeframes, UNICEF has broadened and diversified its supplier base to include producers situated in high-burden nations, such as Africa.

UNICEF promotes and urges nations to utilise only co-packaged ORS and zinc to guarantee increased compliance with WHO treatment recommendations. Co-packaged ORS encourages the best possible care for children's diarrhoea. Research has indicated that in certain nations, zinc and ORS treatment rates for children with diarrhoea are just 15% and 19%, respectively.

Despite the availability of a straightforward treatment, diarrhoea continues to rank among the world's leading causes of under-five child death and is a major contributor to under-five child

malnutrition. Diarrhea-related deaths in children under five are estimated to be 525,000 per year. Just ten Asian and African nations—Bangladesh, the Democratic Republic of the Congo, India, Tanzania, Ethiopia, Kenya, Pakistan, Uganda, Niger and Nigeria—account for 60% of these fatalities. The high death rate from diarrhoea in these areas can be attributed, in part, to the high frequency of high-risk variables associated with the disease, including malnourishment, contaminated water sources, and limited access to necessary medical care.

Because ORS and zinc are both very effective and reasonably priced medications that have the potential to save up to 93% of diarrhoea cases that end in death, the World Health Organisation has recommended combining the two to ensure that patients receive appropriate treatment. Through the Integrated Community Case Management (iCCM) guidelines, the World Health Organisation offers explicit advice on the use of ORS in conjunction with zinc for the treatment of diarrhoea.
Both ORS and zinc are advised for the treatment of acute diarrhoea in children by the World Health Organisation and UNICEF. In an effort to encourage nations to incorporate zinc into their plans through national medicine lists and health budgets, the World Health Organisation added zinc supplementation for the treatment of diarrhoea in children to its Essential Medicine List (EML) in 2005.

The market is examined based on region in the Americas, Asia-Pacific, Europe, Middle East, and Africa. More research is being done on the Americas in the United States, Argentina, Brazil, Canada, and Mexico. More research is done on the United States in the following states: Florida, Illinois, New York, Ohio, Pennsylvania, Texas, and California. Further research is being done on Australia, China, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam, as well as the Asia-Pacific region.

4.4. Market Outlook for ORS 2031

- The ORS market was estimated to be worth US$ 2.55 billion in 2021.
- From 2022 to 2031, the market is expected to grow at a Compound Annual Growth Rate (CAGR) of 9.9%.

- It is projected that the oral rehydration solution (ORS) market would grow to exceed US$ 6.71 billion by 2031.

4.4.1. Analysts' Viewpoint on ORS Market Scenario

The factors driving the size of the ORS market globally include the rise in the prevalence of diarrhoea, the success of government initiatives to manage diarrhoea, and the growing importance and uptake of ORS in sports. In the world, diarrhoea is a leading cause of morbidity and mortality, particularly in young children. With proper sanitation and ORS, a significant percentage of diarrheal illnesses can be cured. Zinc and ORS are suggested by UNICEF and the World Health Organisation (WHO) to treat diarrhoea. Governmental organisations from all around the world are creating efficient campaigns to lower the death rate among children. Manufacturers make large investments in R&D to produce ORS products that are both safe and effective.

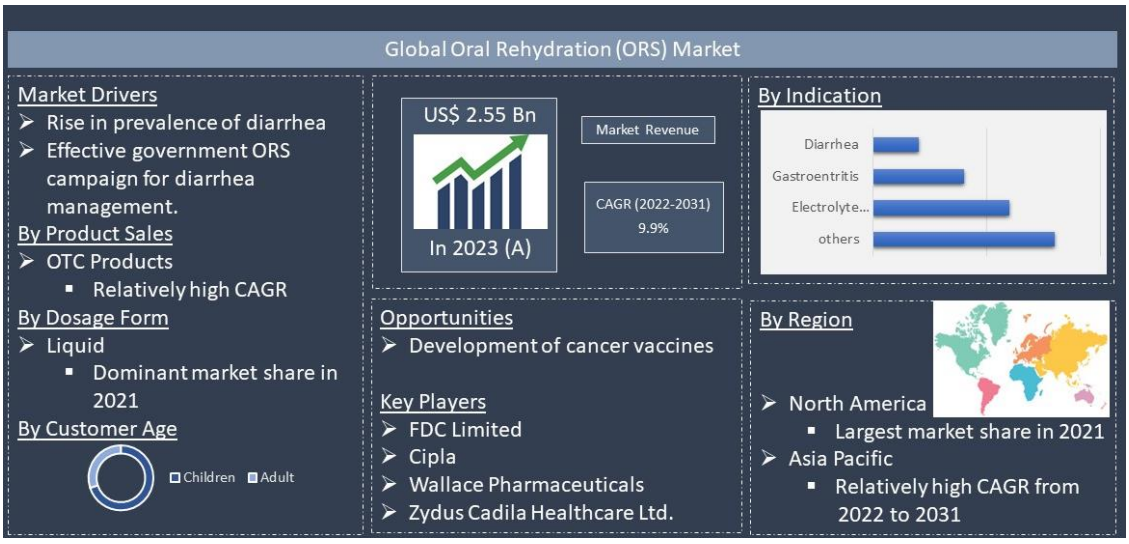

Figure 2 Global ORS Market

4.5. Key Players in Global Oral Rehydration Solution (ORS) Market:

A comprehensive overview of the top companies in the worldwide oral rehydration solution (ORS) market is provided in the study. To gain a larger market share, businesses are implementing partnership, merger and acquisition, divestiture, and product launch tactics. Well-known companies in the global market include FDC

Limited, Wallace Pharmaceuticals, Cipla, Liquid I.V., Zydus Cadila Healthcare Ltd., Mankind Pharma, Intas Pharmaceuticals Ltd., Sun Pharma, Dr. Reddy's, Alkem, Lupin, Cadila, Okasa Pharma Pvt. Ltd. and others.

4.6. COVID-19's Effect on the Market for Oral Rehydration Solutions (ORS)

The COVID-19 virus posed a threat to both national and international healthcare systems through community transmission. The World Health Organisation reports that as of August 2022, there were over 585.0 million confirmed cases of COVID-19 worldwide, with around 6.4 million deaths associated with the virus. The demand for health-related products—including ORS in particular—has surged as a result of the outbreak. Even in cases that are quite moderate, vomiting and diarrhoea are among the most prevalent symptoms of COVID-19. When ORS is used appropriately, it can effectively address the pandemic-related problem of dehydration and has several advantages over alternative rehydration techniques. ORS can be mixed with other vital nutrients and is a non-invasive treatment that doesn't require any specialised equipment to give.

It works pretty well for relieving dehydration and associated problems. As a result, during the course of the forecast period, the COVID-19 pandemic is anticipated to offer fresh chances for the worldwide ORS market.

CHAPTER 5:

ORAL REHYDRATION SALT WITH ZINC

Chapter 5: ORS with Zinc

5.1. Diarrhoea:

• What is diarrhoea?

Worldwide, diarrhoea continues to be one of the main causes of infant mortality. Stools from diarrhoea are frequently referred to as loose or watery stools because they contain more water than usual. In the event that they do include blood, the diarrhoea is referred to as dysentery.

• Which group is most susceptible to diarrhoea?

Children, especially those between the ages of six months and two, are most likely to get diarrhoea. It is typical in infants less than six months who are fed formula or consume cow's milk.

• What are the complications of Diarrhea?

Diarrhoea can persist for up to 14 days or more, which can result in bowel infection. Malnutrition and mortality are diarrhea's two biggest risks. A couple of new developments in the treatment of diarrheal illness can significantly lower the frequency of infant deaths.

• What are the available treatment options for managing diarrhoea?

To stop dehydration, oral dehydration salts (ORS) solution is given; it has a lower concentration of salts and glucose. In light of these developments, international organisations such as UNICEF and WHO highly advise taking zinc supplements in addition to ORS to lessen the likelihood of subsequent episodes of diarrhoea, as well as its duration and severity, in the two to three months after supplementation.

What makes Zinc in combination with ORS better than ORS alone?

Taking zinc supplements help stop diarrhoea in a number of ways, most notably by boosting immunity in kids who are zinc deficient. The immune system's producing B and T cells are fewer in number and have lower functional ability when zinc shortage occurs. Zinc

deficiency damages the intestinal mucosa, lowers brush border enzymes, increases mucosal permeability, and increases intestinal water output. Zinc stabilises cell membranes. Thus, taking zinc supplements during a bout of diarrhoea can lessen its intensity and length. For acute childhood diarrhoea, the World Health Organisation (WHO) suggests oral zinc (tablets or syrups) as an adjuvant therapy in addition to oral rehydration solution (ORS).

5.2. Zinc with Oral Rehydration Salt:

A serious worldwide health concern, diarrhoea and cholera have been linked to seven illnesses. Vibrio cholera's cholera toxin raises the cAMP product. This causes the intestinal lumen to massively store water and electrolytes, which severely dehumidifies the area. Oral rehydration solutions (ORS) are recommended by the World Health Organisation as a treatment for diarrhoea. Standard ORS has been modified with colour to treat both cholera and non-cholera diarrhoea. These include lowering the morbidity and mortality linked to acute diarrhoea by adding zinc, amino acids, and amylase-resistant foods.

An improvement to ORS for the treatment of cholera diarrhoea is the use of zinc with ORS. Zinc increases physical well-being, lowers the chance of recurring diarrhoea episodes, and helps malnourished children with acute diarrhoea by hydrating them. Research conducted in a number of nations revealed that adding zinc might lessen the length and intensity of diarrhoea, which also permits the use of antibacterial and antimicrobial medications to be restricted.

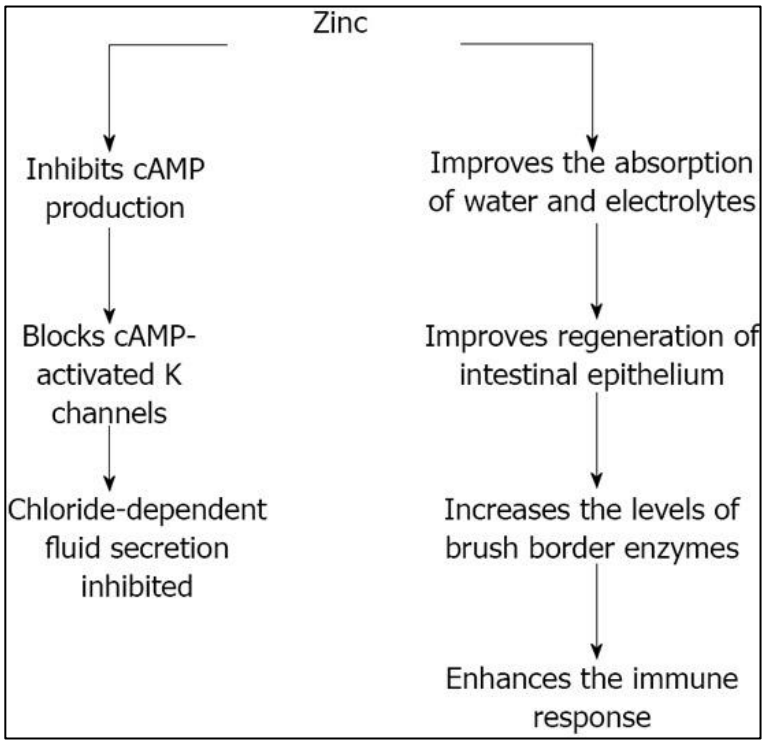

Figure 3 'MOA of Zinc' Source: Europe PMC

Reduced water and electrolyte absorption was the outcome of an intestinal zinc deficit, according to a study conducted on an animal model. Water and electrolyte secretion are brought on by the cholera toxin's increased cAMP synthesis. Zinc lowers cAMP levels and cholera toxin-induced ion secretion and boost ion absorption, however it doesn't stop the heat-stable enterotoxin-induced ion secretion in E. Coli. The impact of zinc on intestinal integrity in children with both acute and chronic diarrhoea is uncertain. Zinc, however, increased mucosal healing in patients with an infection of acrodermatitis enteropathy. Additionally, zinc affects the excretion of urine probe sugars, reducing the excretion of mannitol and boosting the excretion of lactulose.

Zinc deficiency is seen in cholera patients of all ages, including children. Breastfeeding provided protection against diarrhoea in babies, therefore the beneficial effects of zinc supplementation were obscured. daily or weekly administration of zinc supplements schedule reduces diarrheal morbidity without causing negative side effects. Children with cholera who take zinc supplements exhibit shorter bouts of diarrhoea and less faeces

production. Zinc supplementation may help children with diarrhoea, but it's still unclear how best to provide it and at what expense. Zinc deficiency causes decreased water and electrolyte absorption in cases of cholera and diarrhoea. Zinc therefore plays a significant part in symptom relief. It has been demonstrated that zinc, the cholera vaccine, and ORS have beneficial effects in cholera and diarrhea.

CHAPTER 6:

REGULATORY PATHWAY FOR REGISTRATION OF ORS WITH ZINC IN INDIA

Chapter 6: Regulatory Pathway for Registration of ORS with Zinc in India

6.1. SUGAM:

SUGAM is e-Governance system to initiate various functions performed by CDSCO under Drugs and Cosmetics Acts, 1940. is an online portal introduced by CDSCO to digitize and streamline the process of regulatory submissions and approvals for drugs and pharmaceutical products in India.

The key features of the SUGAM portal include:

1. Online submission of applications for various regulatory processes like manufacturing licenses, product registrations, clinical trial approvals, etc.
2. Tracking the status of submitted applications in real-time.
3. Online payment of fees and charges related to the applications.
4. Paperless and transparent application management system.

Figure 4 'Sugam Online Portal' Source: CDSCO website

The benefits of SUGAM include increased efficiency, reduced processing time, improved transparency, and ease of doing business for pharmaceutical companies and stakeholders.

It is a mandatory platform for all regulatory submissions to CDSCO, aimed at simplifying and modernizing the regulatory processes in the Indian pharmaceutical sector through digitization and online systems.

In essence, SUGAM is CDSCO's digital initiative to facilitate online regulatory filings, approvals, and application tracking, thereby enhancing the overall regulatory framework for drugs and pharmaceuticals in India.

This document contains step-by-step guidance to the Applicants (Industry association) of the SUGAM portal with screenshots of the workflow for various application submissions. Following are the sections detailed in this document:

- User Registration & Login
- Applicant Dashboard
- Managing Sub login Accounts
- Form Submission for various processes
- Post Approval Changes

6.2. FIXED DOSE COMBINATION (FDC) PRODUCT APPROVAL PROCESS IN INDIA

The approval process for FDCs in India is a comprehensive and rigorous process governed by the CDSCO. Here are the detailed steps involved in obtaining approval for FDCs in India:

6.2.1. Application Submission:

The manufacturer or marketer of the proposed FDC must submit an application in the prescribed format (Form 44) to the CDSCO, along with the required fees.

The application should be accompanied by a detailed dossier containing the following information:

- Composition of the FDC, including the individual components and their respective strengths
- Dosage form and route of administration
- Proposed therapeutic indications and target patient population
- Detailed manufacturing process and quality control measures

- Stability data and shelf-life determination studies
- Pharmacological, pharmacokinetic, and toxicological data
- Clinical trial data demonstrating the safety and efficacy of the FDC

6.2.2. Screening and Initial Evaluation:

- The CDSCO conducts an initial screening of the application and dossier to ensure completeness and compliance with regulatory requirements.
- If any deficiencies are identified, the applicant may be asked to provide additional information or clarifications.

6.2.3. Evaluation by Subject Expert Committee (SEC):

- The application and dossier are then evaluated by the Subject Expert Committee (SEC), a panel of experts appointed by the CDSCO.
- The SEC comprises experts from various fields, including pharmacology, toxicology, clinical medicine, and pharmaceutical analysis.
- The SEC thoroughly reviews the data provided, assessing the therapeutic justification, safety, efficacy, and rationality of the proposed FDC.
- The SEC may seek additional data, clarifications, or expert opinions if deemed necessary.

6.2.3. SEC Recommendation:

- After a comprehensive evaluation, the SEC provides a detailed recommendation to the Drugs Controller General of India (DCGI) regarding the approval or rejection of the FDC application.
- The recommendation may include specific conditions or restrictions, if any, to be imposed on the approval.

6.2.4. Approval by DCGI:

- The DCGI, the head of the CDSCO, considers the SEC's recommendation and makes the final decision on granting approval for the FDC.

- If approved, the manufacturer or marketer is issued a license or permission to manufacture and market the FDC in India, subject to any conditions or restrictions specified.

6.2.5. Post-Approval Obligations:

- After obtaining approval, the manufacturer or marketer must comply with post-approval obligations, such as conducting periodic safety updates, pharmacovigilance activities, and adhering to labeling and promotional guidelines.
- The CDSCO may impose additional post-marketing surveillance requirements or studies, if deemed necessary.

It's important to note that the approval process for FDCs in India is designed to ensure that only rational and safe combinations are approved, considering the potential risks associated with FDCs, such as drug interactions, toxicity, and inappropriate use.

The CDSCO has implemented various guidelines and measures to regulate FDCs, including the prohibition of certain irrational or potentially harmful combinations. Manufacturers and marketers are advised to consult the latest regulations, guidelines, and notifications issued by the CDSCO to ensure compliance with the FDC approval process in India.
The Indian parliament passed the Drug and Cosmetic Act 1940 and Rules 1945 to control the import, production, distribution, and retailing of pharmaceuticals and cosmetics. Established were the Drugs Controller General (India) [DCGI] office and the CDSCO.
The Indian government amended the 1945 Drug and Cosmetics Rules by adding Schedule Y in 1988. The requirements and guidelines for clinical trials are outlined in Schedule Y, which was updated in 2005 to conform to internationally recognised standards. The modifications include defining terms for Phase I–IV trials and outlining sponsors' and investigators' roles precisely.

The clinical studies had been further divided into two groups in 2006. Clinical trials can be carried out in other markets with capable and developed regulatory frameworks under one category (category A), while the remaining ones fall under a different category (category B) Other than A.

Fast tracking is available for clinical studies of category A (authorised in the United States, United Kingdom, Switzerland, Australia, Canada, Germany, South Africa, Japan, and European Union), which are expected to be approved in eight weeks in India. Category B clinical studies undergo greater review and are approved in 16–18 weeks.

An application for conducting clinical trials in India will be sent to DCGI, together with information about CMC and animal studies. Attached should include the date of the informed consent paperwork, investigator brochures, and study protocol. Clinical trials are only carried out with DCGI and ethical committee approval, and a copy of the application must be provided to them. to ascertain adverse effects, the highest dose that humans can tolerate, etc. Phase I clinical trials use healthy individuals. The therapeutic uses and effective dose ranges are determined in phase II trials on 10–12 patients per dose level. About 100 patients across 3–4 centres participate in Phase III confirmatory trials to validate the drug's efficacy and safety. If the new medicine is not sold abroad, phase III studies should involve 500 patients in 10-15 centres. After clinical trials, form 44 with complete pre-clinical and clinical testing information is used to register a new medicine. It is also necessary to submit information about the product monograph, labels, cartons, samples, testing processes, and prescription. A review of the application may take anything from 12 to 18 months. The revised Indian drug approval procedure is shown in Figure 10. Phase IV trials are when a product is deemed to be in the process of exploring new uses, new populations, long-term impacts, etc. after the NDA approval, at which point a firm is granted permission to distribute and market the product.

The procedure for approving drugs differs between nations. In certain nations, a single agency handles all aspects of drug regulation, including the approval of new medications, granting manufacturing licences, and inspecting production facilities. In the United States, for example, the FDA handles all aspects of drug regulation. Nonetheless, in certain nations, like India, not all duties are carried out by a single regulatory body; instead, state and centralised authorities share this burden. There are other areas where there are differences, such as the length of time it takes to approve a CTA application, evaluate a marketing

authorization application, charge a registration cost, go through the registration procedure, and offer marketing exclusivity.

Certain countries, like the USA, China, and others, have two review processes: the standard review process and the expedited review process. Other countries, like India, only have one review procedure. In a similar vein, the format in which the dossier submitted for a drug's clearance is presented varies. The preparation of the dossier in CTD format is required in some nations, such as the USA, EU, and Japan, but optional in others, including India.

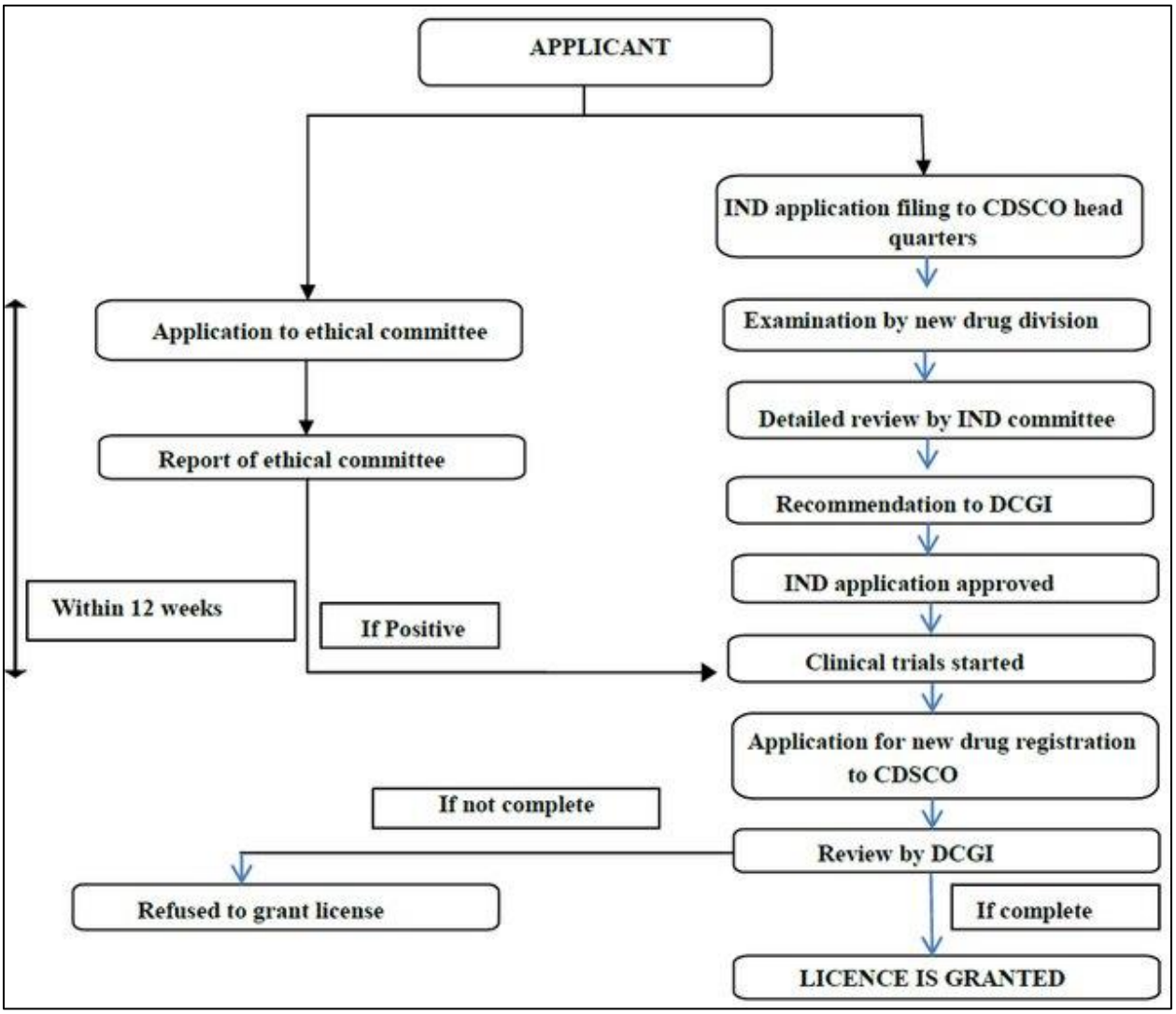

Figure 5 'Online Submission Process for New Drug' Source: [(PDF) A Comparative Study Of Regulatory Requirements For Filing Generic Drug Product Between Usa, India, And China (researchgate.net)]

6.3. CTD GUIDELINE IN INDIA:

Scope:

This guideline covers import, manufacture, and marketing approval of new drugs, including new chemical entities, indications, dosage forms, modified release forms, routes of administration, etc., under Rule 122E of Drugs & Cosmetics rules as finished pharmaceutical products.

