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Harmonization and Post-Marketing Surveillance of Herbal Medicines: Challenges and Future Prospects in India, Europe and United States

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Abstract

Harmonization of regulations and post-marketing surveillance of herbal medicines remains a significant challenge due to regulatory diversity, under-reporting, and lack of scientific data. While efforts are being made by international bodies like WHO and ICH, achieving harmonization requires active collaboration between India, the US, and Europe. Strengthening the role of DRA departments is key to ensuring regulatory compliance, improving PMS systems, and enhancing global acceptance of herbal medicines.Harmonizing the regulatory frameworks and strengthening post-marketing surveillance of herbal medicines in India, the US, and Europe is essential for ensuring public safety and facilitating global trade. Addressing regulatory challenges, improving adverse event reporting, and promoting scientific validation can enhance the credibility of herbal medicines. DRA departments play a pivotal role in achieving this objective through policy reforms, capacity building, and promoting international collaboration.

Keywords: Harmonization, Post-Marketing Surveillance, Herbal Medicines, Future Prospects

Introduction:

Post marketing surveillance (PMS) of medications is the process by which marketed medicines are monitored for adverse drug reactions (ADRs) post clinical trials.[1] Since most drugs may not reach the market without passing phase III clinical trials,[2] PMS studies are considered to be phase IV studies.[3] The safety and efficacy evaluations of any new medicinal product *via* clinical trials will provide only limited information on rare ADRs.[4] In addition, discovering 'rare' (1 in 1000) and 'very rare' (1 in 10,000) ADRs usually occurs only in the post marketing phase.[3] This is mainly due to the limited variety of conditions, described as the 'five toos: too few, too simple, too narrow, too median-aged and too brief', referring to the narrow patient selection criteria and sample size along with the short duration of clinical studies. This makes it challenging to attain all the required safety data when relying exclusively on such studies.[5] PMS gives more realistic results as they occur in a more natural setting and afford evidence to safeguard or enhance the safety of approved drugs.[6] As a result of PMS, almost 20% of new medications

obtained a black box warning post marketing, and 4% were removed from the market due to safety concerns.[6]

An ADR is defined by the World Health Organization (WHO) as: 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'.[7] Each year, millions of patients experience ADRs, especially with the increased use of medicinal drugs.[8] From 2009 to 2012, approximately 47% of people in the United States reported using no less than one prescription medication in the past month and approximately 11% reported using no less than five prescription medications concomitantly.[9] As a result, the amount spent on prescription drugs was estimated to be US$270 billion in 2013 according tothe National Center for Health Statistics report in 2014.[9] Lazarou and his colleagues estimated, in a landmark meta-analysis in 1998