6.3.1. What is CTD?

The CTD is only a format used to send data to CDSCO. The content is not defined by it.

The way that the data is organised differently in each application has complicated the review process and increased the risk of missing important information or analysis, which would cause an unwarranted delay in approval. So, a standard submission structure will be beneficial. CTD guidelines for the US, EU, and Japan were produced through the ICH process. CDSCO took up the CTD as well.

6.3.2. Guidelines for preparation of CTD

CTD: Overview

It can be organized into 5 Modules:-

- Module 1: Administrative and Prescribing Information
- Module 2: Common Technical Documents CTD Summaries
- Module 3: Quality data
- Module 4: Nonclinical study reports
- Module 5: Clinical study reports

For example, the font size should be 12, the style should be in Times New Roman, and the page layout should be 8.5 x 11 for the United States and A4 paper for the European Union.

Enough space should be provided for the left hand, and the information shouldn't be obscured or unclear after binding.

• The regulatory body will undoubtedly accept the common technical document's details, and reviewing it will be simple.

• The submitted paper needs to be signed and dated.

• The document needs to be branded correctly in accordance with national regulatory norms.

• All necessary documents should be sent in accordance with the checklist in order to prevent application rejection or questions, which will expedite the review and approval process.

• Appropriate reference should be made to the reasoning behind specific tests, together with any supporting documentation.

• The dossier must be reviewed and validated for errors after it is completed before being sent.

• All study reports should be attached to the papers in the clinical study report in accordance with module 5 CRF.

• The validation certifications are required by certain approved nations.

• Any changes made to a batch should be explained and supported.

Module -1 Administrative and Prescribing information

It does not belong to CTD; rather, it is region-specific. It provides both administrative and prescription data. This document, which includes the application form and suggested label use for the region, is unique to each region.

Overview of Module 1

• Provides a basic overview of the contents of the extensive table and the covering letter.

• Provides administrative data, such as a synopsis of the company applying. provides the Treasury Challan and Form 44 application that has been properly filled out and signed. In addition to the aforementioned documents, it provides legal and crucial documents such as copies of clinical trials and BEs, no objection letters from the CDSCO, and batch release certificates that may be granted by national regulatory bodies. These documents are

necessary for the production and marketing of finished goods, for example. For example, a copy of the current manufacturing licence on Forms 25 and 28, a copy of Form-29, a certificate of analysis, and application-related coordinates.

• Provides broad details about completed pharmaceutical products;

• Indicates the various countries' regulatory status;

• Describes the internal cost of the completed pharmaceutical product that is used in those nations.

• It can also give a brief overview of the manufacturer's research endeavors.

• It can also give a brief overview of the manufacturer's commercial activity on both the domestic and foreign markets.

• Provides information about the experts' participation.

• It provides details on promotional materials and a medicine product sample.

Module -2 CTD Summaries

Content of module 2:

- Table of content (comprehensive).
- Introduction (general introduction to the pharmaceutical, including its pharmacological class, mode of action, and proposed clinical used.)
- Qualities Overall summaries (The Qualities Overall Summaries (QOS) are an outline of the data presented in module 3).
- Non-clinical overview.
- Clinical overview.
- Non-clinical summaries.
- Clinical summaries

Non-clinical overview

In the non-clinical overview, there is Implications of nonclinical findings for the safe use of the pharmaceutical

- Introduction and GLP statement
- Overview of the Non-Clinical Testing Strategy
- Pharmacology.
- Pharmacokinetics.
- Toxicology
- Integrated Overview and Conclusions
- List of Literature References

Clinical overview

In the clinical overview there is an overview of the clinical data were analysed.it also provides a brief overview of the new clinical findings. Analyses the benefits and risks of the medicinal products in its intended use.

- Product Development Rationale.
- Overview of Biopharmaceutics.
- Overview of Clinical Pharmacology
- Overview of Efficacy
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

Non-clinical summaries

One format for the non-clinical summary is a written tabular version. A summary of the in-vitro and in-vivo pharmacokinetic, pharmacological, and toxicological research is provided, together with information on the species, route, duration, and effects connected to the appropriate age and gender.

Clinical summaries

This section aims to give a thorough, factual summary of all the clinical data in the CTD. This includes data from analyses for which full reports have been included in Module 5, data from clinical study reports, and post-marketing data for goods that have been sold in other areas.

The clinical summary includes

- Biopharmaceutic Studies and Associated Analytical Methods.
- Clinical Pharmacology Studies
- Clinical Efficacy
- Clinical Safety
- Literature References
- Synopses of Individual Studies

Module 3 - Quality data

In this module the quality section of common technical documents (M4Q) provides a compatible structure and format for presenting the chemistry, manufacturing and control (CMC) information in the registration dossier.

The module includes

- Table of content
- Body of data

- Literature references
- Body of data
    - Drug Substance
    - General Information
        - Nomenclature
        - Structure
        - General Properties
    - Manufacture
        - Manufacturer Details
        - Description of Manufacturing Process and Process Controls
        - Control of Materials Control of Materials
        - Controls of Critical Steps and Intermediates
        - Process Validation and/ or Evaluation
        - Manufacturing Process Development
    - Characterization
        - Elucidation of structure and other Characteristics
        - Impurities
    - Control of Drug Substance
        - Specification of Drug Substance
        - Analytical Procedures
        - Validation of Analytical Procedures
        - Batch Analyses

- Justification of Specification

- Reference Stand Reference Standards or Materials or Materials
- Container Closure System
- Stability
  - Stability Summary and Conclusions
  - Post-approval Stability Protocol and Stability Commitment
  - Stability Data

- Drug Product
  - Description and Composition of the Drug Product
  - Pharmaceutical Development
    - Components of Drug Product
    - Drug Product Drug Product
    - Manufacturing Process Development
    - Container Closure System
    - Microbiological Attributes
    - Compatibility

- Manufacture
  - Manufacturer
  - Batch Formula Batch Formula
  - Description of Manufacturing Process and Process Controls
  - Controls of Critical Steps and Intermediates
  - Process Validation Process Validation and /or Evaluation

- Control of Excipients
    - Specifications
    - Analytical Procedures Analytical Procedures
    - Validation of Analytical Procedures
    - Justification of Specifications
    - Excipients of Human or Animal Excipients of Human or Animal Origin
    - Novel Excipients
- Control of Drug Product
    - Specification of Drug Product
    - Analytical Procedures Analytical Procedures
    - Validation of Analytical Procedures
    - Batch Analyses
    - Characterization of Impurities
    - Justification of Specification
- Reference Standards or Materials
- Container Closure System
- Stability
    - Stability Summary and conclusion
    - Post-approval Stability Protocol and Stability Commitment
    - Stability Data

Module - 4 Non-Clinical Study Reports

Module 4 describes the format and organization of the nonclinical (pharmaco-toxicological) data relevant to the application.

- Table of contents
- Study Reports
    - Pharmacology
        - Primary Pharmacodynamic
        - Secondary Pharmacodynamic
        - Safety pharmacology
        - Pharmacodynamic drug interaction
    - Pharmacokinetics
        - Analytical Methods and validation Reports
        - Absorption
        - Distribution
        - Metabolism
        - Excretion
        - Pharmacokinetic Drug Interactions
        - Other Pharmacokinetic studies
    - Toxicology
        - Single-dose toxicity dose toxicity
        - Repeat-dose toxicity
        - Genotoxicity

- Carcinogenicity
- Reproductive and developmental
- Local tolerance
- Other toxicity studies other toxicity studies

- Literature References.

Module - 5 Clinical study report

- Table of Contents
- Tabular Listings of All Clinical Studies
- Clinical Study Reports
- Bioavailability (BA) study Reports
- Comparative BA and Bioequivalence study reports
- In-vitro In-vivo Correlation study reports
- Reports of Bioanalytical and Analytical methods
- Plasma Protein Binding Study Plasma Protein Binding Study Reports
- Reports of Hepatic metabolism and Drug Interaction Studies
- Reports of Studies Using human Biomaterials
- Healthy Subject PK and Initial Tolerability study reports
- Patient PK and Initial Tolerability study reports.
- Intrinsic Factor PK study reports
- Extrinsic Factor PK study reports
- Population PK study reports
- Healthy subject PD and PK/PD study reports

- Patient PD and PK/PD study reports
- Study reports of controlled clinical studies
- Study reports of uncontrolled clinical studies
- Reports of Analyses of data from more than one study
- Other clinical study reports
    - Reports of Post-Marketing Experience
    - Case report forms and Individual patient listings
- List of Key Literature References

CHAPTER 7:

PREPARING DOSSIER/ REGISTRATION APPLICATION FOR INDIA

Chapter 7: Preparing dossier/registration application

7.1. Product Composition and Formulation details:

ORS with Zinc:

Preparation of regulatory dossier as per Indian CTD format and submission in SUGAM.

Product registration dossier:

ORS-Zn Powder-4.4gm

A product of- XYZ ltd.

Marketed by: ABC healthcare

Date of Submission: 23-sept-2023

Brand Name: Zincoralyte ®

Nonproprietary name: ORS-Zn 4.4gm

Dosage Form: Powder

Strength: 4.4gm

Therapeutic Category:

Presentation:

(Type of Packing, Pack Size): 10 x 4.4 g sachets

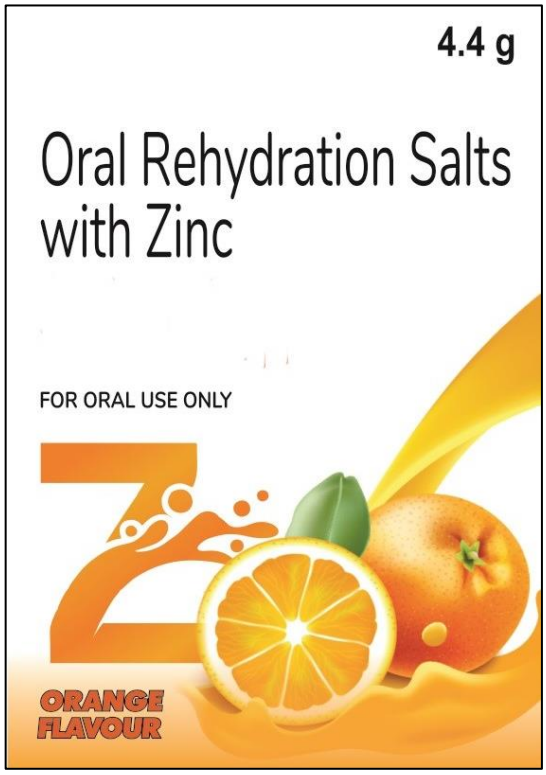

Figure 6 'Draft image of ORS-Zinc 4.4gm'

Indication: For oral rehydration in various etiology

Dosage: Depending upon the degree of dehydration

Children: 1 to 2 liters over a period of 24 hours

Adults: 1 to 3 liters over a period of 24 hours

Storage instructions: Store in dry place. Keep out of reach of children.

Shelf Life: 24 months from the date of manufacturing

Manufacturer: XYZ ltd.

7.1.1. **PRODUCT INFORMATION:** (as per CTD Module 1)

Product Name: ORAL REHYDRATION SALTS WITH ZINC 4.4 GM

Strength: 4.4 gm

Pharmaceutical dosage form: Powder

7.1.2. QUALITY AND QUANTITATIVE COMPOSITION:

Qualitative composition:

Each sachet contains:

Sodium Chloride BP…….....x gm

Potassium Chloride BP …….y gm

Sodium Citrate BP …….z gm

Glucose BP (Anhydrous)……....p gm

Zinc Sulphate Monohydrate BP……q gm

Excipients …….q.s

Table 2: Master Formulation of ORS-Zn 4.4gm

Unit (Master) Formulation					
Sr. no.	**Material Name**	**Reason for inclusion**	**Quantity**	**Unit/Sachet**	**Reference Standards**
Active Ingredients					
1.	Sodium Chloride	Electrolytes	x gm	gm	BP
2.	Potassium Chloride	Electrolytes	y gm	gm	BP

3.	Sodium Citrate	Electrolytes	Xx gm	gm	BP
4.	Anhydrous Glucose	Electrolytes	Xy gm	gm	BP
5.	Zinc Sulphate Monohydrate	Electrolytes	Yy gm	gm	BP
Excipients					
1.	Citric acid anhydrous	Electrolytes	Pp gm	gm	BP
2.	Sucralose	Sweetening agent	Qp gm	gm	USP
3.	Powdarome Orange	Flavoring agent	Rs gm	gm	IHS

Avg. weight of Sachet = 4.4gm

7.1.3. RAW MATERIAL SPECIFICATIONS:

a. SODIUM CHLORIDE

Table 3: RM Specifications of NaCl

Sr. no.	Test Parameters (as per BP)	Specification
1.	Appearance	White or almost white, crystalline powder or colorless crystals or white or almost white pearls.
2.	Solubility	Freely soluble in water, practically insoluble in anhydrous ethanol.
3.	Identification	A. Gives the reactions of chlorides. B. Gives the reactions of sodium.

4.	Appearance of solution	Solution is clear and colorless.
5.	Acidity or alkalinity	NMT 0.50ml of 0.01M hydrochloric acid or 0.01M sodium hydroxide is required to change the colour of the indicator.
6.	Bromides	NMT 100 ppm
7.	Ferrocyanides	No blue colour develops within 10 min.
8.	Iodide	The mixture shows no blue colour
9.	Nitrites	The absorbance of the sample solution is not greater than 0.01 at 354 nm.
10.	Phosphates	NMT 25 ppm.
11.	Sulphates	NMT 200 ppm
12.	Arsenic	NMT 1 ppm
13.	Barium	Any opalescence produced in the sample solution is not more than that of the comparison solution.
14.	Iron	NMT 2 ppm
15.	Magnesium and alkaline earth metals	NMT 2.5 ml
16.	Loss on drying	NMT 0.50% w/w at 105°C for 2 hours.
17.	Assay	99.0 % to 100.5% (dried substance)

b. POTASSIUM CHLORIDE

Table 4: RM Specifications of KCL

Sr. no.	**Test Parameters**	**Specification**

	(as per BP)	
1.	Appearance	White or almost white, crystalline powder or colorless crystals.
2.	Solubility	Freely soluble in water, practically insoluble in anhydrous ethanol.
3.	Identification	A. Gives the reactions of chlorides. B. Gives the reactions of potassium.
4.	Appearance of solution	Solution is clear and colorless.
5.	Acidity or alkalinity	NMT 0.5 ml of 0.01M hydrochloric acid or 0.01M sodium hydroxide is required to change the colour of the indicator.
6.	Bromides	NMT 0.1%
7.	Iodide	Show no blue colour after 5 mins.
8.	Sulphates	NMT 300 ppm
9.	Barium	Solution is not more opalescence than a mixture of 5ml of solution A and 6 ml of water.
10.	Iron	NMT 20 ppm
11.	Magnesium and alkaline earth metals	Show no blue colour after 5 mins.
12.	Loss on drying	NMT 1.00% w/w at 105°C for 3 hours.
13.	Assay	99.0 % to 101.0% (dried substance)

c. SODIUM CITRATE

Table 5: RM Specifications of Sodium Citrate

Sr. no.	Test Parameters	Specification
1.	Appearance	White or almost white, crystalline powder or white or almost white, granular crystals, slightly deliquescent in moist air.
1.	Solubility	Freely soluble in water, practically insoluble in ethanol
2.	Identification	A. The solution gives reaction to citrates. B. The solution gives reaction to sodium.
3.	Appearance of solution	Solution is clear and colorless.
4.	Acidity or Alkalinity	NMT 0.2 ml of 0.1 M hydrochloric acid or 0.1M sodium hydroxide is required to change the colour of the indicator.
5.	Readily Carbonisable substances	The solution is not more intensely colored than reference solution
6.	Chlorides	NMT 50 ppm
7.	Oxalates	NMT 300 ppm
8.	Sulfates	NMT 150 ppm
9.	Water	11.0% to 13.0%
10.	Assay	99.0% to 101.0%

d. ANHYDROUS GLUCOSE

Table 6: RM Specifications of Anhydrous Glucose

Sr. no.	Test Parameters	Specification

1.	Appearance	White or almost white crystalline powder.
2.	Solubility	Freely soluble in water. Very slightly soluble in ethanol (96%).
3.	Identification	A. By specific optical rotation: NLT +52.50 and NMT +53.30 (anhydrous substance) B. By HPLC: The principal peak in the chromatogram obtained with the test solution is similar in the retention time and size to the principal peak in the chromatogram obtained with reference solution. C. By TLC: The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution. D. A red precipitate is formed. E. Water: Check the compliance with the test of water.
4.	Appearance of solution	The sample solution is clear and not more intensely colored than the reference solution.
5.	Conductivity	NMT 20 $\mu s.cm^{-1}$.
6.	Related substances • Sum of impurities A and B	By HPLC NMT 0.4%

	• Impurity C • Impurity D • Unspecified impurities • Total impurities	NMT 0.2% NMT 0.15% NMT 0.10% NMT 0.5%
7.	Dextrin	The substance dissolves completely.
8.	Soluble Starch, Sulfite	NMT 15 ppm
9.	Water	NMT 1.00% w/w
10.	Assay	97.5% to 102.0%
11.	Microbial Enumeration Tests: (IH) Total aerobic microbial count Total combined yeast and molds count	 NMT 10^3 cfu per g. NMT 10^2 cfu per g.
12.	Particle Size: (IH) Particles should pass through 30# sieve.	 NLT 100% w/w

e. ZINC SULPHATE MONOHYDRATE

Table 7: RM Specifications of Zn-S monohydrate

Sr. no.	Test Parameters	Specification

1.	Description	A white or almost white, crystalline powder, or colorless, transparent crystals.
2.	Solubility	Very soluble in water, practically insoluble in ethanol (96%)
3.	Identification	A. Gives the reactions of sulfates. B. Gives the reactions of zinc.
4.	Appearance of solution	Solution is clear and colorless
5.	pH	4.0 to 5.6
6.	Chloride	NMT 300 ppm
7.	Iron	NMT 100 ppm
8.	Assay	99.0% to 101.0%

f. CITRIC ACID ANHYDROUS

Table 8: RM Specifications of Citric Acid Anhydrous

Sr. no	**Test Parameters**	**Specifications**
1.	Appearance	White or almost white, crystalline powder, colorless crystals or granules.
2.	Solubility	Very soluble in water, freely soluble in ethanol (96%)
3.	Melting Point	About 153°C, with decomposition.
4.	Identification	A. The solution is strongly acidic. B. IR absorption spectrophotometry C. A red colour develops.

		D. A white precipitate is formed. E. Water
5.	Appearance of solution	The solution is clear and colorless or not more intensely colored than reference solution.
6.	Readily carbonisable substances	The solution is not more intensely colored than a mixture of 1 ml of red primary solution and 9 ml of yellow primary solution.
7.	Oxalic acid	NMT 360 ppm
8.	Sulfates	NMT 150 ppm
9.	Aluminium	NMT 0.2 ppm
10.	Water	NMT 1.0 %
11.	Sulfated ash	NMT 0.1 %
12.	Assay	99.5 % to 100.5% (anhydrous substance).

g. SUCRALOSE

Table 9: RM Specifications of Sucralose

Sr. no.	**Test Parameters (as per USP)**	**Specifications**
1.	Description	White or almost white powder; odorless; taste-sweet
2.	Identification	A. By IR B. By HPLC C. By HPLC
3.	Specific optical rotation	Between +84.0° and +87.5° at 20°

4.	Water	NMT 2%
5.	Residue on Ignition	NMT 0.7%
6.	Heavy metals	NMT 0.001%
7.	Limit of hydrolysis products	NMT 0.1%
8.	Limit of Methanol	NMT 0.1%
9.	Related compounds	NMT 0.5%
10.	Assay	98.0 % to 102.0 %

h. POWDAROME ORANGE

Table 10: RM Specifications of Powdarome Orange

Sr. no	**Test Parameters (In-house)**	**Specifications**
1.	Appearance	Off-white to pale yellow powder, odorless and tasteless.
2.	Water Content	NMT 8.0 %
3.	Particle Size	NLT 99.0 % w/w particles should pass through 20# sieve.

7.1.4. DRUG PRODUCT DESCRIPTION:

Generic Name: ORS with Zinc Powder

Appearance: White to creamy white, amorphous or crystalline powder with orange flavor.

Component of Drug Product:

7.1.4.1. Active Ingredient:

Label claim

Sodium Chloride BP…….x g

Potassium Chloride BP…….y g

Sodium Citrate BP……....z g

Anhydrous Glucose BP…….p g

Zinc Sulfate Monohydrate BP...q g

Excipients…….…. q.s.

- Sodium Chloride

Appearance: White to off-white, white crystalline powder or colorless crystals.

Solubility: Freely soluble in water & practically insoluble in Ether & Ethanol.

- Potassium Chloride

Appearance: White crystalline powder odorless

Solubility: Freely soluble in water & practically insoluble in Ether & Ethanol.

- Glucose (Anhydrous)

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water, sparingly soluble in ethanol (96%).

- Zinc Sulfate Monohydrate

Appearance: White or almost, crystalline powder. Astringent, metallic taste, solutions are acid to litmus.

Solubility: Soluble in water, ethanol and glycerol.

7.1.4.2. Excipients:

Table 11: Excipients Used

Sr. no.	Ingredients	Specification
1.	Citric acid	BP
2.	Sucralose	USP
3.	Powdarome Orange	IHS

7.1.5. Labeling and Packaging Information

Administration:

One sachet's whole contents should be dissolved in 200 millilitres of previously heated and cooled water. Use the prepared solution within 24 hours, and dispose of the leftover solution.

Dosage:

Depending upon the degree of dehydration

Children: 1 to 2 liters over a period of 24 hours

Adults: 1 to 3 liters over a period of 24 hours

Recommended Storage instructions:

Store in dry place. Keep out of reach of children.

Side Effect and Special Precautions:

1. Oral Rehydration Salts: None stated
2. Zinc Sulfate Monohydrate:

Zinc salts may cause discomfort in the abdomen, dyspepsia, nausea, vomiting, diarrhea, gastric irritation and gastritis. Lethargy, headaches, and irritability have also been reported in some cases.
Reduced copper levels and perhaps copper insufficiency can result from zinc's interference with copper absorption. Long-term treatment (e.g., if zinc insufficiency is no longer evident) and/or higher doses of zinc may increase the risk of copper deficiency.

Interactions:

1. Oral Rehydration Salts: None stated
2. Zinc Sulfate Monohydrate:

- Copper: Zinc may inhibit the absorption of copper.
- Tetracycline antibacterials: Zinc may reduce the absorption of concurrently administered tetracycline
- Quinolone antibacterials: Zinc may reduce the absorption of quinolones; ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin.
- Calcium Salts: The absorption of zinc may be reduced by calcium salts.
- Iron: The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.
- Penicillamine: The absorption of zinc may be reduced by penicillamine, also the absorption of penicillamine may be reduced by zinc.
- Trientine: The absorption of zinc may be reduced by trientine, also the absorption of trientine may be reduced by zinc.

Warnings & Precautions:

1. Oral Rehydration Salts:

Under medical supervision, diarrhoea that is severe and persistent should be treated. Consult a physician if symptoms last longer than 24 to 48 hours. Unable to consume or hold onto fluids need medical care.

- Children:
  - Rehydration therapy should only be administered to infants under the age of one year per physician recommendation.
  - See a chemist, doctor, or other healthcare provider for advice if a small kid (especially one under 6 months old) has diarrhoea and/or vomiting. The youngster needs to see a doctor right away if the vomiting and/or diarrhoea are severe.
- Renal Impairment
  - Medical supervision is necessary in patients with renal disease, including anuria and prolonged oliguria.
- Hepatic Impairment
  - Diabetes; low sodium and Potassium Diets.
  - Treatment should be supervised by a physician.
  - This product contains glucose. Patients with rare-glucose-galactose malabsorption should not take this medicine.

2. Zinc Sulfate Monohydrate:

- Zinc accumulation may arise in renal failure.

Contraindications:

1. Oral rehydration Salts:

   Patients who are hypersensitive to any of the components or who have phenylketonuria should not use this product. In cases like severe dehydration, which calls for parenteral fluid therapy, or intestinal blockage, oral treatment is inappropriate.

2. Zinc Sulfate Monohydrate:

   Hypersensitivity to the active substance or any of the excipients.

7.1.6. Pharmacological Properties:

7.1.6.1. Pharmacodynamic Properties:

Sodium and glucose are two of ORS's main ingredients. The utilisation of sodium-glucose co-transports in the small intestine, a mechanism that is mostly unaltered by acute infectious diarrhoea, is the fundamental idea behind oral rehydration treatment (ORS). Therefore, glucose-driven salt absorption (transcellular route), which results in passive water absorption by the paracellular route, is largely responsible for the effectiveness of ORS. Usually, quick rehydration and acidosis correction are the clinical outcomes.

Zinc Sulfate Monohydrate:

A vital trace element, zinc is a part of numerous enzyme systems. In children, severe insufficiency results in skin lesions, baldness, diarrhoea, heightened susceptibility to infections, and underdevelopment. Less severe deficiency symptoms include poor wound healing and altered or nonexistent taste and smell senses.
More than 70 distinct enzymes have been shown to require zinc as a cofactor, including RNA and DNA polymerase, lactic dehydrogenase, and alkaline phosphatase. Zinc aids in wound healing, normal skin hydration, normal development rates, and taste and smell perception.

7.1.6.2. Pharmacokinetic Properties:

Oral Rehydration Salts:

The membrane actively transports glucose and sodium into the enterocytes. Following the extrusion of sodium into the intercellular spaces, an osmotic gradient is created, which draws water and electrolytes from the gut and into the circulation.

Zinc Sulfate Monohydrate:

The gastrointestinal system absorbs zinc, which is then dispersed throughout the body. The areas with the largest concentrations are the bone, eyes, hair, and male reproductive organs. Liver, kidney, and muscle contain lower quantities. 80% of blood is made up of erythrocytes. Between 70 and 110 μg/dl of zinc are found in plasma, with roughly half of that amount being loosely linked to albumin. The remaining portion is firmly attached to alpha 2-macroglobulins and other proteins, making up around 7% of the total.

7.1.6.3.**Preclinical Safety Data:**

The main constituents of oral rehydration salts with Zinc are physiological and when used appropriately are not toxic.

Overdose:

When a substantial overdose occurs, serum electrolytes should be assessed very once, anomalies should be corrected as needed, and levels should be tracked until they return to normal. This is crucial in cases of severe renal or hepatic failure especially in the very young.

CHAPTER: 8

SUBMITTING DOSSIER TO CDSCO

Chapter 8: Submitting Dossier to CDSCO:

8.1. Registration process:

1. To register yourself, open the "**www.cdscoonline.gov.in**" link and select "**Sign Up Here**" (highlighted), as illustrated in Figure 7.

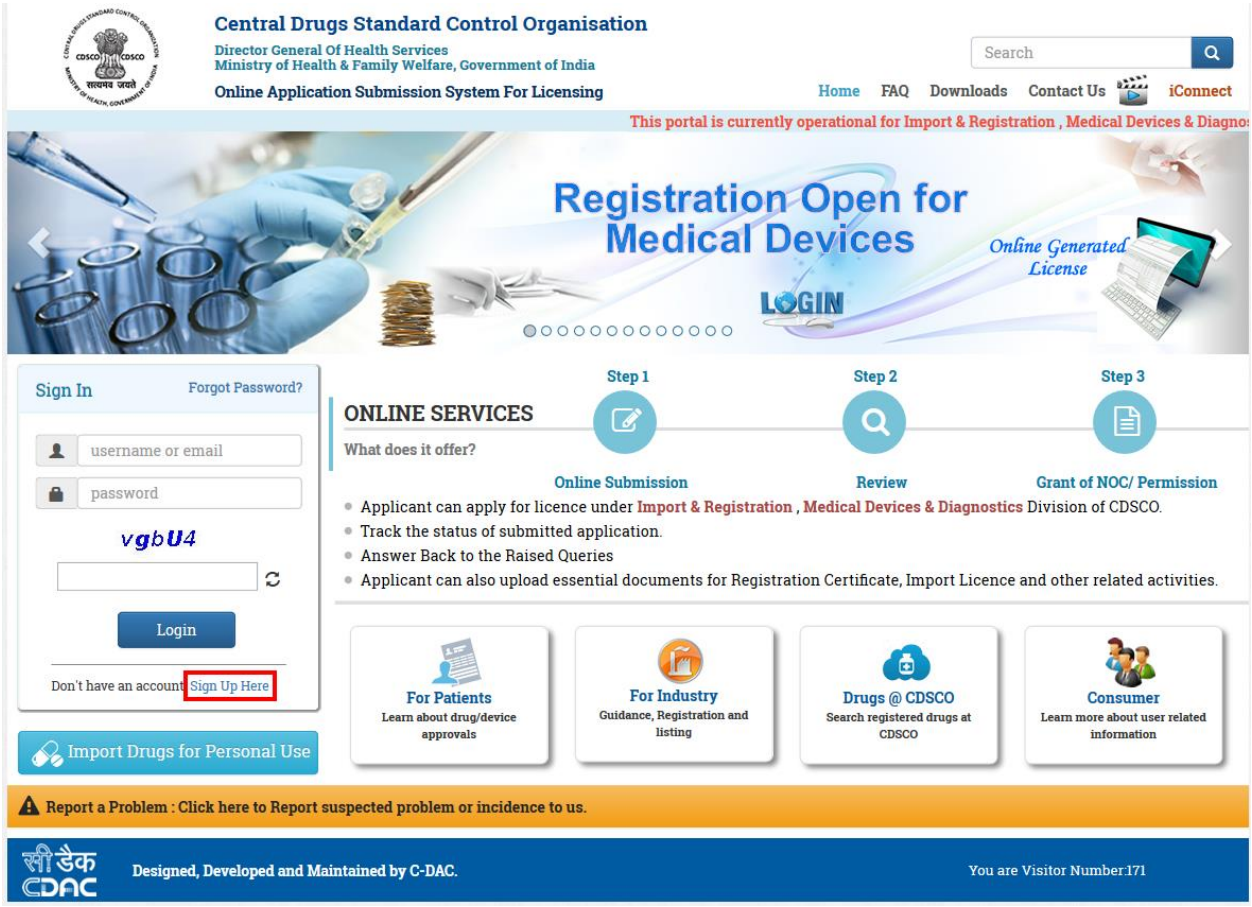

Figure 7 Registration Sign up Window Source: CDSCO Portal

2. A new window will emerge as indicated in the figure after selecting the "**Sign Up Here**" link for the "**Registration Purpose**" on the site.

A drop down list will appear, user can choose any of the registration purpose drom the drop down list as per their requirement. (Here as chosen “for import or manufacture of drugs”).

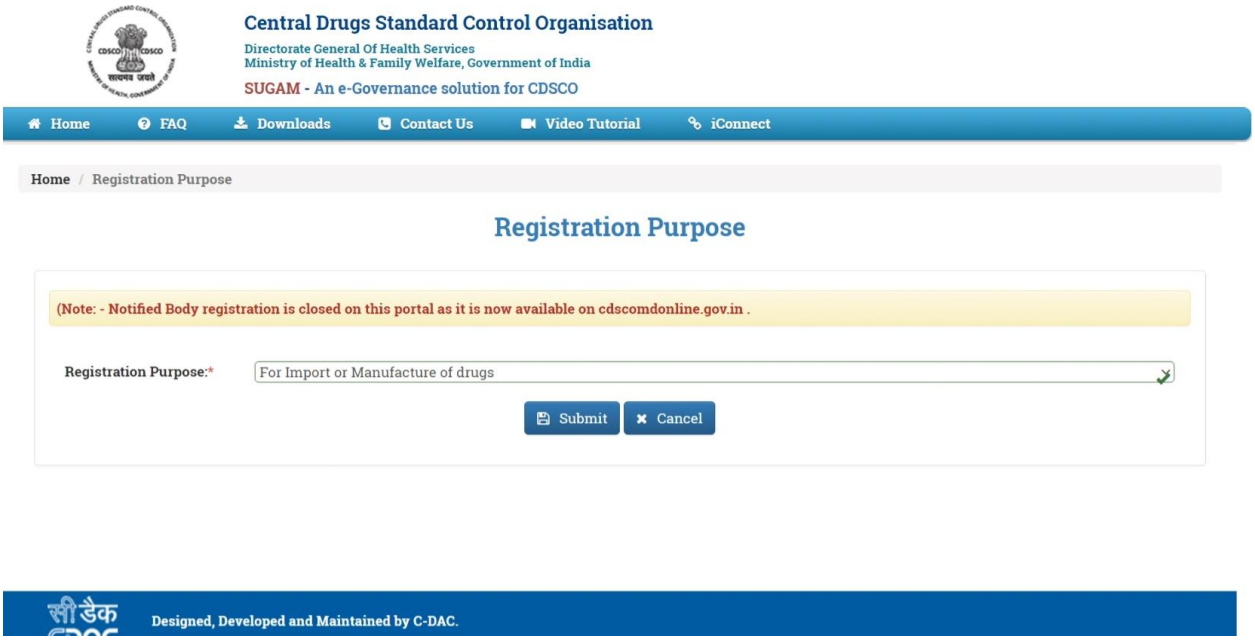

Figure 8 Registration Purpose Source: CDSCO Portal

- The user has to click the "**Submit**" button to complete the registration process after choosing the purpose.
- By selecting the "**Cancel**" option, the user may terminate the registration purpose.

3. Application registration form will be shown in the site after submitting the registration purpose.

- The username, which can be used as a user name in the future, will be the company email address. It must be unique.
- A password must contain a minimum of six characters, with a minimum of one numeric, one capital, one lowercase, and one special character.
- Before completing the sign-up process, the user must submit the required documents, which include **the ID proof details, power of attorney, proof of corporate address, and details of the manufacturing licence or wholesale licences (Form 20B & Form 21B)**. The user should have these documents ready in PDF format.

- You will receive a registration and verification message on your registered mobile phone upon registration if you check the "Do you want to receive SMS alerts?" box.

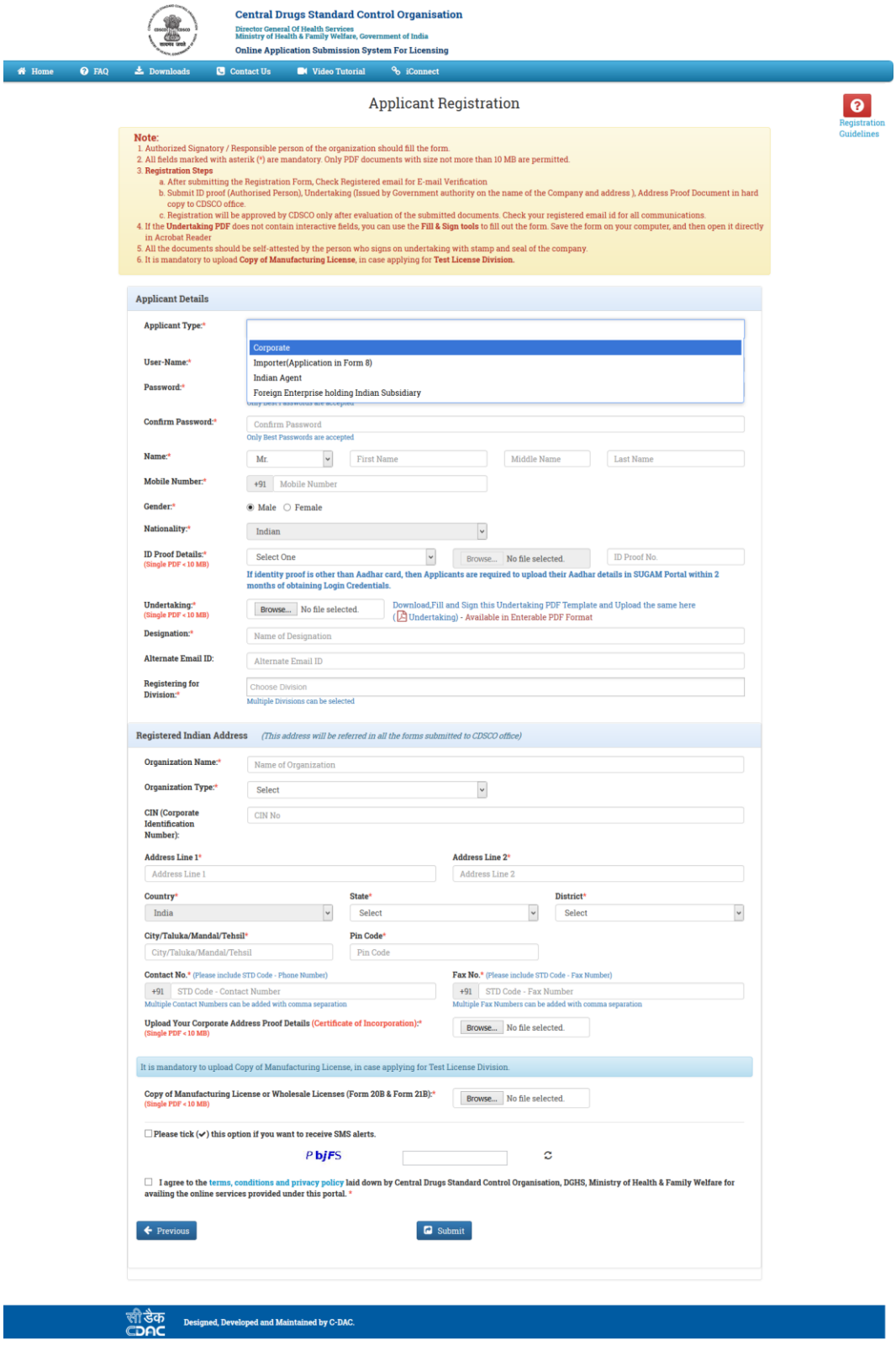

Figure 9 Application Registration Source: CDSCO Portal

4. User can register by filling the registration form as shown in the figure 10:

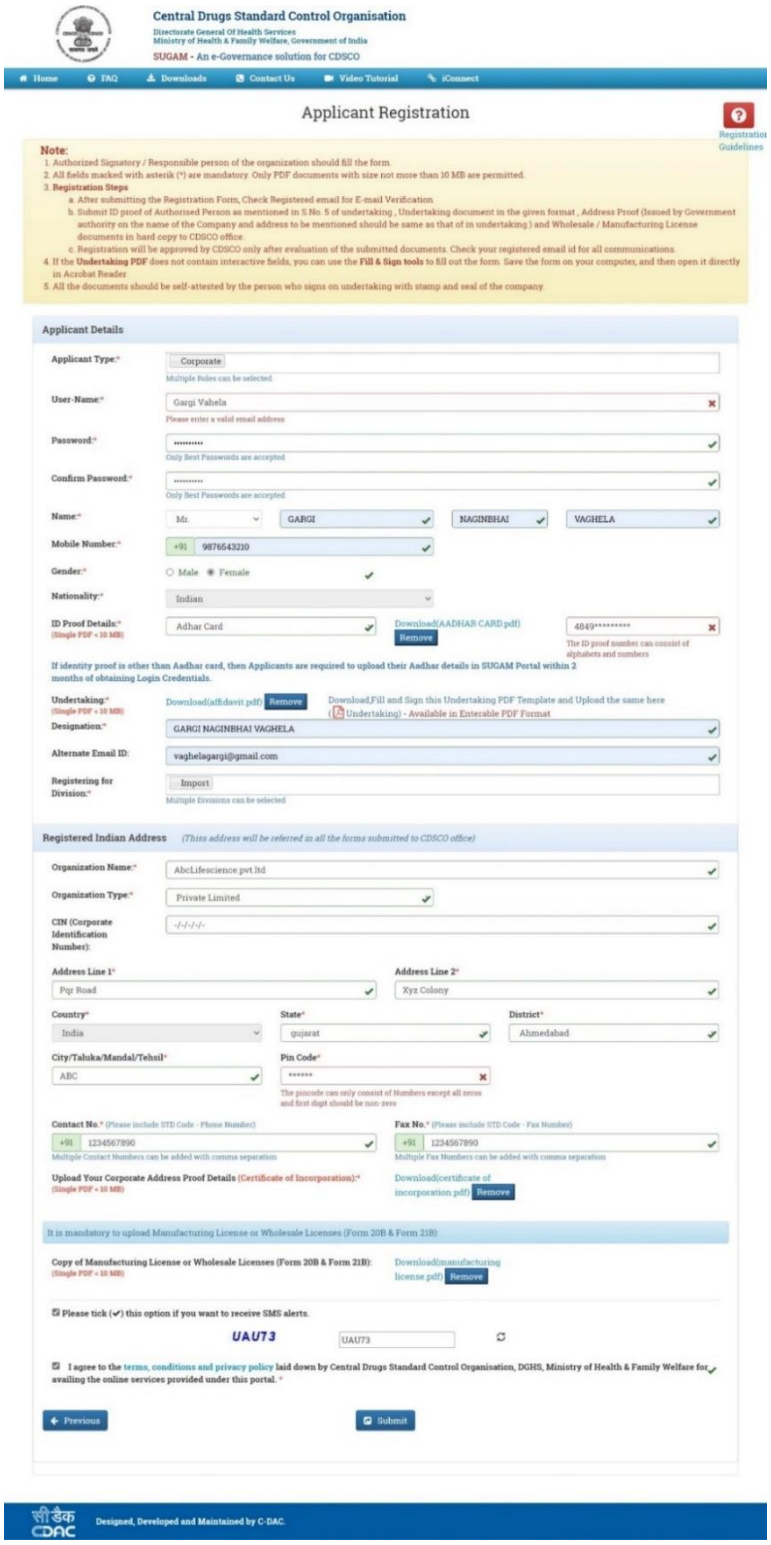

Figure 10 Draft Filled Application Source: CDSCO Portal

- To confirm registration, a confirmation link will be given to the user's registered email address when they click the "Submit" button.
- By clicking on the link supplied to the registered email address, the user can activate their account.
- Upon clicking the verification link that was supplied to the user's registered email address, the application will be forwarded to the relevant authorities (CDSCO Officials) for approval.
- If the application is accepted, the user's registered email address will receive an email.
- Should an application be denied, the user's registered email address will receive a rejection email.
- By clicking the "Previous" button, users can also go back to the previous stage.

5. Once the registration process is successful, a common window will open after you fill out the form and click the Submit button, as seen in Figure 11.

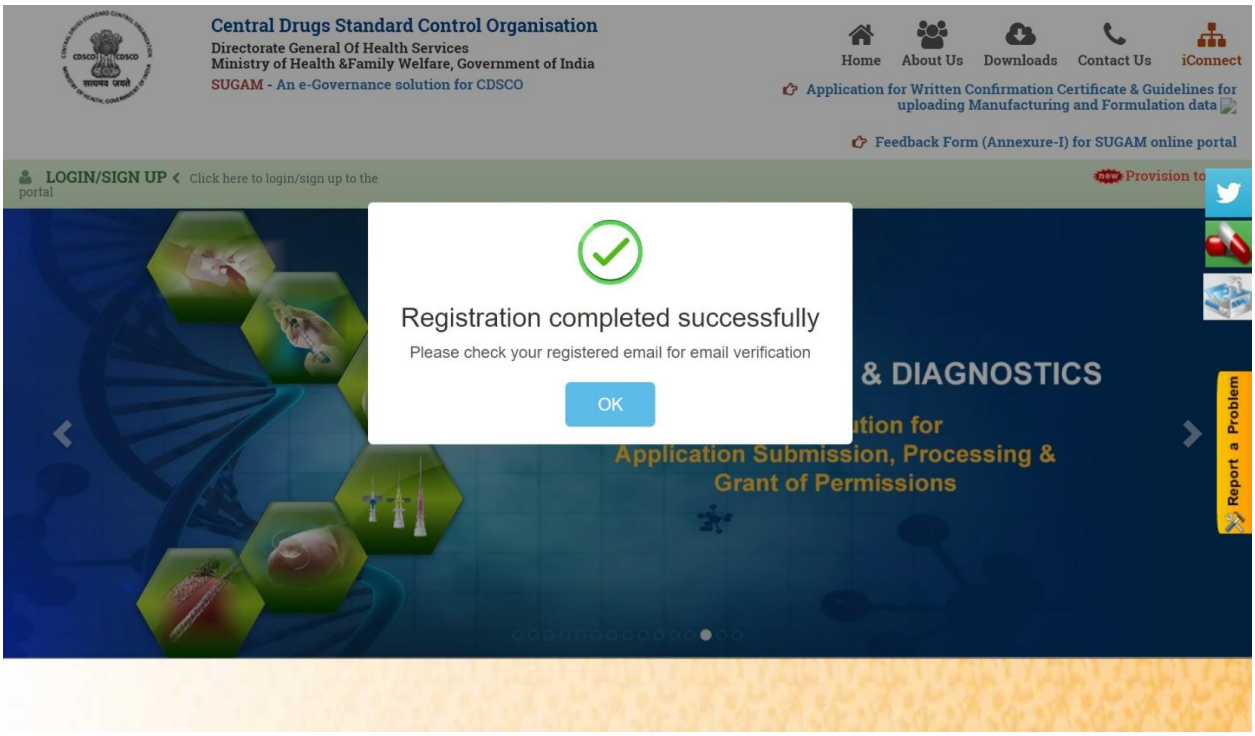

Figure 11 Registration Completed Source: CDSCO Portal

- As indicated in Figure 11, a confirmation link to confirm registration will be issued to the user's registered email address following receipt of the "Successful Registration" message.

- By clicking on the link supplied to the registered email address, the user can activate their account.

- Upon clicking the verification link that was supplied to the user's registered email address, the application will be forwarded to the relevant authorities (CDSCO Officials) for approval.

- Once the application is accepted, the user's registered email address will receive an email. If an application be denied, the user's registered email address will receive a rejection email.

6. Following the "OK" button, enter your login credentials in the sign-in box and select "Login", as seen in Figure 12.

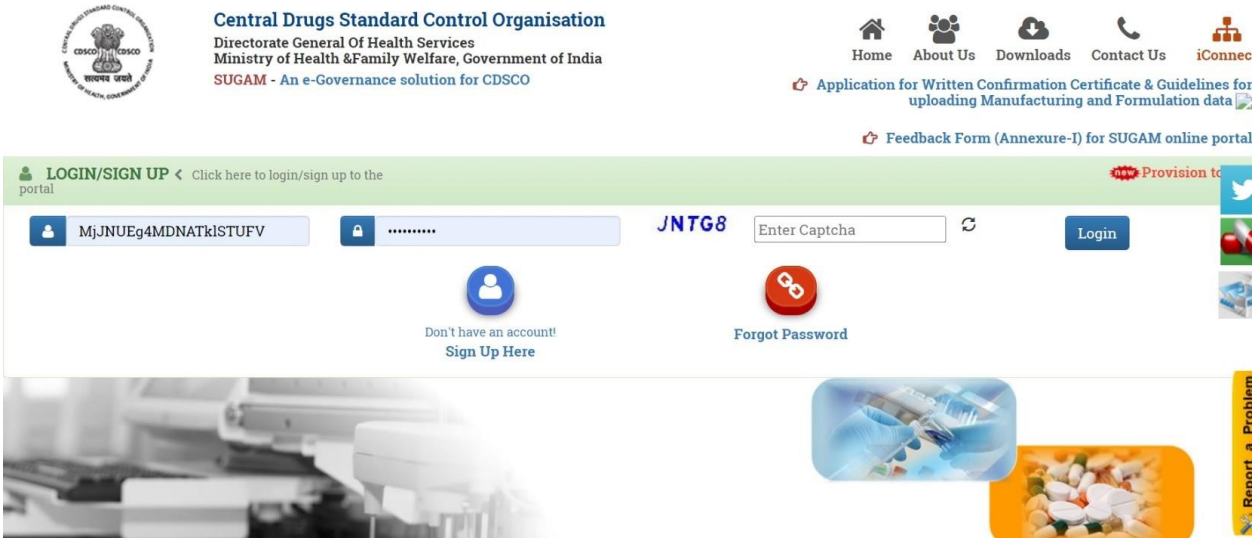

Figure 12 Login Page Source: CDSCO Portal

• The user can apply for the application via the portal by logging in with their valid login information, which consists of their username and password.
• The user is encouraged to periodically verify that their valid registered phone number and email address are up to date, as all correspondence prior to a successful registration procedure will be conducted via the user's registered phone number and email address (by SMS).

CHAPTER 9:

REGULATORY PATHWAY FOR REGISTRATION OF ORS WITH ZINC IN AFRICAN COUNTRIES

Chapter 9: Regulatory Pathway for Registration of ORS with Zinc in African Countries

9.1. African Union:

Objectives:

- Encourage solidarity and cohesion among African nations;
- Organise and step up development cooperation.
- Preserve each member state's territorial integrity and sovereignty.

African Medicines Agency (AMA):

- An initiative under the AU aimed at harmonizing regulatory processes for medicines to improve access to quality and safe healthcare products.

- Establishment and Mandate:
    - The establishment of the African Medicines Agency was proposed as part of the AU's efforts to create a more coordinated and harmonized regulatory framework for medicines in Africa.
    - The AMA is designed to facilitate the regulation and oversight of medical products, including pharmaceuticals, vaccines, and other health technologies.
- Harmonization of Regulatory Processes:
    - One of the primary objectives of the AMA is to harmonize regulatory processes for medicines across African countries.
    - Harmonization aims to streamline the approval and monitoring of medicines, ensuring that regulatory standards are consistent and that safe and effective products reach the market more efficiently.
- Benefits of Harmonization:
    - Harmonization can lead to faster and more predictable regulatory decisions, reducing delays in getting medicines to patients.
    - It encourages collaboration and information-sharing among African regulatory authorities.

    - Improved regulatory processes can enhance the quality, safety, and efficacy of medical products.
- Collaboration with Regional Economic Communities:
    - The AMA collaborates with regional economic communities and existing regulatory bodies to achieve its objectives.
    - Regional collaboration is essential for addressing specific healthcare challenges and tailoring regulatory approaches to regional needs.
- Capacity Building:
    - The AMA may be involved in capacity-building initiatives to strengthen the regulatory capabilities of national agencies.
    - This includes training regulatory professionals and supporting the development of robust regulatory systems.

Regulatory Submission in African Continent

African member states has following the data submission in following ways:

 Common Technical Document

 Country specific dossier

9.2.Organization of Common Technical Documents

The CTD is a standard way of specifying how dossiers are formatted and organised. It is used to format and organized marketing authorisation applications as well as most post approval applications.

The CTD is structured in to five different modules and module 1 is region specific. Modules 2, 3, 4, and 5 are proposed to be common for all counties. Conformance with this guideline should confirm that these four modules are providing in a format acceptable to the regulatory authorities.

1. Administrative and prescribing information: This module contains documents of each specific region for example application forms or the proposed label for use in the region. The content and format of this module is specified by the regulatory authority.

2. Common technical document summaries: In this module, includes general information

about the drug including its pharmacological class, mode of action and proposed indication. Information or introduction should not be more than one page.

Module 2 contains following 7 sections:

- CTD Table of Contents
- CTD introduction
- Quality Overall Summary (QOS)
- Non clinical overview
- Clinical overview
- Non clinical written and tabulated summaries
- Clinical summary

The organization of the above reviews is described in Guidelines M4Q, M4S and M4E.

3. Quality: This segment in the module includes details about quality and is presented in the proper format presenting CMC (Chemistry, Manufacturing and Control) and the format is explained in M4Q guidance document.

4. Non-Clinical study reports: this segment in module is presented and organized according to the guidance M4S. Non clinical overview includes evaluation of pharmacokinetics, pharmacologic and toxicologic of the pharmaceutical product (not exceed 30 pages). Non clinical tabulated summaries provides more intensive non clinical information on pharmacology, pharmacokinetic and toxicology (100-150 pages).

5. Clinical study reports: This section includes reports on human study (clinical) & raw data and other related guidance information is given in the guidance M4E. Clinical overview is short document that describes critical assessments of clinical data while Clinical summary is an informative long document which focusses on data summarisation and integration.

9.3. Regulatory Requirements for drug registration in African Countries

Table 12 : List of common regulatory requirements for drug registration in African Countries:

Sr. no.	Common regulatory requirement for drug registration in African countries
1.	Free sale certificate and Certificate of Pharmaceutical product
2.	Manufacturing license
3.	GMP certificate
4.	Artwork (Labels, Package insert, patient information leaflet)
5.	CMC document
6.	Substance part (DMF) ▪ Nomenclature ▪ General properties ▪ Name of the Manufacturer and Site of manufacture ▪ Route of Synthesis, flow diagram in brief ▪ Structural Elucidation ▪ Impurities ▪ Specifications and Method of Analysis ▪ Container closure system ▪ Stability testing ▪ API specification and Method of Analysis ▪ COA of API by applicant
7.	Drug product part ▪ Description of the product ▪ Batch formula ▪ Manufacturing process ▪ Flow chart of manufacturing process ▪ BMR ▪ Batch analysis

	▪ Excipients (spec, TSE/BSE certificate, MOA) ▪ Finished product specification and MOA ▪ Finished product COA ▪ Stability protocol ▪ Stability data

CHAPTER 10:

CONCLUSION

Chapter 10: CONCLUSION

ORS formulations containing Zinc helps in the management of diarrheal symptoms and requires regulatory pathways both in domestic market and across different regions. In India, the regulatory framework for registering ORS with Zinc is governed by CDSCO involving a comprehensive process that includes obtaining manufacturing licenses, conducting stability studies, preparing dossiers, and ultimately securing marketing authorization.

On the other hand, the regulatory landscape in African countries is shaped by regional harmonization initiatives, such as the African Medicines Regulatory Harmonization (AMRH) that aim to streamline regulatory requirements and promote harmonization across participating countries, potentially facilitating the registration and access to essential medicines like ORS with zinc.

This study compared the regulatory pathways for registering ORS with Zinc in India and African nations, Identifying areas of potential harmonization. Streamlining regulatory processes through collaborative efforts is crucial for facilitating access to essential medicines like ORS-zinc.

10.1. Comparative Tabular summary

Table 14: Tabular Summary contrasting India and Africa for Registration of FDCs:

Sr. no.	Requirements	India	Africa
1.	Regulatory Authority	CDSCO	Kenya- PPB Uganda- NDA Tanzania- TMDA Zimbabwe- MCAZ Ghana- FDA Botswana- BOMRA Zambia- ZAMRA Ethiopia- EFDA
2.	Dossier Format	CTD	CTD
3.	Dossier Language	English	English
4.	COPP	Required	Required from country of origin as per WHO format
5.	Manufacturing License	Required	Required
6.	Registration Validity	3 years	Life time validity Annually retention TZ/BW – 5 years ET – 5 years GH – 3 years
7.	Registration Time	Within 9 months of application	2-18 months

8.	Inspection/Audit	Required	Required
9.	Stability Zone	Zone IV	Zone IVa and Zone IVb
10	Minimum Stability data	LT- 12 months Acc- 6 months	LT- 12 months Acc- 6 months
11	Stability guideline reference	ICH	National and ICH
12	Labeling Requirement	Yes	Yes
13	BE Study (for Generic)	Comparative BE study is required	The comparative BE study profile is required against US/ EU innovator is carried out.

Annexures:

(Attached)

Annexure 1: Application for CT 10 of ORS with Zinc to CDSCO

Annexure 2: Online Forms Submission

Annexure 3: Form CT-10: Application details

Annexure 4: Form CT-10: Indian/Overseas manufacturer & Manufacturing Site(s)

Annexure 5: Form CT-10: Non-Biologicals Drug Details

CHAPTER 11:

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ANNEXURES

[redacted]

November 21, 2023

To,
Central Drug Standards Control Organization.,
Air Cargo Complex, Airport,
Ahmedabad-380 003,
Gujarat

Sub. : Application for the CT 10 of Oral Rehydration Salts with Zinc

Dear Sir,

With reference to our application, Pls find enclosed Documents as mentioned below

1. Covering letter of firm

2. Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/28D or loan license issued by SLA or DSIR approval in case of R&D

3. Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes

4. Upload status of new drug (API and its formulation) – approved in India or in other countries

5. Proposed SOP for manufacturing

6. Proposed SOP for analysis /testing

7. List of manufacturing equipments

8. List of analytical instrument/facility

9. Proposed specification and STP

10. Source and specification of active raw material for formulation

11. In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated

Thanking you,

Your
For [redacted],

Authorized Signatory

Central Drugs Standard Control Organisation

Directorate General Of Health Services
Ministry of Health & Family Welfare,
Government of India

Online Forms Submission

Select Department:

Test License

Select Form:

Form CT-10

☐ I agree that I will provide accurate information and I will be solely responsible for any false or inaccurate information provided to the division.

Proceed

GENERAL INSTRUCTIONS

**** User can proceed to Online Form Submission only if the User Profile is complete.***

Please read the below instructions carefully before proceeding to Online Form Submission

1. *Online Form Submission* is divided into few simple steps like:
   - Filling of Form
   - Uploading Essential Documents in checklist
   - Payment (if applicable) and
   - Final Form Upload.
2. User is required to download **pdf** in *Full Preview step*. After downloading, perform the following steps:
   - Sign and Stamp the form
   - Scan the Signed and Stamped Form
   - Upload this form in the *Upload Form step*
3. Please ensure that you have all the required documents ready to upload them in checklist section. Please view the checklist from here (/CDSCO/resources/app_srv/cdsco/global/Sample Docs.pdf)

User Profile

Permissions Owned

Application Submission

Online Payment

Designed, Developed and Maintained by C-DAC.

Central Drugs Standard Control Organisation

Directorate General Of Health Services
Ministry of Health & Family Welfare,
Government of India

Form CT-10

[See Rule 52]

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Application Details

Purpose of Application

* For Examination, Test or Analysis

Place from where application is being made

Sanand *

Test or Analysis Site

Note: Application is forwarded to zone based on State selection here.

Select Site Type

* Manufacturing/R&D Site

Select Manufacturing Site / R&D Centre

*[redacted]

Sites address in this section are fetched from Manufacturing Sites / R&D Centres added under User Profile.
If testing to be done at **Central Drugs Testing Laboratory** then Select option **CDSCO Labs**.

User Profile

Permissions Owned

Application Submission

Online Payment

Manufacturer Address

Note: Please enter the address where drug is being manufactured.

Country

* India

Address Line 1

Abc Lifescience pvt ltd. PQR road, Ahmedabad

Address Line 2

State/Province/Region

Gujarat

City

Sanand

Zip/Postal code

382213

Landline No. (Please include Country Code - State Code - Landline Number)

+ +919876543210

Multiple Contact Numbers can be added with comma separation.

Fax No. (Please include Country Code - State Code - Fax Number)

+ Country code- State code- Fax number

Multiple Fax Numbers can be added with comma separation.

Address Details

Note: Kindly select below listed addresses for required in section 3 & 5 of Form CT-10 as per new Drugs & CT rules 2019 Addresses in this section are fetched from Add Address Details tab added under User Profile.

Corporate or Registered Office Address

* Abc Lifescience pvt ltd.

Correspondence Address

User Profile

Permissions Owned

Application Submission

Online Payment

Save Reset

Designed, Developed and Maintained by C-DAC.

Central Drugs Standard Control Organisation

Directorate General Of Health Services
Ministry of Health & Family Welfare,
Government of India

Form CT-10

[See Rule 52]

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Indian/Overseas Manufacturer & Manufacturing site(s)

Manufacturer, Manufacturing site(s) details

Type of Drug

Formulation

Manufacturer, Manufacturing site(s) Details

Manufacturing Site Address - [redacted]

Addresses in this section are fetched from Add Address Details tab added under User Profile.

Previous Save Next

Address Details

Search:

	Site Type	Manufacturer Name	Site Address	Type of Drug

User Profile

Permissions Owned

Application Submission

Online Payment

	Site Type	Manufacturer Name	Site Address	Type of Drug
☐	✚ Manufacturing Site Address	Abc Lifescience pvt ltd.	Ahmedabad	Formulation

Designed, Developed and Maintained by C-DAC.

Central Drugs Standard Control Organisation

Directorate General Of Health Services
Ministry of Health & Family Welfare,
Government of India

Form CT-10

[See Rule 52]

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Non-Biologicals Drug Details

Type of Drug

* Formulation

Name of Drug/Formulation

Oral Rehydration Salts with Zinc *

Brand Name

Zincoralyte ®

Class of Drug

* Other class of Drugs (if any details)

Drug Strength

4400 *

* milligram (mg)

Quantity

1000 *

* sachets

Composition

Sodium Citrate IP 0.580 gm
Potassium Chloride IP 0.300 gm
Sodium Chloride IP 0.520 gm
Dextrose Anhydrous IP 2.700 gm

Indication

For Diarrhea

Regulatory Status of drug in other countries, as appropriate

Regulatory Status

Not Approved Anywhere

Reason/Remarks

Same Formulation in other Dosage Form (Liquid ORS) is approved by DCGI (15/04/2021)

Save Reset

Previous

Designed, Developed and Maintained by C-DAC.

MINOR

“The Regulatory Perspective of Real-World Data in the US, Europe, and the UK”.

Abstract:

Real-world evidence (RWE) and real-world data (RWD) are vital for drug development, regulatory compliance, and decision-making, and as such, they are gaining importance in the pharmaceutical sector and Drug Regulatory Agencies (DRAs) worldwide.

Although limited systematic documentation is known about the combination of RWE, it is utilised by DRAs to evaluate experimental treatment modalities and monitor post-market safety.

The purpose of this study was to examine and talk about how DRAs' opinion is incorporated into the regulatory decision-making process regarding RWE. Review and comparison of several development methodologies used by DRAs in the US, Europe, and the UK to create and implement RWE were conducted, along with a discussion of what challenges they faced. It was discovered that the FDA, EMA, and MHRA employed various approaches in the development of RWE. The UK's adoption of RWE was comparatively restricted as compared to the US and EU, and this was largely influenced by the country's unique pharmaceutical environment and developmental phases. The development of RWE involves several inputs, activities, outputs, and consequences that must be understood to guide actions that will optimise RWD and use RWE to improve health care decisions.

Real-World Data (RWD) has become more widely available, which has altered the global landscape for medication development and decision-making of regulation. Regulatory bodies in the US, UK, and EU now recognise the value of RWD in supplementing traditional clinical trial data to create a more complete picture of a product's safety and effectiveness.

CHAPTER 1:

INTRODUCTION

CHAPTER 1: INTRODUCTION

Real-world data (RWD) is being used increasingly by the pharmaceutical and healthcare sectors to aid in post-market surveillance, regulatory decisions, and medication development. However, there are potential and challenges for businesses operating in the US, UK, and EU due to the considerable differences in the regulatory frameworks governing the use of RWD in different regions. This thesis focuses to see how the regulatory environment for real-world evidence (RWE) is changing in these important areas, highlighting the main distinctions, similarities, and best practices for managing the ethical and legal use of RWE across the drug development lifecycle.

RWD is the term that describes information gathered from various sources about the health status of a patient, the provision of medical care, and medical behaviour in everyday clinical settings. Examples of data sources include patient information gathered from a range of devices, medical databases, Electronic Health records (EHRs), and medical claim data. The term "Real-World Evidence" (RWE) refers to the examination of clinical research data produced by RWD about the application of pharmaceuticals and their possible advantages or disadvantages. The regulatory science and the creation of national healthcare policy have a profound connection to the meanings and uses of RWE. Randomised clinical trials (RCTs) have historically been the primary, if not the only, basis for regulatory approvals of novel drugs.

The thorough design of RCTs necessitates the establishment of subject's inclusion and exclusion based on eligibility criteria in order to guarantee the uniformity and representativeness of the research results.

To guarantee the internal validity of the results, RCTs frequently exclude individuals with a variety of comorbidities. To some degree, the exclusion of population subsets in RCTs can potentially undermine the depiction of individuals with numerous comorbid conditions. It is inevitable that there will be gaps in the critical data needed to build a foundation of knowledge regarding how an intervention or treatment should be used for population subgroups that RCTs may produce.

When compared to RCTs, RWE is a valuable supplement that provides essential data from real-world practices over the course of drug's lifetime that aid in the making of regulatory decisions. According to the updated international draft of "General considerations for clinical studies, ICH E8 (R1)", RWE produced by pragmatic trials that incorporate randomization into EHR and claims data may help clarify post-marked safety issues, guide clinical care procedures, and prevent adverse events. It is challenging to recruit sufficient patient populations for RCT designs when developing therapy treatments for rare diseases.

Additional data sources, such as EHRs, claim data, other social media data, and a substantial amount of data produced by medical devices. Thus, RWE could offer advantages and work in collaboration with RCTs. Currently, RWE is being utilised more and more to guide regulatory choices. The variety of RWE rules is influenced by variations in the definition, extent, applications, and constitutions of RWE among nations.

The significance amount of existing literature on the reproducibility and validity RWE pertains to the application of RWE to support drug development and evaluation, aid in drug regulatory decision-making, assess the effects of clinical treatments, and efficiently derive RWE from RWD. In order to improve the effectiveness of regulatory measures, less thought has been given to the organisational viewpoint on how to create, implement, and progress RWD. Additionally, there is potential for this sort of approach to be implemented in all regulatory domains. Specifically, there was little of comprehensive studies about the potential use of RWE by the DRAs.

The DRAs in the US and the EU have gained a great deal of practical knowledge of utilizing RWD to analyse medical product safety during the last few decades. Two new guideline documents, the first of which will be released by the MHRA, describe the factors to take into account when organising a randomised clinical study that makes use of real-world data. Therefore, to identify the recent development and implementation status within the framework of three typical healthcare authorities was assessed and contrasted. Thus, this paper aims to evaluate and investigate the integration of RWE into regulatory decision-making processes from the perspective of DRAs in the US, EU, and UK.

CHAPTER 2:

AIM & OBJECTIVES

CHAPTER 2. AIM & OBJECTIVES:

1. To gather data on RWD/RWE in a systematic way from many sources, such as scholarly databases and the official websites of the three DRAs including US, Europe, and UK.
2. Examine the development and implementation of the RWD/RWE in the US, EU, and UK; and
3. Compare and contrast regulatory requirements of RWD/RWE in the US, EU, and UK.

CHAPTER 3:

LITERATURE REVIEW

CHAPTER 3. LITERATURE REVIEW:

1. FDA's Center for Devices and Radiological Health (CDRH) first released "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Guidance for Industry and Food and Drug Administration Staff" on August 31, 2017.
    - The primary topics covered were the regulatory landscape, the definition and application of RWD/RWE, and essential characteristics of medical devices.
    - This guideline included examples that were generalised from the real applications of RWE to support regulatory decision-making. These examples included post-approval device surveillance as approval conditions, post-market surveillance studies, expanding indications, control groups, additional data, and goals and standards for objective performance.

2. The U.S. Department of Health and Human Services (HHS) and FDA jointly issued the "Use of Electronic Health Record Data in Clinical Investigations: Guidance for Industry" on July 18, 2018.
    - This guidance intends to encourage the use of EHR data in clinical research and streamline clinical research.
    - This recommendation presented best practices for the use of EHR in clinical research and detailed HER interoperability and integration approaches.

3. FDA released "Framework for FDA's Real-World Evidence Program" on December 6, 2018.
    - This framework can be used to examine how RWE could possibly be utilised for facilitating decision-making and provides a reasonably clear road map for doing so.

4. On May 8, 2019, FDA's Center CDER and the Center for Biologics Evaluation and Research (CBER) jointly issued "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry".
    - This guideline explained how businesses might utilise RWD/RWE to assist their FDA applications and how RWD/RWE could be utilised to support safety and efficacy-related regulatory decision-making.

CHAPTER 4:

OVERVIEW OF REAL-WORLD DATA

CHAPTER 4: OVERVIEW OF REAL-WORLD DATA

4.1. Defining Real-World Data and Real-World Evidence

The term "real-world data" (RWD) describes information gathered from sources other than conventional clinical trials, including patient-generated information, claims data, electronic health records, and illness registries. The clinical evidence that is obtained from the examination of RWD is known as real-world evidence (RWE), and it offers information about the efficacy, utility, and safety of healthcare interventions in real-world situations.

The US FDA, Europe, and the UK have defined RWD and RWE as follows:

- **United States (US FDA):**

  Real-World Data (RWD):

  "Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as electronic health records (EHRs), claims and billing data, product and disease registries, and data collected through personal devices and health applications." (FDA, 2022)

  Real-World Evidence (RWE):

  "The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD" (FDA, 2022)

- **Europe (European Medicines Agency):**

  Real-World Data (RWD):

  "Data collected from a variety of sources outside typical clinical trials, such as electronic health records, claims and billing data, product and disease registries, and data gathered through personal devices and health applications." (EMA, 2020)

  Real-World Evidence (RWE):

  "Evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of real-world data." (EMA, 2020)

- **United Kingdom (MHRA):**

  Real-World Data (RWD):

  "Data collected outside the constraints of conventional randomised controlled trials, including data from electronic health records, disease registries, patient-reported outcomes, and data gathered through mobile devices and applications." (MHRA, 2021)

  Real-World Evidence (RWE):

  "The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of real-world data." (MHRA, 2021)

4.2. Importance of RWD and RWE in the pharmaceutical and healthcare industries

The significance of RWD and RWE in both the healthcare and pharmaceutical industries is summarised as follows:

4.2.1.1. Facilitating Clinical Trial Design and Patient Recruitment:

RWD can help in clinical trial design by providing insights on patient demographics, treatment trends, and disease epidemiology.

In order to increase the viability and generalizability of clinical trials, RWD can also assist in identifying and recruiting suitable patient populations.

a. Informing Clinical Trial Design:

Research on the epidemiology and natural history of a disease can yield important insights that aid in the selection of the most applicable endpoints, study populations, and study designs for clinical trials.

In order to make sure the clinical trial is set up to produce the most relevant and useful evidence possible, analysis of RWD can help in the selection of suitable comparator treatments, dosage schedules, and outcome measures.

Additionally, RWD could benefit researchers in comprehending the heterogeneity of a patient population, enabling them to customize stratification elements and inclusion/exclusion criteria to guarantee that the study sample is typical of patients in the real world.

b. Enhancing Patient Recruitment:

Researchers can more effectively discover and locate possible study volunteers by using RWD from sources such as electronic health records, claims data, and patient registries.
Researchers can more effectively target and interact with eligible patients by gaining a better understanding of the disease features, treatment patterns, and demographics of the target patient population through the analysis of RWD.

Researchers can create better patient-centric recruiting approaches by utilising the insights that RWD can offer on patient preferences, participation barriers, and other aspects that may affect recruitment and retention.

c. Improving Trial Feasibility and Generalizability:

Researchers can increase the viability of conducting clinical trials, especially for rare diseases or patient populations that are difficult to reach, by utilizing RWD to inform trial design and patient recruitment.
The study population can be made more representative of actual patients by using RWD, which would increase the trial results' generalizability and clinical practice relevance.

d. Minimising Costs and Timelines:

RWD insights can be used by researchers to optimize patient recruitment and clinical trial design, which leads to more beneficial and cost-effective trials.
The time and resources needed to finish clinical investigations can be decreased with improved trial viability and patient enrollment, hastening the drug development process.

Overall, the strategic use of RWD and RWE in informing clinical trial design and patient recruitment can lead to more robust, relevant, and efficient clinical studies, ultimately

contributing to the development of safer and more effective treatments for patients.

4.2.1.2. **Incorporating Information from Clinical Trials to Regulatory Approvals:**

RWE can be used to augment the data from clinical trials, especially in the case of rare diseases or patient subgroups for which conventional clinical trials would be difficult.
Regulatory bodies like the FDA and EMA are becoming more receptive to the use of RWE in order to facilitate the approval of drugs and the expansion of their labels.

a. Addressing Clinical Trial Limitations:
Randomised controlled trials (RCTs) might have issues with sample size, patient diversity, and generalizability to real-world settings, even though they are thought to be the best method for assessing the safety and efficacy of novel medications.
RWD can fill in these gaps by offering more information on how a medication or technology functions in a larger, more varied patient population under real-world circumstances.

b. Supporting Regulatory Decisions:
In situations when traditional studies are challenging or are not practical, regulatory bodies like the FDA and EMA are becoming more receptive to the use of RWE to augment clinical trial data.
RWD can be used to offer additional evidence on a product's efficacy, value, and safety, which can assist labelling decisions, regulatory approvals, and Post-Market Surveillance.

c. Enabling Accelerated approvals:
Based on scant clinical trial data, regulatory bodies may occasionally grant accelerated or conditional clearances for rare diseases or unmet medical needs.
RWD can assist produce more data on the product's performance in the real world after approval and offer supplementary proof to support these accelerated approvals.

d. Expanding Indications and Updates to Labels:

RWD analysis can uncover novel therapeutic uses for medicines that have already been licenced or point to patient populations that might benefit from current treatments.
By utilising this data, label expansions can be supported, and the value of pharmaceutical products can be optimised during their whole lifecycle.

e. Reducing Regulatory Uncertainty:
RWD can offer important insights to assist regulatory bodies in making better decisions in situations where clinical trial data may be limited or unclear.
Regulatory bodies can more accurately evaluate a product's overall benefit-risk profile and expedite approvals by integrating RWD with clinical trial data.

The strategic use of RWD to supplement clinical trial data has become a critical component of the regulatory approval process, as it allows for a more comprehensive and real-world understanding of a product's performance. This, in turn, can lead to faster approvals, more informed decision-making, and ultimately, improved patient access to innovative and effective healthcare solutions

4.2.1.3. **Tracking Post-Market Safety and efficacy:**

RWD can be utilised for post-market surveillance, adverse event detection, and long-term drug safety and efficacy tracking using sources such as electronic health records, claims data, and patient registries.
This can offer important information for risk-benefit analyses as well as aid in the discovery of novel safety indicators.

a. Pharmacovigilance and Adverse Event Monitoring:
To identify and examine adverse occurrences connected to marketed products, RWD can be gathered from sources such as electronic health records, claims data, and spontaneous reporting systems.
Together with the information acquired during clinical trials, this real-world data can offer a more complete and up-to-date overview of the safety profile of a product.

RWD analysis can be used to track the frequency and severity of established side effects, find novel safety signals, and discover unexpected or recurring adverse events.

b. Evaluating Long-Term Effectiveness:

Clinical trials frequently have short follow-up times, which might not be enough to thoroughly evaluate a product's long-term efficacy in practical situations.

RWD can be used to assess a product's performance in the real world across a range of patient groups, track changes in patient outcomes over time, and investigate the long-term impacts of treatment.

This data is essential for determining the real effect of a product on patient health, guiding clinical practice recommendations, and influencing reimbursement choices.

c. Comparative Effectiveness Research:

RWD can be used to assess how well various therapies or treatments work in actual clinical settings, offering important information on how well healthcare items perform in relation to one another.

Clinical decision-making can be guided by this kind of comparative effectiveness study, which can assist in determining the most effective treatment options for particular patient populations.

d. Risk-Benefit Assessments:

Regulatory bodies can carry out more thorough and thorough risk-benefit analyses by integrating information on a product's efficacy and safety from both clinical trials and real-world contexts.

This makes sure that a product's advantages outweigh any possible drawbacks, especially when it comes to decisions made after approval, including label modifications or risk management techniques.

e. Regulatory Compliance and Lifecycle Management:

Since RWD contributes to maintaining the efficacy and safety of marketed products, regulatory bodies frequently mandate continuous monitoring of RWD.
RWD analysis can help with post-approval research, regulatory compliance, and product lifecycle management choices including label extensions and risk management plan modifications.

Throughout a product's lifecycle, RWD must be integrated into post-market surveillance and efficacy monitoring in order to improve patient safety, maximise clinical results, and assist regulatory decision-making. As RWD becomes more accessible and of higher quality, its importance in this field is anticipated to increase even more.

4.2.1.4. **Finding New Indications and Patient Subgroups:**

RWD analysis can find patient subgroups who might profit from current therapies or new possible indications for established medications.
In addition to helping to maximise the value of pharmaceutical goods throughout their lives, this may result in label extensions.

a. Identifying New Indications:
Because RWD analysis offers insights into how goods are used in actual clinical settings, it can help identify novel or unexpected uses for currently available medications or devices.
Through the examination of off-label use patterns, treatment outcomes, and disease characteristics, researchers are able to identify novel indications for a medication that were not previously investigated during its development.

Subsequently, this data can be employed to facilitate label extensions and optimise a product's worth during its whole existence.

b. Finding Underserved Patient Subgroups:

RWD can assist in identifying patient subgroups that were either underrepresented or understudied in the initial clinical trials, but may benefit from a product.
Analysing RWD can reveal groups who might react differently to a treatment and provide insights into the clinical, socioeconomic, and demographic aspects that impact a product's performance.

This information can help to expand a product's approved indications to reach these underserved patient populations or guide the design of targeted clinical studies.

c. Developing Specific Approaches to Treatment:

RWD can be used to create prediction models and algorithms that assist in identifying biomarkers, patient traits, and other variables that might affect a person's reaction to a specific treatment.
This data can direct the creation of more individualised treatment plans, enabling medical professionals to customize treatments to each patient's particular requirements and profile.

d. Optimizing Clinical Trial Design:
RWD insights can help researchers better target and enroll the most suitable patient populations for assessing novel indications or subgroups. This allows for improved clinical trial design in the future.
This may enhance the effectiveness and success of these trials, raising the possibility that novel applications for currently available goods may be found and confirmed.

e. Supporting Regulatory submissions:
Regulatory submissions for label extensions or new product approvals may be supported by the discovery of new indications or patient subgroups based on RWD analysis.
In these situations, regulatory bodies like the FDA and EMA are becoming more open to using RWE to supplement traditional clinical trial data.

Pharmaceutical and healthcare organizations can find innovative ways to address unmet medical requirements, diversify their product lines, and ultimately enhance patient outcomes by utilising the insights that RWD provides. For the purpose of promoting innovation and optimising the value of currently available healthcare solutions, the strategic application of RWD is becoming more and more important.

4.2.1.5. **Evaluating the Real-World Effect and Worth of Healthcare Interventions:**

RWE can shed light on the practicality, affordability, and patient-reported results of healthcare interventions.

When assessing the worth of novel treatments, payers, health technology assessment (HTA) organisations, and other stakeholders are becoming more and more dependent on this data.

a. Assessing Real-World Effectiveness:

Although clinical trials are intended to evaluate a healthcare intervention's effectiveness in controlled environments, their results may not accurately represent the intervention's real-world success.

RWD can offer insights into how well a treatment or intervention performs in real-world settings by accounting for variables like patient adherence, comorbidities, and a set of clinical practices.

Understanding the genuine effect of a healthcare intervention on patient outcomes in standard clinical practice is important for regulators, payers, and healthcare providers.

b. Evaluation of Patient-Reported Outcomes and Life Quality:

Quality of life information and patient-reported outcomes (PROs) can be obtained directly from patients using RWD sources including patient registries and mobile health apps.

This data offers a more thorough comprehension of how a healthcare intervention affects patients' functional status, lived experiences, and general well-being.

PROs and quality of life metrics obtained via RWD can be used to assess a treatment's actual worth from the patient's point of view.

c. Undertaking Economic Assessments:

RWD is a useful tool for evaluating the actual costs of a healthcare intervention, encompassing direct medical expenses, indirect costs (e.g. lost productivity), and long-term expenses linked to continued treatment or complications.

Researchers can carry out thorough economic evaluations, such as cost-effectiveness studies and budget impact analyses, by merging effectiveness and cost data from RWD sources.

Payers, health technology assessment (HTA) organisations, and healthcare decision-makers depend on these economic analyses to establish the worth and distribute resources among various solutions.

d. Informing Reimbursement and Coverage Decisions:

By offering a greater understanding of a healthcare intervention's value proposition, the real-world evidence produced by RWD analysis can encourage reimbursement and coverage decisions.

This data can help payers and HTA authorities make judgements about new treatment or technology access, pricing, and reimbursement.

e. Encouraging Value-Based Healthcare Models:

RWD can be very helpful in facilitating the shift to value-based healthcare models, in which patient value and real-world results are used to determine how much is paid.

Healthcare providers, payers, and manufacturers can measure the effectiveness of interventions and put value-based payment models or risk-sharing agreements into place by regularly monitoring and assessing RWD.

The use of RWD and RWE can lead to improved patient outcomes, more efficient drug development processes, and better-informed regulatory and clinical decision-making. As a result, the pharmaceutical and healthcare industries have recognized the growing importance of leveraging real-world data and evidence to drive innovation and enhance patient care.

4.3. Overview of the regulatory landscape in the US, Europe, and the UK

4.3.1. United States

In the US, the Food and Drug Administration (FDA) has been a key driver of the RWD revolution. In the year 2016, the 21st Century Cures Act was passed that mandated the FDA to develop a framework for assessing the use of RWD and RWE to support regulatory decisions. Since then, the FDA has published a series of guidance documents outlining its expectations for the collection, analysis, and application of RWD. Key priorities include ensuring data quality, minimizing bias, and establishing robust study designs that can generate credible RWE. The agency has demonstrated willingness to accept RWE for purposes such as supporting product label modifications, fulfilling post-approval study requirements, and even informing initial approval decisions in certain cases.

4.3.2. European Union

Across the Atlantic, the European Medicines Agency (EMA) has also embraced the role of RWD in regulatory science. In the year 2019, the EMA launched its Regulatory Science Strategy to 2025, which identified the increased use of RWD as a critical objective. The agency has provided guidance on topics like data quality, study methods, and the validation of RWD sources.

The EMA's RWD framework emphasizes the need for transparency, reproducibility, and alignment with good pharmacoepidemiological practices. It also underscores the importance of integrating RWD into a broader evidence ecosystem that includes traditional clinical trials, registries, and other data sources.

4.3.3. United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has likewise recognized the value of RWD in regulatory decision-making. In 2021, the agency published a strategy for the use of RWD that outlines key principles and use cases.

The MHRA's approach focuses on establishing robust data governance frameworks, fostering public-private partnerships, and building specialized RWD expertise within the agency. It also

highlights the potential for RWD to support a wide range of regulatory activities, from benefit-risk assessments to post-authorization safety monitoring.

4.3.4. Global Regulatory landscape of RWD & RWE:

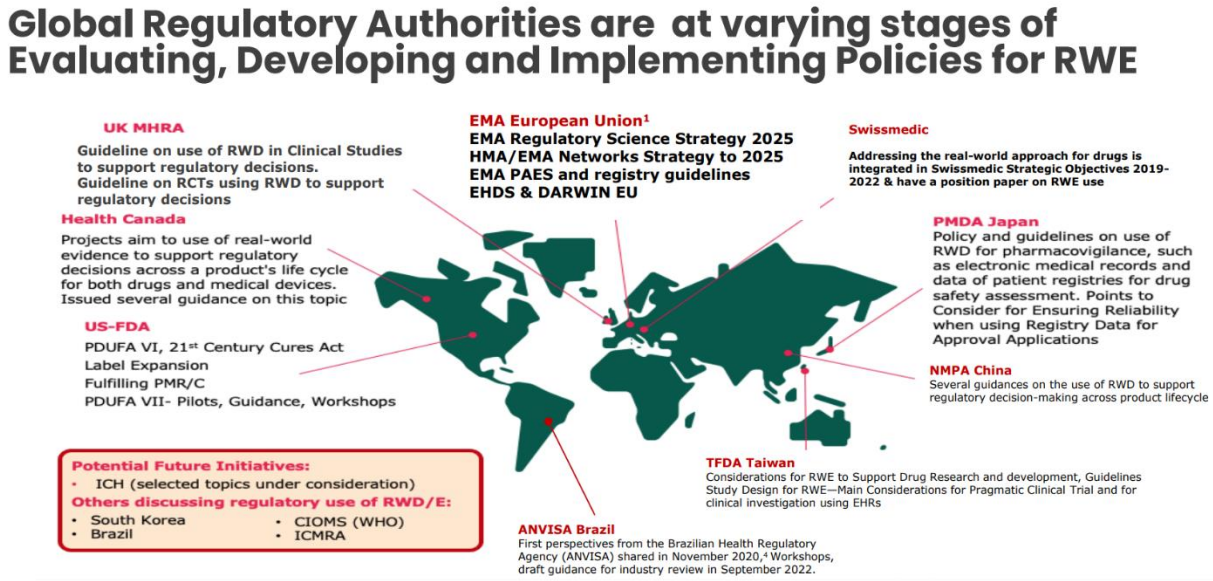

Figure 1 'Global Regulatory Authorities for RWE' Source: PowerPoint Presentation (europa.eu)

Some examples of real-world data include:

1. Electronic health records (EHRs) - Data collected during routine patient care, such as diagnoses, treatments, lab results, etc.
2. Claims and billing data - Information gathered from insurance claims and reimbursement records.
3. Patient-generated data - Data collected directly from patients, such as through mobile apps, wearable devices, or patient surveys.
4. Registry data - Information collected through disease or product registries, often focused on specific conditions or therapies.
5. Observational studies - Data collected through observational research on how treatments or interventions are used in everyday clinical practice.

CHAPTER 5:

THE REGULATORY LANDSCAPE OF THE RWD IN THE US

5. THE REGULATORY LANDSCAPE OF RWD IN THE UNITED STATES

5.1. Fragmented approach to data privacy and RWD regulations

Due to the absence of a comprehensive national law, the United States has a fragmented approach to data privacy and regulations governing the use of real-world data (RWD). The following are some salient features of this disjointed approach:

Sectoral Approach: The United States has sector-specific laws that regulate data privacy and the use of RWD in various sectors or circumstances, as opposed to a single comprehensive legislation. Examples of these laws include:

- HIPAA regulations regarding medical data
- FCRA for information on consumer credit
- GLBA for data related to finances

State-Level Laws: In the lack of a comprehensive federal law, several states have passed their own data privacy legislation, further contributing to the patchwork of regulations. As examples, consider:
The Virginia Consumer Data Protection Act (CDPA), the Colorado Privacy Act (CPA), and the California Consumer Privacy Act (CCPA)

5.2. RWD/RWE initiatives in the USA

5.2.1. HIPPA (Health Insurance Portability and Accountability Act)

- HIPAA establishes national standards to guarantee sensitive, persistent health information stored by protected entities like health plans, healthcare clearinghouses, and suppliers.

- It administers the utilize and divulgence of secured wellbeing data (PHI), which incorporates RWD inferred from electronic wellbeing records (EHRs) and other healthcare information sources.
- HIPAA requires shields for information protection, security, and persistent assent for certain employments of PHI.

RWD and HIPPA

- The main goal of HIPAA is to safeguard personally identifiable health information (PHI).
- HIPAA is applicable if RWD contains PHI, such as names, addresses, or illnesses connected to specific individuals.
- When utilising or sharing such data, covered entities (healthcare providers, health plans, etc.) are required to adhere to HIPAA standards.

5.2.2. Federal Policy for the Protection of Human Subjects (Common Rule):

- Research using RWD is subject to regulatory restrictions and ethical guidelines that are outlined in the Common Rule.
- It asks for getting participants' informed consent, reducing risks, and making sure study data privacy and confidentiality are protected.

5.2.3. 21st Century Cures Act:

- This act encourages the FDA to support its regulatory decision-making with real-world evidence (RWE) collected via RWD.
- It mandates that the FDA set up a programme to assess the possible application of RWE for post-market surveillance, label extensions, and medication and medical device approvals.
- Enacted on December 13, 2016, the 21st Century Cures Act (Cures Act) aims to expedite the development of medical products and provide patients with new advancements and breakthroughs more quickly and effectively.

> The law expands on FDA's current efforts to include patient perspectives in the development of pharmaceuticals, biological products, and devices throughout FDA decision-making. The utilisation of real-world evidence and clinical outcome assessments, which Cures improves, will enable us to modernise clinical trial designs and expedite the creation and review of novel medical products, including medical countermeasures.

Act mandates for a new section 505F on *"Utilizing real world evidence"* to be included in the 'Federal Food, Drug, and Cosmetic Act' (FD&C Act)

5.2.4. Framework for the FDA's Real-World Evidence Program

Among other provisions, the Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Pursuant to this section, the Food and Drug Administration (FDA) has created a framework for evaluating the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy drug postapproval study requirements. In addition to drug and biological products approved under section 505(c), this framework is also intended for application to biological products licensed under the Public Health Service Act. The framework does not cover medical devices.

The RWE framework defines a three-part approach to guide the FDA's RWE Program or, more specifically, the FDA's decision-making when being provided with RWE to demonstrate product effectiveness:

1. the assessment of the fitness of the RWD to be used in regulatory decision-making,
2. the assessment of the suitability of the study design used to generate satisfactory evidence to answer the research question
3. and the assessment whether or not FDA requirements are met in regard to study conduct.

The RWE framework defines action items to be executed by the FDA under its RWE Program.

- Guidance development on how to assess the relevance and reliability of RWD obtained from different sources when used to generate RWE to support product effectiveness
- Review of potential gaps in RWD sources and development of guidance on strategies to address the gaps identified
- Exploration of the potential of digital tools and technologies, for example, wearables, biosensors, and mobile technologies to fill gaps in RWD sources
- Development of guidance for designing randomized clinical trials including pragmatic design elements that are aimed at generating evidence of drug product effectiveness
- Guidance development on the use of RWD as a basis for control arms in externally controlled clinical trials
- Development of further guidance, building on the existing 'Pharmacoepidemiologic Guidance', on observational study designs, including whether and how such studies might provide RWE to support decisions about the effectiveness
- Consideration of reporting requirements for observational studies aimed at supporting decisions about effectiveness

5.2.5. The Sentinel Initiative:

FDA's vision for the Sentinel System is to achieve a sustainable national resource to monitor the safety of marketed medical products and expand real-world data (RWD) sources use to evaluate medical product performance.

FDA's strategic plan for the Sentinel System reflects several Agency objectives:

• Accelerate use of the Sentinel System within FDA and scale capabilities to meet needs

• Explore the utility of real-world data as a tool to support drug development and assess medical product performance

• Facilitate response to legislative mandates regarding medical product safety and effectiveness evaluation

• Expand the Sentinel System by facilitating its use by other stakeholders, and foster innovation and development.

FDA's five-year strategy aims to provide a concrete roadmap for the Sentinel System to achieve its vision and objectives. The strategy sets clear aims and defines underlying initiatives to measure progress.

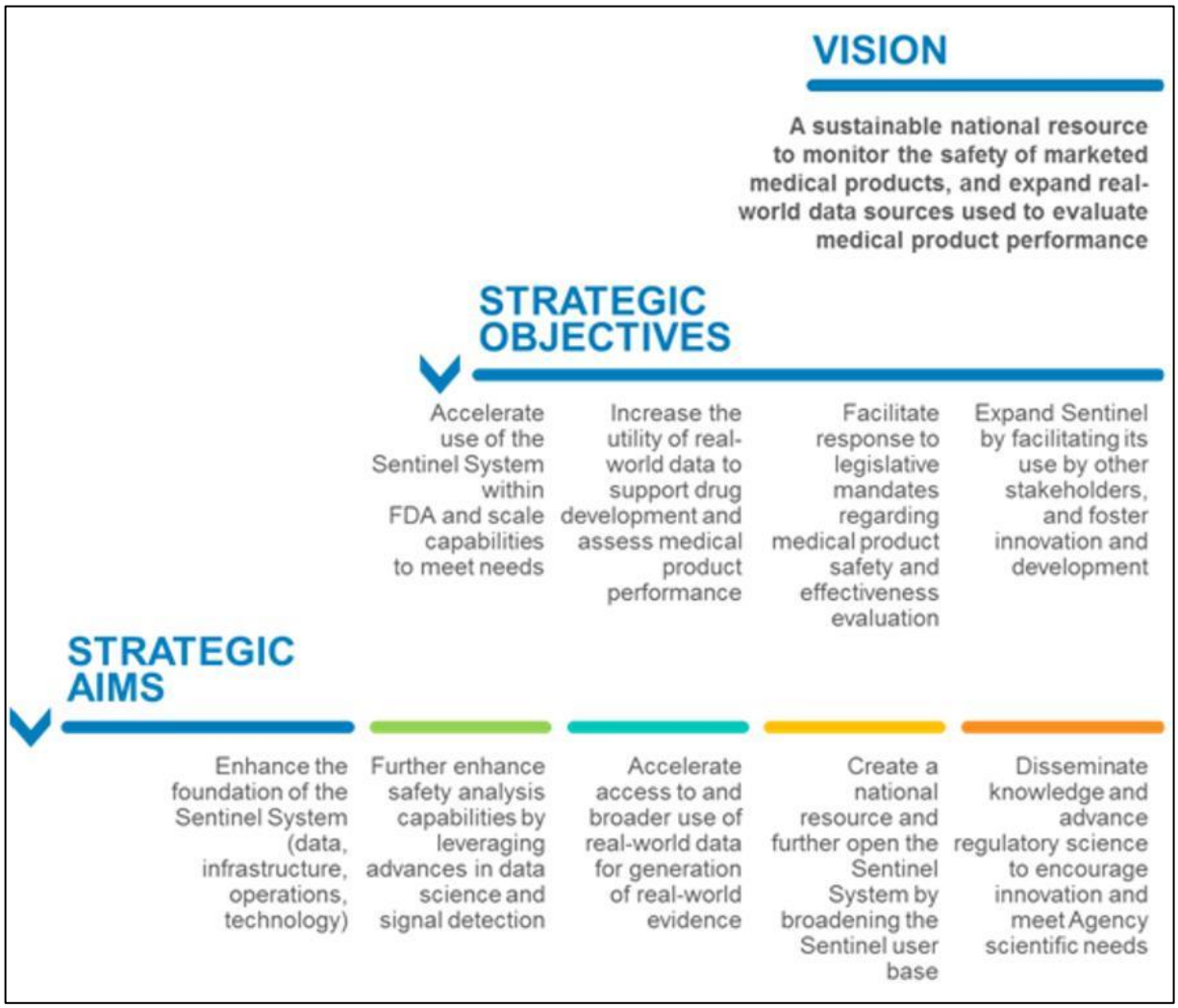

Fig 2: 'Vision, Strategic objectives and aims of Sentinel System' Source: Exhibit 1 [Sentinel System 5-Year Strategy 2019-2023 (fda.gov)]

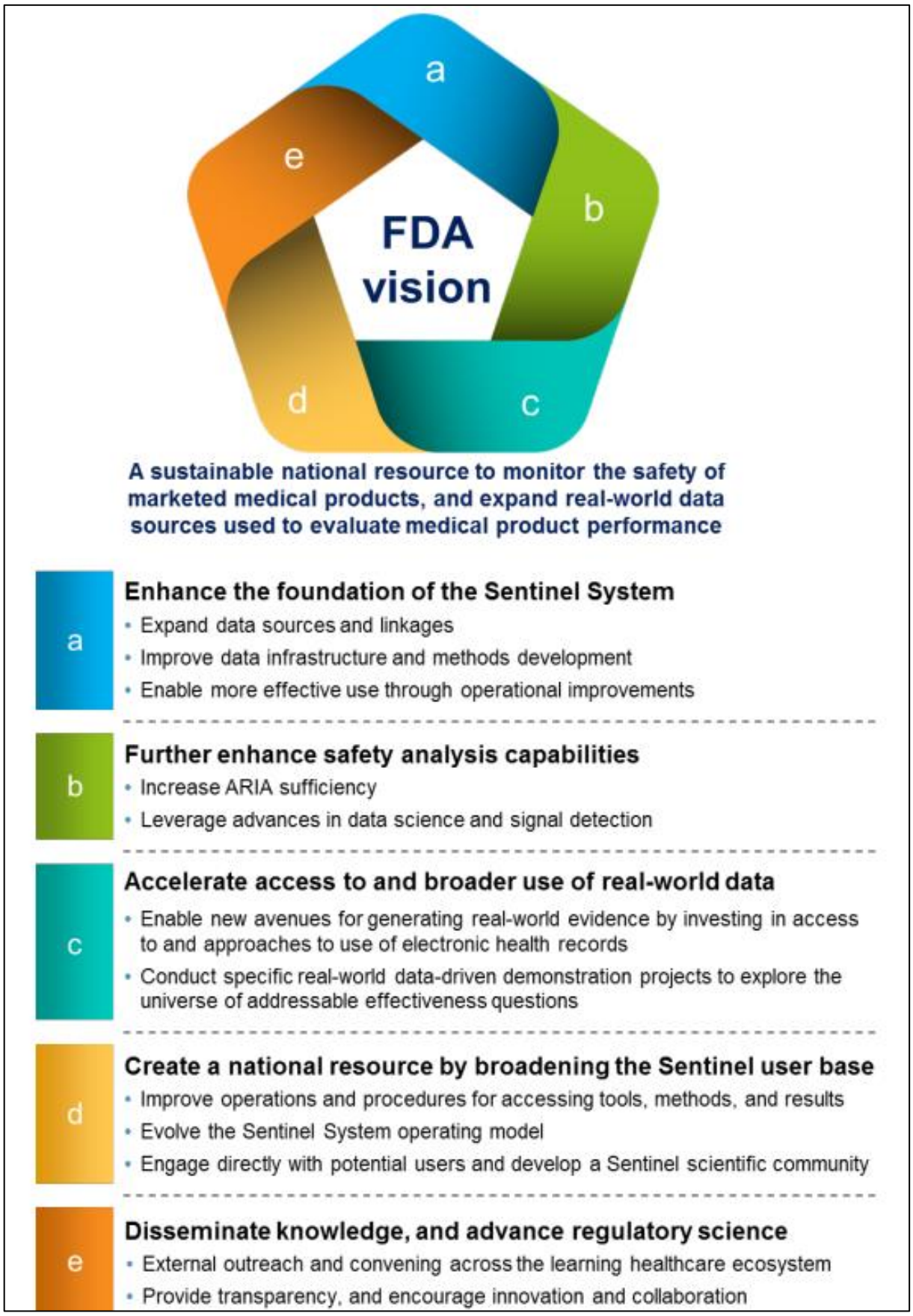
a
b
c
d
e
FDA vision
A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance
a
Enhance the foundation of the Sentinel System
• Expand data sources and linkages
• Improve data infrastructure and methods development
• Enable more effective use through operational improvements
b
Further enhance safety analysis capabilities
• Increase ARIA sufficiency
• Leverage advances in data science and signal detection
c
Accelerate access to and broader use of real-world data
• Enable new avenues for generating real-world evidence by investing in access to and approaches to use of electronic health records
• Conduct specific real-world data-driven demonstration projects to explore the universe of addressable effectiveness questions
d
Create a national resource by broadening the Sentinel user base
• Improve operations and procedures for accessing tools, methods, and results
• Evolve the Sentinel System operating model
• Engage directly with potential users and develop a Sentinel scientific community
e
Disseminate knowledge, and advance regulatory science
• External outreach and convening across the learning healthcare ecosystem
• Provide transparency, and encourage innovation and collaboration

Fig 3: 'Five years strategy for the Sentinel System' Source: Exhibit 3 Sentinel System 5-Year Strategy 2019-2023 (fda.gov)

5.2.6. The National Evaluation System for Health Technology (NEST)

- Launched in 2018 by the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER).
- Aims to evaluate the use of real-world data (RWD) from electronic health records (EHRs), medical claims data, and other sources for safety signal detection, validation, and evaluation of medical products.
- Objectives include developing novel methodologies for safety signal detection using RWD, exploring the use of RWD to supplement traditional safety surveillance systems, and facilitating the integration of RWD and real-world evidence (RWE) into FDA's regulatory decision-making processes related to product safety evaluation.
- Key focus areas are safety signal detection, validation, and evaluation using RWD sources.
- Involves collaborations with academic institutions, healthcare organizations, data partners, and industry partners to facilitate data sharing, methodological development, and evaluation of RWD sources and analytical approaches.
- Has conducted pilot studies and demonstrations in various therapeutic areas to evaluate the use of RWD sources like EHRs, claims data, patient registries, and social media data for safety signal detection and validation.
- Aims to inform and shape FDA's regulatory guidance and policies related to the use of RWD and RWE for medical product safety evaluation.
- Findings and methodologies from the program are expected to contribute to the broader adoption and integration of RWD and RWE into FDA's safety surveillance and regulatory decision-making processes, ultimately enhancing patient safety.

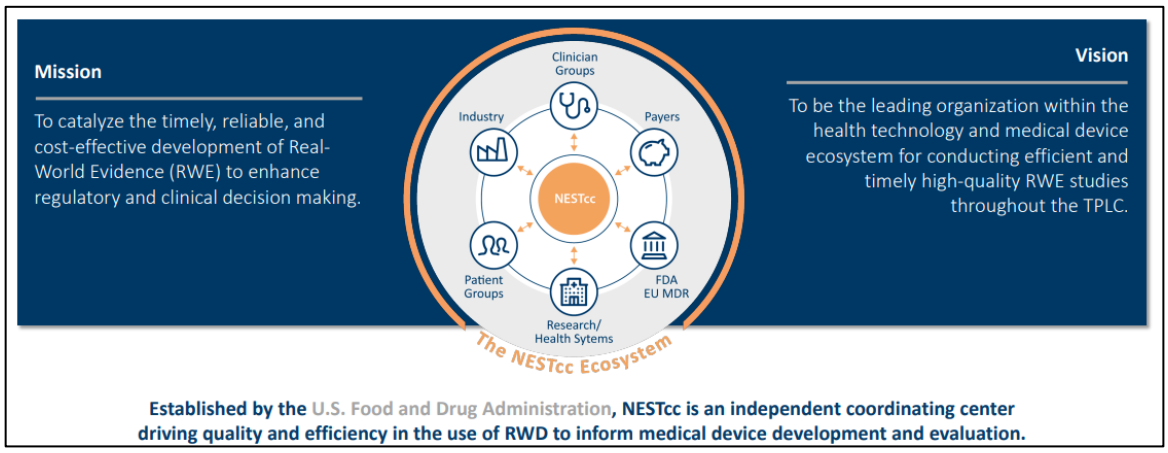

Fig 4 'The NESTcc Ecosystem' Source: [The National Evaluation System for health Technology Coordinating Center (NESTcc) – Key Learnings in Enhancing the Access to Generate Real-World Evidence (RWE) for Medical Devices (fda.gov)]

5.3. Challenges and opportunities in leveraging RWD for regulatory decision-making

5.3.1. Challenges:

- Data complexity and presenting large volumes of complex data responsively
- Security and compliance with strict regulatory standards and guidelines
- Integration with legacy systems and applications
- Stakeholder buy-in and overcoming resistance to change

5.3.2. Opportunities:

- Improved accessibility and inclusivity across devices and platforms
- Increased efficiency by streamlining processes and optimizing user experience
- Enhanced user experience with intuitive, visually appealing, and easy-to-navigate interfaces
- Future-proofing digital infrastructure to remain functional across emerging devices
- Improved collaboration, transparency, and public trust in regulatory processes

While leveraging RWD for regulatory decision-making presents challenges related to data complexity, security, legacy systems, and stakeholder buy-in, it also offers opportunities for improved accessibility, efficiency, user experience, future-proofing, and enhanced collaboration and transparency in regulatory processes.

5.4. Guidance Documents:

5.4.1. "Use of Electronic Health Record Data in Clinical Investigations" (2018):

Provides recommendations on the use of electronic health record (EHR) data in clinical investigations, including best practices for data quality, security, and privacy.

5.4.2. "Real-World Evidence Program" (2018):

Outlines the FDA's approach to evaluating the potential use of RWE to support the approval of new indications for approved drugs or to help satisfy post-approval study requirements.

5.4.3. "Framework for FDA's Real-World Evidence Program" (2018):

Describes the FDA's overarching program to evaluate the potential use of RWD and RWE to help support the approval of new indications for approved drugs or to help satisfy post-approval study requirements.

5.4.4. "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics" (2019):

Provides recommendations to industry on how to submit RWD and RWE to the FDA to support regulatory decisions for drugs and biological products.

5.4.5. "Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products" (2021):

Provides guidance on the use of RWD derived from EHRs and medical claims data to support regulatory decisions for drug and biological product submissions.

5.4.6. "Data Standards for Drug and Biological Product Submissions Containing Real-World Data" (2022):

Outlines recommendations for data standards and formatting for RWD submitted to the FDA as part of regulatory submissions for drugs and biological products.

5.4.7. "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" (2022):

Provides guidance on the use of RWD and RWE to support regulatory decisions for drug and biological product submissions, addressing data quality, study design, and analysis considerations.

CHAPTER 6:

THE REGULATORY LANDSCAPE OF RWD IN EUROPE

6. THE REGULATORY LANDSCAPE IN EUROPE:

Here is an overview of the regulatory landscape for real-world data (RWD) and real-world evidence (RWE) in Europe:

6.1. The European Union's General Data Protection Regulation (GDPR)

The General Data Protection Regulation (GDPR) is a foundational law that governs data privacy and protection and governs the handling of personal data in the European Union (EU) and the European Economic Area (EEA).
Organisations that handle personal data are subject to stringent regulations, including those pertaining to data minimization, purpose limitation, and individual rights over personal data.

The GDPR has a big impact on how RWD is used in research, regulatory filings, and other applications because it contains a lot of personal health information.
Getting express consent, putting data protection by design into practice, and making sure that personal data is processed lawfully are all essential GDPR criteria.
Any organisation that uses RWD and operates in Europe must comply with the GDPR.

Here are the key details about the GDPR and its implications for the use of real-world data (RWD):

Scope and Applicability:

Any organisation that processes personal data of individuals within the EU or EEA is subject to the GDPR, regardless of its location.
It regulates how personal data is processed, encompassing tasks like gathering, storing, using, and transferring information.
RWD is governed by GDPR standards since it frequently contains personal health information, especially when data comes from sources like patient registries and electronic health records.

Principles of Data Protection:

The GDPR outlines a number of requirements for data processing, including lawfulness, fairness, and transparency; purpose limitation; data minimization; accuracy; storage limitation; integrity and confidentiality; and accountability.
To guarantee data privacy and protection, certain guidelines must be followed when gathering, utilising, and managing RWD.

Lawful Basis for Processing:
According to the GDPR, processing personal data must have a legitimate reason, such as consent, a need to fulfil a contract, a legal need, vital interests, the public interest, or legitimate interests.
Depending on the particulars, organisations may rely on permission, the public interest, or legitimate interests as the legal foundation for RWD utilised in research or healthcare settings.

Impact Assessments of Data Protection:
Organisations must conduct Data Protection Impact Assessments (DPIAs) before processing any data that is thought to seriously jeopardise the rights and freedoms of an individual.
To identify and reduce potential hazards, a DPIA is frequently needed when using RWD, especially when dealing with sensitive health data.

Individual Rights:
Individuals have rights under the GDPR over their personal data, including the ability to access, rectify, erase, restrict, and oppose processing of their data.
Establishing procedures to protect these individual rights and address requests from data subjects is crucial for organisations that handle RWD.

Security and Privacy by Design
The General Data Protection Regulation (GDPR), which requires companies to implement the required organisational and technical protections to ensure data security and privacy, emphasises the ideas of data protection by design and by default.
Data minimization, encryption, access controls, and anonymity are some of the measures that are involved in managing RWD.

Accountability and Governance:

Organisations must use thorough data protection policies, procedures, and governance frameworks to show that they are in compliance with the GDPR.
This entails keeping records up to date, carrying out routine audits, and, in certain situations, designating a Data Protection Officer.
Any company using RWD and operating in Europe must comply with the GDPR, as noncompliance can result in hefty fines and harm to one's reputation. The GDPR seeks to achieve a balance between safeguarding individuals' basic rights and liberties and promoting data-driven innovation.

6.2. The role of the European Medicines Agency (EMA) in RWD/RWE guidance

The EU regulatory agency in charge of assessing and monitoring pharmaceuticals among its member states is the EMA.
When it comes to creating guidelines and procedures for applying RWD and RWE in regulatory decision-making processes, the EMA has been actively involved.
Expectations and recommendations were outlined in the "Guidance on the qualification and reporting of RWD and RWE for regulatory purposes," released by the EMA in 2020.
The use of RWD/RWE is covered in this guidance in a number of situations, including post-authorization investigations, label modifications, and applications for marketing authorization.
Through collaborations with business, academia, and healthcare professionals, the EMA works to ensure that RWE is used responsibly and effectively throughout the lifecycle of a product.

The European Medicines Agency (EMA) plays a key role in providing guidance and frameworks for the use of real-world data (RWD) and real-world evidence (RWE) in the regulatory decision-making process within the European Union. Here are the details regarding the EMA's role in RWD/RWE guidance:

- Guidance Development:

    - The EMA has developed specific guidance documents to outline their expectations and recommendations for the use of RWD and RWE in various regulatory contexts.
    - In 2020, the EMA published the "Guidance on the qualification and reporting of real-world clinical data and real-world evidence for regulatory purposes."
    - This guidance document provides a framework for the generation, collection, and reporting of RWD/RWE to support regulatory submissions, such as marketing authorization applications, post-authorization studies, and label updates.
- Regulatory Acceptance:
    - The EMA recognizes the potential value of RWE in complementing evidence from traditional clinical trials and supporting regulatory decision-making.
    - The agency has outlined scenarios where RWE can be used, including supporting efficacy and safety evaluations, exploring new indications or populations, and informing risk management plans.
    - However, the EMA emphasizes the importance of ensuring the quality, relevance, and reliability of RWD and RWE through robust methodologies and data governance practices.
- Scientific Advice and Protocol Assistance:
    - The EMA provides scientific advice and protocol assistance to pharmaceutical companies and researchers regarding the use of RWD/RWE in their development programs.
    - This advisory service helps organizations understand the acceptability of their proposed RWD sources and study designs, ensuring alignment with regulatory expectations.
- Stakeholder Collaboration:
    - The EMA actively collaborates with various stakeholders, including industry, academia, healthcare professionals, and patient organizations, to promote the responsible and effective use of RWE in the drug development lifecycle.

    - This collaboration involves gathering input, sharing best practices, and fostering dialogue to advance the integration of RWD/RWE into regulatory processes.
- Methodological Research:
    - The EMA supports and encourages methodological research aimed at developing robust approaches for generating and analyzing RWE from various data sources.
    - This includes exploring methods for addressing potential biases, handling missing data, and ensuring the validity and generalizability of RWE.
- Regulatory Convergence:
    - The EMA works towards regulatory convergence and harmonization of RWD/RWE standards and practices with other major regulatory agencies, such as the FDA and PMDA.
    - This collaborative effort aims to facilitate the acceptance and use of RWE across different regulatory jurisdictions, promoting efficiency and consistency in drug development and decision-making processes.

By providing comprehensive guidance, fostering stakeholder collaboration, and supporting methodological advancements, the EMA plays a crucial role in shaping the responsible and effective integration of RWD and RWE into regulatory processes within the European Union.

6.3. Harmonization of RWD/RWE standards and best practices across EU member states

Although the EMA offers general guidelines, member states may interpret and apply RWD/RWE standards and practices differently.

In an effort to promote cross-border cooperation and data exchange, efforts are being made to standardise RWD/RWE standards and best practices among EU member states.

The goal of initiatives such as the European Health Data Space is to establish a unified market for digital health goods and services, encompassing cross-border RWD sharing.

To facilitate smooth data integration and analysis between member states, harmonisation entails coordinating data coding schemes, data models, and interoperability standards.

Enhancing the quality, consistency, and comparability of RWE produced from RWD sources within the EU region is the goal of common standards and best practices.

The harmonization of real-world data (RWD) and real-world evidence (RWE) standards and best practices across European Union (EU) member states is a crucial endeavor to facilitate cross-border collaboration and data sharing.

- The Difficulties of Fragmentation
- Initiatives for Harmonisation
- Data Standards and Interoperability
- Data Quality and Governance
- Regulatory Collaboration
- Stakeholders Engagement

By establishing common standards, interoperability frameworks, and best practices for RWD/RWE, the EU aims to enhance the quality, reliability, and comparability of RWE generated from RWD sources across member states. This harmonization effort is crucial for enabling cross-border collaboration, facilitating evidence-based decision-making, and ultimately improving patient outcomes and healthcare delivery within the EU.

6.4. Key players in the Field of RWD/RWE:

6.4.1. The European Medicines Regulatory Network (EMRN)

The EMRN is a collaboration between the European Medicines Agency (EMA) and the national competent authorities of the European Union (EU) member states. It aims to facilitate the exchange of information and coordination among regulatory authorities in the EU. In the context of Real-World Data (RWD) and Real-World Evidence (RWE), the EMRN plays a crucial role in promoting harmonized approaches and best practices for the generation and use of RWD and RWE across the EU.

6.4.2. The European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP)

ENCePP is a network coordinated by the EMA that brings together academic and non-academic organizations that conduct pharmacoepidemiology and pharmacovigilance studies. The network aims to enhance the monitoring of the benefit-risk balance of medicinal products by facilitating the conduct of multi-center, independent studies based on RWD. ENCePP has developed methodological guidance, tools, and resources for the effective use of RWD in pharmacoepidemiological and pharmacovigilance studies.

6.4.3. Innovative Medicines Initiative (IMI)

The IMI is a public-private partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). It aims to promote the development of innovative medicines and foster collaboration between academia, industry, and regulatory authorities.

6.4.4. OPTIMAL framework for RWE

In 2019, a scientific article authored by three senior representatives of the EMA was published, outlining the European perspective on the use of RWD for regulatory decision-making.The authors provided definitions of RWD and RWE and proposed a framework, based on three pillars, to address the operational, technological and methodological challenges posed by the utilization of RWD: the *"OPerational, TechnIcal, and MethodologicAL framework (OPTIMAL) for regulatory use of real-world evidence (RWE)".*

The objective underlying the framework is an *"appropriate use of valid RWE"* for regulatory use cases such as safety, efficacy and benefit-risk monitoring. To meet this objective, the frame-work request for RWE, and the RWD it is based on, to satisfy the following acceptance criteria:

• the data source/s the RWE is derived from should be of proven good quality,

• internal and external validity of the RWE should be given,

• consistency of the RWE across the data sources used/ countries covered should be given

• and the RWD/ RWE should be adequate in terms of depth and breadth (including adequate precision, time period and range of elements covered).

Operational challenges include feasibility, governance and sustainability.

Technical Challenges cover aspects such as missing data, challenges related to data linkage, inadequate coverage of the full range of relevant data elements, heterogeneity in content of datasets, inconsistencies in terms of the use of data formats and terminologies as well as challenges associated with the collection, recording and management of data in a consistent, accurate and timely manner.

Methodological Challenges includes inadequate capture of potential confounders and effect modifiers, potential biases, missing data and, in case of multi-database studies, potential heterogeneity in content.

6.4.5. HMA-EMA joint Task

Established in 2017 by the EMA and HMA to provide a strategic direction for the use of big data in medicines regulation.
The task force aims to explore the potential of big data sources, such as electronic health records, registries, and social media, for regulatory activities like pharmacovigilance, clinical trials, and benefit-risk assessment.
It brings together representatives from national competent authorities, the EMA, and other stakeholders to develop recommendations and guidelines for the use of big data in regulatory processes.

DARWIN (Data Analysis and Real-World Interrogation Network):

- DARWIN is a project launched in 2019 as part of the HMA-EMA Joint Big Data Task Force's activities.

- It aims to establish a network of data sources and analytics capabilities across Europe to support the analysis of real-world data (RWD) for regulatory decision-making.
- The network will enable federated analysis of RWD from various sources, such as electronic health records, registries, and claims databases, while maintaining data privacy and security.
- DARWIN will develop methodologies and tools for data standardization, data quality assessment, and advanced analytics, including artificial intelligence and machine learning techniques.

The key objectives of these initiatives include:

- Exploring the potential of big data and RWD for regulatory activities like pharmacovigilance, benefit-risk assessment, and health technology assessment.
- Developing frameworks and guidelines for the responsible and effective use of big data and RWE in regulatory processes.
- Fostering collaboration and data sharing among regulatory authorities, healthcare providers, and other stakeholders across Europe.
- Promoting data standardization, data quality assurance, and advanced analytical techniques for RWD analysis.
- Ensuring data privacy and security while enabling the generation of robust RWE for regulatory decision-making.
- The range of approved **healthcare databases** enabling distributed data access via DARWIN EU will evolve and expand over time.
- The former **HMA/EMA Big Data Task Force** originally recommended developing DARWIN EU. The creation of DARWIN EU features in the **EMA-HMA Big Data Steering Group** workplan and the European medicines agencies network strategy to 2025.

Fig 5: 'Key figures of DARWIN EU' Source: Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (europa.eu)

CHAPTER 7: THE REGULATORY LANDSCAPE OF RWD IN THE UNITED KINGDOM

7. THE REGULATORY LANDSCAPE OF RWD IN THE UK:

7.1. The UK's adaptation of the GDPR (UK GDPR)

The General Data Protection Regulation (GDPR) of the EU was complemented by the UK's own data protection framework that was created after Brexit. The EU GDPR was superseded as the primary data protection regulation in the UK by the UK GDPR, which went into effect in January 2021. The fundamental principles of the EU GDPR—such as legitimate grounds for processing, individual rights, and organisational accountability—remain intact.
The UK has, however, made several adjustments to fit its unique national setting and regulatory framework. Businesses that handle personal data in the UK, including real-world data (RWD), are required to abide by the strict regulations set forth by the UK GDPR.

7.1.1. Background:

- After leaving the European Union, the UK needed to establish its own data protection framework to replace the EU's GDPR.
- The UK GDPR came into effect on January 1, 2021, serving as the UK's primary data protection law.

7.1.2. Alignment with EU GDPR:

- The UK GDPR is largely aligned with the EU's GDPR, retaining most of the core principles, requirements, and individual rights.
- This alignment was intentional to maintain consistency and facilitate data transfers between the UK and the EU.

7.1.3. Key Provisions:

- Like the EU GDPR, the UK GDPR outlines principles for data processing, such as lawfulness, fairness, transparency, purpose limitation, and data minimization.
- It grants individuals rights over their personal data, including the right to access, rectify, erase, and object to processing.
- Organizations must have a lawful basis for processing personal data, such as consent, legal obligation, or legitimate interests.

- The UK GDPR requires organizations to implement appropriate technical and organizational measures to ensure data security and privacy by design.

7.1.4. Modifications and Adaptations:

- While largely consistent with the EU GDPR, the UK has made some modifications and adaptations to suit its national context and regulatory environment.
- These include changes to certain definitions, terminology, and provisions related to cross-border data transfers and supervisory authorities.
- The UK GDPR also includes specific provisions related to immigration and law enforcement data processing.

7.1.5. Data Protection Authority:

- The Information Commissioner's Office (ICO) is the independent supervisory authority responsible for enforcing the UK GDPR and promoting data protection compliance.
- The ICO has the power to investigate potential breaches, issue fines, and provide guidance and advice to organizations.

7.1.6. Implications for RWD:

- The UK GDPR has significant implications for the handling and processing of real-world data (RWD), as much of this data contains personal health information.
- Organizations operating in the UK and utilizing RWD must comply with the specific requirements of the UK GDPR, including lawful bases for processing, individual rights, and data protection measures.

While maintaining alignment with the EU GDPR's principles, the UK GDPR reflects the UK's national context and regulatory environment, allowing for a degree of divergence and adaptation as the UK's data protection framework evolves independently.

7.2. The role of the Medicines and Healthcare products Regulatory Agency (MHRA)

- The executive body in charge of policing pharmaceuticals and medical devices in the UK is the MHRA.
- The MHRA offers guidelines and frameworks for the use of real-world evidence (RWE) and RWD in regulatory decision-making.
- The MHRA came up with a guidance note in 2021 titled "Guidance Note: The utility of real-world data to support decision making," which described its approach and purpose.
- The guidelines address the use of RWD/RWE in risk-benefit analyses, post-authorization studies, and marketing authorization applications.
- Working together with industry, academics, and healthcare professionals, the MHRA aims to encourage the appropriate and efficient use of RWD/RWE.

The Medicines and Healthcare products Regulatory Agency (MHRA) plays a crucial role in the regulatory landscape for real-world data (RWD) and real-world evidence (RWE) in the United Kingdom. Here are the key details regarding the MHRA's role:

7.2.1. Regulatory Authority:

- The MHRA is an executive agency of the Department of Health and Social Care, responsible for regulating medicines, medical devices, and blood components for transfusion in the UK.
- It oversees the entire lifecycle of these products, from clinical trials and marketing authorization to post-market surveillance and safety monitoring.

7.2.2. Guidance and Frameworks for RWD/RWE:

- The MHRA recognizes the potential value of RWD and RWE in supporting regulatory decision-making processes.
- In 2021, the MHRA published the "Guidance Note: The utility of real-world data to support decision making," outlining its approach and expectations for the use of RWD/RWE.

- This guidance document covers the use of RWD/RWE in various regulatory contexts, such as marketing authorization applications, post-authorization studies, and risk-benefit evaluations.

7.2.3. Regulatory Acceptance of RWE:

- The MHRA acknowledges that RWE can complement and enhance evidence from traditional clinical trials, particularly in certain scenarios or for specific purposes.
- RWE can be used to support efficacy and safety evaluations, explore new indications or patient populations, and inform risk management plans and post-market surveillance activities.
- However, the MHRA emphasizes the importance of ensuring the quality, relevance, and reliability of RWD and RWE through robust methodologies and data governance practices.

7.2.4. Stakeholder Collaboration:

- The MHRA engages and collaborates with various stakeholders, including pharmaceutical companies, academic institutions, healthcare professionals, and patient organizations, to promote the responsible and effective use of RWD/RWE.
- This collaboration involves gathering input, sharing best practices, and fostering dialogue to advance the integration of RWD/RWE into regulatory processes.

7.2.5. Scientific Advice and Support:

- The MHRA provides scientific advice and support to organizations seeking guidance on the use of RWD/RWE in their development programs or regulatory submissions.
- This advisory service helps ensure alignment with the MHRA's expectations and requirements for the generation and reporting of RWE.

7.2.6. Alignment with International Efforts:

- The MHRA collaborates with other major regulatory agencies, such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), to align and harmonize approaches to RWD/RWE where possible.

- This alignment aims to facilitate the acceptance and use of RWE across different regulatory jurisdictions, promoting efficiency and consistency in drug development and decision-making processes.

By providing guidance, fostering stakeholder collaboration, and supporting the responsible use of RWD/RWE, the MHRA plays a central role in shaping the regulatory landscape for real-world evidence in the United Kingdom.

7.3. Alignment and divergence from the EU's regulatory approach to RWD/RWE

The regulations in the UK are mostly in line with the RWD/RWE guidelines and principles set forth by the European Union.
However, several aspects have been modified to align with the national setting of the United Kingdom.
Certain changes to the UK GDPR have an effect on how personal data is handled and processed, including RWD.
Though there may be some differences in the MHRA's guidance's particular standards or interpretations, overall it is compatible with the EMA's.
The data infrastructure, healthcare system, and regulatory environment in the UK have an impact on the generation, analysis, and application of RWD/RWE.
There may be future developments that deviate even more from the EU's approach if the UK builds its own autonomous framework.

Here are the details on the alignment and divergence of the United Kingdom's regulatory approach to real-world data (RWD) and real-world evidence (RWE) from the European Union's approach:

7.3.1. Alignment:

a. Data Protection and Privacy Frameworks:

The EU's GDPR and the UK's GDPR (General Data Protection Regulation) share several of similar guidelines, rules, and protections for handling personal data, including RWD.

The goal of this alignment is to provide strong data protection while facilitating the easy transfer of personal data between the EU and the UK.

b. Recognition of RWE's Value:

The European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK acknowledge the potential use of RWE in bolstering data from conventional clinical trials.

They recognise the contribution that RWE makes to regulatory decision-making processes, including applications for marketing authorization, label extensions, and post-market surveillance.

c. Guidance and Methodological Approaches:

The EMA's guidance publications and the MHRA's guidance on the application of RWD/RWE in different regulatory situations, such as the "Guidance Note: The utility of real-world data to support decision making," are nearly identical.

When creating and evaluating RWE, both organisations stress the significance of sound techniques, high-quality data, and governance procedures.

d. Stakeholder Engagement and Collaboration:

The purpose of the MHRA and EMA's engagement with stakeholders is to encourage the responsible and efficient use of RWD/RWE throughout the product lifecycle.

These stakeholders include industry, academia, and healthcare professionals.

In order to progress the integration of RWE into regulatory processes, this collaboration entails obtaining feedback, exchanging best practices, and promoting discussion.

7.3.2. Divergence:

a. Regulatory Independence:

The UK has created its own autonomous regulatory structure in the wake of Brexit, which permits future deviations from the EU's stance as it changes over time.

With this newfound freedom, the MHRA can modify its guidelines and rules to better suit the specific requirements, goals, and changing circumstances of the United Kingdom.

b. Interpretations and Nuances:

Although the general guidelines and concepts are similar, the UK and EU may treat RWD/RWE differently in terms of particular needs, interpretations, or complexities.

These subtleties could result from differences between the UK and EU member states' healthcare systems, data infrastructures, legislative frameworks, or business dynamics.

c. Pace of Adoption and Implementation:

There may be differences in the rate of adoption and implementation of new RWD/RWE frameworks or guidelines between the UK and the EU.

Since the UK's autonomous framework develops at its own pace in response to local objectives and advances, regulatory divergence may eventually become more noticeable.

d. Future Regulatory Developments:

There's a chance that the UK's autonomous regulatory environment will deviate even more from the EU's RWD/RWE policy.

This discrepancy might result from changing objectives for regulations, new developments in technology, changes in the pharmaceutical and healthcare industries at home, or the need to adjust to changing conditions in the UK.

CHAPTER 8:

NAVIGATING THE EVOLVING REGULATORY LANDSCAPE OF RWD

8. NAVIGATING THE EVOLVING REGULATORY LANDSCAPE OF RWD

8.1. Strategies for aligning RWD/RWE initiatives with regional regulatory requirements

8.1.1. Conduct Comprehensive Regulatory Gap Analysis:

- Review all applicable laws, guidelines, and standards for RWD/RWE in the relevant regions (e.g., US, EU, UK).
- Determine the main variations in areas like RWE acceptance criteria, methodological requirements, data privacy, and data quality standards.
- Examine how these variations might affect upcoming or current RWD/RWE projects.

8.1.2. Develop a Compliance Roadmap:

- Create a detailed compliance roadmap that outlines the actions and modifications needed for each location based on the regulatory gap analysis.
- Set deadlines for resolving compliance gaps and prioritise issues that need to be addressed right away.
- Establish precise roles, duties, and accountability for carrying out the compliance roadmap.

8.1.3. Establish Cross-Functional Teams:

- Bring together multidisciplinary groups with knowledge of regulatory affairs, privacy, analytics, data governance, and related therapeutic fields.
- Ensure team members' cooperation and coordination to handle regulatory needs in a comprehensive manner.
- Utilise the many viewpoints and expertise within the team to recognise possible hazards, difficulties, and prospects.

8.1.4. Implement Robust Data Traceability and Audit Trails:

- Throughout RWD's lifecycle, track its origin, processing, and transformation by putting in place reliable data traceability procedures.
- Establish thorough audit trails to record all decisions, actions, and procedures pertaining to the gathering, analysing, and reporting of RWD.
- Assure compliance with pertinent regulations for data traceability and audit trails, which will promote transparency and ease regulatory audits and inspections.

8.1.5. Conduct Regulatory Engagement and Consultation:

- Actively communicate with regulatory bodies to get direction, elucidation, and agreement regarding their standards for particular RWD/RWE projects.
- Use scientific and regulatory advisory processes to get input on suggested RWD sources, study designs, and analytical techniques.
- To aid in the creation of RWD/RWE frameworks, take part in cooperative projects, pilot programmes, and regulatory discussions.

8.1.6. Monitor and Adapt to Regulatory Changes:

- Provide systems for keeping an eye on and staying informed about modifications to RWD/RWE-related guidelines, rules, and best practices in all pertinent locations.
- Review and update the compliance roadmap and strategy on a regular basis to keep them in line with changing regulatory environments.
- Maintain all RWD/RWE initiatives agile and adaptable so you may adjust them as needed to maintain compliance and alignment with local regulations.

8.2. Establishing robust data governance and privacy frameworks

Develop and implement comprehensive data governance policies and procedures that address data quality, integrity, security, and privacy concerns.

Implement technical and organizational measures to ensure data protection by design and by default, such as pseudonymization, encryption, and access controls.

Establish clear roles and responsibilities for data stewardship, including the appointment of a Data Protection Officer where required.
Conduct regular Data Protection Impact Assessments (DPIAs) to identify and mitigate risks associated with the processing of personal data, including RWD.
Implement processes for managing individual rights, such as data subject access requests, rectification, and erasure, in compliance with regional data privacy regulations.

By establishing robust data governance and privacy frameworks, organizations can ensure the responsible and compliant handling of RWD, protect individual privacy rights, and maintain the integrity and quality of the data used for generating RWE. These frameworks also help build trust with regulatory authorities, stakeholders, and the public, promoting the ethical and transparent use of RWD in healthcare decision-making.

8.3. Engaging with regulatory authorities to build trust and alignment

Proactively engage with regulatory authorities, such as the FDA, EMA, and MHRA, to seek guidance and clarification on their expectations for RWD/RWE.
Participate in regulatory consultations, pilot programs, and collaborative initiatives to contribute to the development of RWD/RWE frameworks.
Leverage regulatory advice and scientific advice procedures to obtain feedback on proposed RWD sources, study designs, and analytical methodologies.
Maintain transparency and open communication with regulators, addressing any concerns or questions regarding the generation and use of RWE.

Engaging with regulatory authorities to build trust and alignment regarding the use of real-world data (RWD) and real-world evidence (RWE) is a critical aspect of navigating the evolving regulatory landscape.

8.4. Adopting industry-wide standards and best practices for RWD/RWE

a. Data Sources and Data Quality:

- Establish precise standards for choosing pertinent and appropriate data sources, such as patient registries, claims data, electronic health records (EHRs), and patient-reported outcomes.
- Establish procedures for data validation, cleaning, and quality control to guarantee the data's accuracy and comprehensiveness.
- Create common data formats and standardised data models to help with data integration and interoperability between various sources.

b. Data Privacy and Ethics:
   - Maintain patient privacy, make sure that personal health information is used appropriately, and abide by applicable data privacy regulations (such as HIPAA and GDPR).
   - Provide strong data governance guidelines and protocols for the use, sharing, and access of data.
   - Use the proper anonymization and de-identification methods to safeguard patient privacy and maintain the usefulness of the data.

c. Study Design and Methodology:
   - For conducting RWE studies, adhere to established methodological guidelines and frameworks, such as those created by regulatory agencies such as the FDA and EMA, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the International Society for Pharmacoepidemiology (ISPE).
   - Prior to starting RWE investigations, clearly describe the study objectives, outcomes, and research questions.
   - To address potential biases and confounding factors, use suitable study designs (e.g., prospective, retrospective, observational, pragmatic trials) and analytical techniques (e.g., propensity score matching, instrumental variable analysis).

d. Data Transparency and Reproducibility:

- To guarantee openness and repeatability, thoroughly record and disclose study procedures, data sources, and analysis techniques.
- Think about implementing standardised reporting guidelines, like the REporting of research Conducted using Observational Routinely-collected health Data (RECORD) statement or the Strengthening the Reporting of Observational research in Epidemiology (STROBE) declaration.
- To support independent validation and replication of findings, promote data sharing and collaboration among researchers, subject to adequate data governance and privacy controls.

e. Stakeholder Engagement and Collaboration:
    - In order to guarantee that RWE studies take into account the requirements and interests of pertinent stakeholders, such as patients, doctors, payers, and regulatory bodies, engage with them.
    - Work together with regulatory agencies, academic institutions, and business associations to create and improve standards, guidelines, and best practices for the creation and application of RWD/RWE.

f. Continuous Improvement and Education:
    - Maintain a close eye on how best practices are being applied, assess them frequently, and update them to reflect evolving techniques, legal requirements, and technological advancements.
    - To increase the knowledge and skills of researchers, medical professionals, and other stakeholders in RWD/RWE, funding should be allocated to training and educational initiatives.

By adopting these industry-wide standards and best practices, organizations can enhance the quality, reliability, and acceptance of RWE, ultimately contributing to better healthcare decision-making and patient outcomes.

CHAPTER 9:

CASE STUDIES

9. Case Studies

9.1. Successful examples of RWD/RWE utilization in drug development and lifecycle management

Comparative Effectiveness and Safety Studies:

The Sentinel Initiative by the FDA has used electronic healthcare data from multiple sources to monitor the safety of medical products, including drugs, biologics, and medical devices, after they have been approved for use in the general population.

The SAVER (Safety Assessment for Vertex's Enriched Clinical Studies) program by Vertex Pharmaceuticals utilized RWD from cystic fibrosis registries and electronic health records to assess the real-world safety and effectiveness of their cystic fibrosis therapies.

Drug Repurposing and Label Expansions:

AstraZeneca used RWE from electronic health records and insurance claims data to support the label expansion of their drug Calquence (acalabrutinib) for the treatment of chronic lymphocytic leukemia (CLL).

Pfizer used RWD from patient registries and electronic medical records to support the repurposing of their drug Ibrance (palbociclib) for the treatment of certain types of breast cancer.

Patient Recruitment and External Control Arms:

Genentech used RWD from cancer registries and electronic health records to identify and recruit eligible patients for clinical trials of their immunotherapy drugs, reducing the time and cost of patient recruitment.

Flatiron Health has provided synthetic control arms derived from RWD to support regulatory submissions and approvals for several oncology drugs, reducing the need for placebo arms in clinical trials.

Pharmacovigilance and Post-Marketing Surveillance:

The FDA's Sentinel System has used RWD from various sources, including electronic health records and claims data, to monitor the safety of approved medical products, leading to the identification and mitigation of potential safety risks.
Pharmaceutical companies like Novartis and Amgen have used RWD from patient registries and electronic health records to monitor the long-term safety and effectiveness of their approved drugs in real-world settings.

Here are some detailed examples of successful utilization of Real-World Data (RWD) and Real-World Evidence (RWE) in drug development and lifecycle management:

9.1.1. AstraZeneca: Label Expansion for Calquence (acalabrutinib)

- AstraZeneca used RWE to support the label expansion of their drug Calquence (acalabrutinib) for the treatment of chronic lymphocytic leukemia (CLL).
- They leveraged RWD from electronic health records and insurance claims databases to conduct a retrospective observational study.
- The study compared the effectiveness and safety of Calquence to other standard-of-care treatments in a real-world setting.
- The RWE generated from this study, along with clinical trial data, supported the FDA's approval of Calquence for the treatment of CLL in 2019, expanding its initial approval for mantle cell lymphoma.

9.1.2. Roche: Patient Identification and Recruitment for Clinical Trials

- Roche's Genentech division used RWD from cancer registries and electronic health records to identify and recruit eligible patients for clinical trials of their immunotherapy drugs.
- They developed a platform called the CONVERSANCE Cancer Patient Data Engine, which integrates RWD from multiple sources to create a comprehensive view of patient characteristics and treatment patterns.
- This platform allowed Roche to identify and pre-screen potential trial participants more efficiently, reducing the time and cost associated with patient recruitment.

- It also enabled the identification of underrepresented patient populations, increasing the diversity and representativeness of clinical trial participants.

9.1.3. Flatiron Health: Synthetic Control Arms for Regulatory Submissions

- Flatiron Health, a healthcare technology company, has provided synthetic control arms derived from RWD to support regulatory submissions and approvals for several oncology drugs.
- They used RWD from electronic health records and other real-world sources to create synthetic control cohorts that match the characteristics of clinical trial populations.
- These synthetic control arms served as external comparators, reducing the need for placebo arms in clinical trials and enabling more efficient study designs.
- For example, Flatiron Health provided a synthetic control arm for the regulatory approval of Lilly's CYRAMZA (ramucirumab) for the treatment of advanced gastric cancer, based on RWD from over 30,000 patients.

9.1.4. Novartis: Post-Marketing Surveillance and Safety Monitoring

- Novartis has utilized RWD from patient registries and electronic health records to monitor the long-term safety and effectiveness of their approved drugs in real-world settings.
- For their multiple sclerosis drug Gilenya (fingolimod), Novartis established a post-marketing surveillance program called PREFERENCE, which collected RWD from over 10,000 patients across multiple countries.
- This RWD allowed Novartis to monitor the drug's safety profile, identify potential adverse events, and assess its effectiveness in a diverse patient population.
- The insights gained from this RWE helped inform risk management strategies, product labeling, and healthcare decision-making.

9.1.5. Amgen: Comparative Effectiveness and Safety Studies

- Amgen has leveraged RWD from various sources, including electronic health records and claims databases, to conduct comparative effectiveness and safety studies for their approved products.
- For their osteoporosis drug Prolia (denosumab), Amgen used RWD to evaluate its real-world effectiveness compared to other osteoporosis treatments and to assess the risk of rare adverse events.
- These RWE studies provided valuable insights into the drug's performance in real-world clinical practice, complementing the evidence from clinical trials.
- The findings from these studies have informed treatment guidelines, risk-benefit assessments, and healthcare decision-making for osteoporosis management.

These examples highlight how pharmaceutical companies have successfully leveraged RWD and RWE across various stages of the drug development lifecycle, from patient recruitment and clinical trials to regulatory submissions, post-marketing surveillance, and lifecycle management. The insights gained from RWE have helped to optimize drug development processes, inform regulatory decisions, and ultimately improve patient care and outcomes.

Table 1 Lesson Learnt and Challenges Overcomed

	Lesson Learnt	**Challenges Overcome**	**Example**
I. Data Quality and Standardization	Ensuring data quality and completeness is crucial for generating reliable RWE. Incomplete or missing data can lead to biased results and incorrect conclusions.	Organizations have developed robust data cleaning, validation, and standardization processes to address data quality issues. This includes implementing automated data quality checks, manual review processes, and data imputation techniques to handle missing data.	Flatiron Health, a leader in RWD analytics, has developed a comprehensive data quality framework that includes processes for data cleaning, deduplication, and standardization to ensure the integrity of their RWD sources.

II. Data Integration and Interoperability:	RWD often comes from diverse sources with different data structures, formats, and coding systems, making data integration and interoperability a significant challenge.	Organizations have adopted common data models, such as the Observational Medical Outcomes Partnership (OMOP) Common Data Model, to standardize and harmonize data from multiple sources. They have also developed data mapping and transformation tools to facilitate data integration.	The Observational Health Data Sciences and Informatics (OHDSI) initiative has developed a suite of open-source tools, including the OMOP Common Data Model and the Automated Analytic Pipeline, to enable seamless data integration and analysis across disparate RWD sources.

III. Bias Mitigation and Confounding Control:	RWD is subject to various biases and confounding factors, such as selection bias, information bias, and unmeasured confounders, which can compromise the validity of RWE.	Organizations have employed advanced analytical methods and study designs to mitigate biases and control for confounding factors. These include propensity score matching, instrumental variable analysis, sensitivity analyses, and the use of negative control outcomes.	In their RWE study supporting the label expansion of Calquence, AstraZeneca used propensity score matching to balance the characteristics between treatment groups and minimize selection bias.
IV. Data Privacy and Governance:	Ensuring patient privacy and adhering to data privacy regulations (e.g., HIPAA, GDPR) is essential when working with RWD, which often contains sensitive personal health information.	Organizations have implemented robust data governance frameworks, including data access controls, de-identification processes, and secure data storage and transfer protocols, to protect patient privacy while enabling responsible data use.	Novartis established the PREFERENCE post-marketing surveillance program with strict data governance measures, including data anonymization, secure data transfer, and restricted access to patient-level data.

V. Stakeholder Engagement and Acceptance	Gaining acceptance and trust from stakeholders, such as regulators, healthcare providers, and patients, is crucial for the widespread adoption of RWE in decision-making.	Organizations have engaged in collaborative efforts with stakeholders, including regulatory agencies, patient advocacy groups, and healthcare professional organizations, to align on methodological standards, reporting guidelines, and data transparency practices.	The FDA's Sentinel Initiative has involved extensive stakeholder engagement, including public-private partnerships and advisory committees, to develop best practices and build confidence in the use of RWD for post-marketing safety surveillance.

VI. Workforce Development and Education:	Utilizing RWD and generating RWE requires specialized skills and expertise in areas such as data management, analytics, epidemiology, and regulatory affairs.	Organizations have invested in workforce development and training programs to build the necessary skills and expertise within their teams. They have also collaborated with academic institutions and industry organizations to develop educational resources and curricula.	The International Society for Pharmacoepidemiology (ISPE) has developed various educational resources, including webinars, courses, and training programs, to upskill professionals in the field of RWD and RWE generation and utilization.

9.2. Emerging trends and future outlook for the regulatory embrace of RWD

9.2.1. Increasing Regulatory Guidance and Frameworks:

- Regulatory agencies like the FDA and EMA are actively developing guidance documents and frameworks to provide clarity on the acceptable use of RWD and Real-World Evidence (RWE) in various stages of drug development and regulatory decision-making.

FDA Guidance:

- The FDA has released several guidance documents and frameworks to provide clarity on the use of RWD and RWE in regulatory decision-making.

- The "Real-World Evidence Program" aims to evaluate the potential use of RWE to support the approval of new indications for approved drugs or to satisfy post-approval study requirements.
- The "Framework for FDA's Real-World Evidence Program" outlines the agency's approach to evaluating the potential use of RWD and RWE to help support the approval of new indications for approved drugs or to help satisfy post-approval study requirements.
- The "Use of Electronic Health Record Data in Clinical Investigations" guidance provides recommendations on the use of electronic health record (EHR) data in clinical investigations, including best practices for data quality, security, and privacy.

EMA Guidance:

- The European Medicines Agency (EMA) has released several guidelines and initiatives related to RWD and RWE.
- The "Initiation and Conduct of Complex Clinical Trials" guideline outlines the use of RWD for external control arms and addresses data quality, study design, and analysis considerations.
- The "Patient Registries Initiative" aims to develop guidance on the use of patient registries as sources of RWD for regulatory decision-making.
- The "Big Data Task Force" is exploring the use of big data and RWD in various areas, including drug development, pharmacovigilance, and health technology assessment.

ICH Guidelines:

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is developing guidelines related to RWD and RWE.
- The "E8(R1) General Considerations for Clinical Studies" guideline includes considerations for the use of RWD and RWE in clinical studies.

- The "E19 Optimisation of Safety Data Collection" guideline addresses the use of RWD for safety data collection and pharmacovigilance activities.

National and Regional Initiatives:

- Various national and regional regulatory agencies are developing their own guidance and frameworks for RWD and RWE.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) has released guidance on the use of RWE in health technology assessments and reimbursement decisions.
- The National Institute for Health and Care Excellence (NICE) in the UK has published guidance on the use of RWD in the evaluation of health technologies.
- The Pharmaceutical and Medical Devices Agency (PMDA) in Japan has established a working group to explore the use of RWD and RWE in regulatory decision-making.

The purpose of these frameworks and regulatory guidance guidelines is to promote uniformity and clarity in the application of RWD and RWE at different phases of the product lifecycle, such as post-marketing surveillance, regulatory submissions, and medication development. By addressing important factors such data quality, research design, analytical techniques, and reporting requirements, they support the development of regulatory confidence and industry acceptance of RWE among healthcare providers, industry stakeholders, and regulators.

9.2.2. Integration of RWD into Clinical Trials:

The integration of Real-World Data (RWD) into various aspects of clinical trials is an emerging trend that offers significant potential benefits.

a. Patient Recruitment and Enrollment
b. External Control Arms
c. Long-term Follow-up and Post-Approval Studies
d. Study Design and Enrichment
e. Pragmatic Clinical Trials

The integration of RWD into clinical trials offers opportunities to enhance trial efficiency, reduce costs, increase patient diversity, and generate more relevant and generalizable evidence. However, it also introduces challenges related to data quality, privacy, and analytical methods that need to be addressed through robust data governance frameworks and methodological standards.

9.2.3. Digital Health Technologies and Novel Data Sources:

The increasing adoption of digital health technologies is leading to the generation of novel sources of Real-World Data (RWD) that can complement traditional data sources like electronic health records (EHRs) and claims data.

a. Wearable Devices and Biosensors:

- Wearable devices, such as smartwatches and fitness trackers, can collect a wide range of physiological data, including heart rate, sleep patterns, physical activity levels, and more.
- Continuous glucose monitoring devices and other biosensors can provide real-time data on various biomarkers, offering insights into disease progression and treatment responses.
- These data sources can provide a more comprehensive view of patient behaviors, adherence, and outcomes in real-world settings, enhancing the breadth and depth of RWE.

b. Mobile Health Applications:

- Mobile health (mHealth) applications can capture patient-reported outcomes (PROs), symptom data, medication adherence information, and other relevant data points directly from patients.
- These apps can serve as digital diaries, allowing patients to record their experiences, side effects, and quality of life measures in real-time.
- The data collected through mHealth apps can provide valuable insights into patient perspectives and experiences, complementing clinical data from traditional sources.

c. Telehealth and Remote Monitoring:

- Telehealth platforms and remote monitoring technologies enable virtual consultations, remote monitoring of patients, and data collection outside of traditional healthcare settings.
- These technologies can capture data on patient-provider interactions, treatment adherence, and disease progression in real-world environments.
- The data generated through telehealth and remote monitoring can inform RWE studies, particularly in areas where access to healthcare is limited or for chronic disease management.

d. Digital Therapeutics and Connected Devices:

- Digital therapeutics, such as software-based interventions or connected medical devices, can generate data on treatment adherence, clinical outcomes, and patient engagement.
- These digital interventions can provide valuable insights into the real-world use, effectiveness, and safety of these novel therapeutic approaches.
- The data generated by digital therapeutics and connected devices can contribute to RWE generation and inform regulatory decision-making for these emerging technologies.

e. Social Media and Online Communities:

- Social media platforms and online patient communities can serve as sources of patient-generated data, including experiences, perspectives, and self-reported outcomes.
- While these data sources may require advanced natural language processing and text mining techniques, they can provide valuable insights into patient experiences and unmet needs.
- This information can complement traditional RWD sources and inform drug development, patient support programs, and healthcare delivery models.

As these digital health technologies continue to evolve and become more integrated into healthcare delivery, they will generate increasingly rich and diverse sources of RWD. However, leveraging these novel data sources for RWE generation will require addressing challenges related to data quality, privacy, and analytical methods. Regulatory agencies, such as the FDA's Digital Health Center of Excellence, are actively exploring the use of data from consumer-based digital health technologies to support regulatory decision-making.

9.2.4. Artificial Intelligence and Advanced Analytics

The application of artificial intelligence (AI) and advanced analytics techniques is emerging as a powerful tool for analyzing and deriving insights from large and complex Real-World Data (RWD) sets.

a. Machine Learning and Predictive Analytics

- With RWD, machine learning algorithms—such as supervised and unsupervised learning strategies—can be used to find trends, anticipate outcomes, and produce theories for more research.
- RWD can be used to build predictive analytics models that forecast clinical outcomes, pinpoint patient populations at high risk, or anticipate treatment outcomes based on a variety of patient attributes and real-world data.
- Clinical decision-making, risk assessment, and focused therapies can all benefit from the use of these predictive models, which will eventually enhance patient outcomes and healthcare delivery.

b. Natural Language Processing (NLP)

- Using natural language processing (NLP) approaches, pertinent information and insights can be extracted from unstructured data sources such clinical notes, medical literature, and patient-reported outcomes.
- Key clinical concepts, adverse events, and treatment patterns can be extracted from unstructured text data using natural language processing (NLP), making it possible to incorporate these data sources into the creation of RWEs.

- More complex natural language processing (NLP) models, including transformer-based language models (BERT, GPT), can improve the precision and scalability of insights extracted from unstructured data sources.

c. Deep Learning and Computer Vision

- Medical imaging data, such as X-rays, CT scans, and MRI pictures, can be processed using deep learning algorithms and computer vision techniques to help with disease diagnosis, treatment planning, and monitoring.
- In order to create AI-powered decision support systems that integrate clinical, imaging, and patient-reported data to guide treatment decisions and produce RWE, these techniques can be integrated with RWD sources.
- Additionally, automated data extraction from medical records can be facilitated by computer vision, which minimises manual labour and makes RWD gathering and analysis more effective.

d. Knowledge Graphs and Ontologies

- Diverse RWD sources can be represented and integrated using knowledge graphs and ontologies, which can capture relationships between different things (e.g., diseases, therapies, patient characteristics) and facilitate semantic reasoning and querying.
- These knowledge representations can help the creation of RWE from heterogeneous data sources by facilitating the integration of data, knowledge discovery, and hypothesis formulation.

e. Federated Learning and Privacy-Preserving Analytics

- Federated learning approaches solve privacy and data governance issues by allowing cooperative machine learning models to be trained on decentralised data sources without the need for data consolidation.
- The analysis of RWD can be made possible while maintaining patient privacy and complying with data protection laws thanks to privacy-preserving analytics such differential privacy and secure multi-party computation.

- These methods handle privacy and security issues and enable cooperative RWE generation and data sharing across many organisations and governments.

Regulatory agencies, such as the FDA's "Innovative Science and Technology Approaches for Real-World Evidence (RWE) Integration" initiative, are actively exploring the use of AI and advanced analytics in RWE generation and utilization. However, the adoption of these techniques also requires addressing challenges related to algorithmic bias, interpretability, and regulatory acceptance of AI-based decision support systems.

9.2.5. Interoperability and Regulatory Harmonization:

a. Interoperability Standards and Frameworks:

- Interoperability standards and frameworks are being developed to enable the seamless exchange and integration of RWD across different systems, platforms, and organizations.
- Initiatives such as the HL7 Fast Healthcare Interoperability Resources (FHIR) standard and the Observational Medical Outcomes Partnership (OMOP) Common Data Model aim to standardize data formats, terminologies, and data models for RWD.
- These standards facilitate data sharing, data mapping, and the integration of RWD from diverse sources, enabling more comprehensive and scalable RWE generation.

b. International Regulatory Collaborations:

- International collaborations among regulatory agencies are underway to harmonize regulatory requirements and methodological standards for the acceptance and use of RWE in drug development and regulatory decision-making.
- The International Coalition of Medicines Regulatory Authorities (ICMRA) is a collaboration among regulatory authorities from various regions, including

the FDA, EMA, and Health Canada, focused on enhancing regulatory collaboration and harmonization.

- The ICMRA has established workstreams specifically dedicated to RWE and exploring the use of RWD in regulatory decision-making, with the goal of developing aligned approaches and guidance.

c. ICH Guidelines and Standards:

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is developing guidelines and standards related to RWD and RWE.
- The ICH E8(R1) guideline on "General Considerations for Clinical Studies" includes considerations for the use of RWD and RWE in clinical studies, promoting harmonized approaches across regions.
- The ICH E19 guideline on "Optimisation of Safety Data Collection" addresses the use of RWD for safety data collection and pharmacovigilance activities, enabling more consistent and efficient post-marketing surveillance.

d. Regional Initiatives and Collaborations:

- Regional initiatives and collaborations are also underway to promote interoperability and harmonization within specific geographic regions or economic blocs.
- The European Health Data & Evidence Network (EHDEN) project aims to harmonize RWD sources across Europe, enabling federated analyses and evidence generation across multiple countries.
- The Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee has established a workstream focused on RWD and RWE, promoting collaboration and alignment among regulatory agencies in the Asia-Pacific region.

e. Cross-Border Data Sharing and Privacy Considerations:

- As RWD and RWE generation increasingly involves cross-border data sharing, there is a need to address data privacy and security considerations, as well as potential legal and ethical issues.
- Initiatives such as the Global Alliance for Genomics and Health (GA4GH) are developing standards and frameworks for responsible and secure data sharing across borders, while ensuring compliance with relevant data protection regulations.
- Efforts are underway to harmonize data privacy and governance frameworks, enabling the seamless and secure exchange of RWD across different jurisdictions.

Achieving interoperability and regulatory harmonization is a complex challenge that requires collaboration among various stakeholders, including regulatory authorities, industry organizations, academic institutions, and patient advocacy groups. By aligning standards, guidelines, and regulatory approaches, the use of RWD and RWE can be streamlined, facilitating more efficient drug development processes and informed decision-making across different regions and jurisdictions.

CHAPTER 10:

CONCLUSION

10. CONCLUSION

10.1. Comparative study:

Table 1 Comparative study of RWD in the US, Europe and the UK

1.	**Regulatory Initiatives and Frameworks**
US	The FDA has established several initiatives focused on RWD and RWE, including the Real-World Evidence Program, the Sentinel Initiative, and the NEST (New Evaluation Safety Technology) Program. These initiatives aim to evaluate the use of RWD and RWE in regulatory decision-making, safety surveillance, and post-marketing studies.
Europe	The European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) have established the Joint Big Data Task Force and the DARWIN (Data Analysis and Real-World Interrogation Network) project to explore the potential of big data and RWD in regulatory activities. The European Health Data & Evidence Network (EHDEN) and the European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) also play crucial roles in promoting the use of RWD and RWE in Europe.
UK	The Medicines and Healthcare products Regulatory Agency (MHRA) has launched the Innovative Licensing and Access Pathway (ILAP) and the MHRA Real-World Data Alliance to facilitate the use of RWD and RWE in drug development and regulatory decision-making. The UK also participates in EU initiatives such as DARWIN and EHDEN.

2.	**Regulatory Guidance and Best Practices**

US	The FDA has issued guidance documents on the use of electronic health record data in clinical investigations, submitting RWD and RWE to the agency, and data standards for RWD submissions. Additionally, the agency has provided frameworks and recommendations for its RWE Program and the use of RWE in regulatory decision-making.
Europe	The EMA has released guidance on the initiation and conduct of complex clinical trials, including considerations for the use of RWD and RWE. The agency has also outlined its Regulatory Science Strategy to 2025, which includes a focus on RWE.
UK	The MHRA aligns with EU guidance on RWD and RWE and has also developed its own guidance on the use of RWD and RWE for medicines development and evaluation.

3.	**Data Sources and Infrastructure**
US	The FDA's Sentinel System integrates electronic health records (EHRs) and claims data from multiple data partners. The NEST Program explores the use of additional data sources like patient registries and social media data for safety signal detection and evaluation.
Europe	The DARWIN Network aims to establish a federated network of data sources across Europe, including EHRs, registries, and claims databases. The EHDEN project also facilitates the integration and analysis of RWD across multiple European countries.
UK	The Clinical Practice Research Datalink (CPRD) is a major source of RWD in the UK. The country also participates in the DARWIN and EHDEN initiatives, enabling access to broader European data sources.

4.	**Stakeholder Engagement and Collaborations**
US	The FDA has established public-private partnerships, such as the RWE Analytics Collaborative, and engages with stakeholders through public workshops and advisory committees.
Europe	The HMA-EMA Joint Big Data Task Force and the ENCePP network foster stakeholder engagement and collaboration across the European regulatory network.
UK	The MHRA Real-World Data Alliance brings together stakeholders from industry, academia, and healthcare to facilitate the use of RWD and RWE. The UK also participates in EU stakeholder initiatives.

5.	**International Harmonization and Collaboration**
US	All regions participate in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and contribute to the development of guidelines related to RWD and RWE, such as ICH E8(R1) and ICH E19. The International Coalition of Medicines Regulatory Authorities (ICMRA) serves as a platform for collaboration and harmonization efforts among regulatory authorities worldwide, including the use of RWD and RWE.
Europe	
UK	

10.2. Summary:

RWD and RWE are increasingly being used all through the whole drug development lifecycle, from clinical trials to post-marketing surveillance. Robust data governance frameworks are the result of significant progress achieved in resolving bias, standardisation, privacy, and quality issues with data.

Growing regulatory guidance, using AI and analytics, collaborative data ecosystems, new sources of digital health data, and integrating RWD into clinical trials are some of the emerging themes. To encourage the widespread adoption of RWE, efforts are being made to harmonise regulations and foster international cooperation.

Adoption of RWD/RWE can have a big impact on collaborations, data sharing, patient outcomes, healthcare delivery, medication development, and regulatory decisions. It can also make more individualised interventions possible. Organisations may promote innovation, enhance outcomes, and advance healthcare internationally by effectively employing RWD/RWE, all the while proactively managing the changing regulatory landscape in line with best practices.

10.3. Implications for the pharmaceutical and healthcare industries

Drug development processes can become more efficient, cost-effective, and patient-centric by leveraging RWD for patient recruitment, external control arms, and long-term follow-up studies.

Regulatory decision-making can be better informed by RWE, leading to more accurate assessments of drug safety, effectiveness, and value in real-world settings.

Healthcare delivery and patient care can be improved through the use of RWE to optimize treatment strategies, identify high-risk patient populations, and personalize care based on real-world outcomes.

Collaborations and data sharing across stakeholders, including researchers, healthcare providers, regulatory agencies, and patient organizations, can foster a more comprehensive understanding of patient experiences, treatment patterns, and unmet medical needs.

The adoption of digital health technologies and novel data sources can provide more granular and longitudinal insights into patient behaviors, adherence, and outcomes, enabling the development of more targeted and personalized interventions.

10.4. Recommendations for navigating the evolving regulatory landscape for RWD/RWE

As the regulatory landscape for RWD and RWE continues to evolve, organizations should consider the following recommendations:

- By staying informed about the latest regulatory guidance, frameworks, and best practices issued by agencies such as the FDA, EMA, and ICH, and align internal processes and methodologies accordingly.
- Investing in data governance, privacy, and security measures to ensure the responsible and compliant use of RWD, building trust and confidence among stakeholders.
- Establishing collaborations and participate in data sharing initiatives, leveraging common data models and interoperability standards to facilitate seamless data integration and analysis.
- Building internal capabilities and expertise in areas such as data management, analytics, epidemiology, and regulatory affairs through workforce development and training programs.
- Engaging with regulatory authorities, patient advocacy groups, and other stakeholders to align on methodological standards, reporting guidelines, and data transparency practices, fostering acceptance and trust in RWE generation and utilization.
- Monitoring of the emerging trends and innovations in digital health technologies, artificial intelligence, and advanced analytics, and explore their potential applications in RWD and RWE generation.
- Contributing to international collaborations and harmonization efforts, ensuring alignment with global regulatory requirements and facilitating the acceptance of RWE across different regions and jurisdictions.

CHAPTER 11:

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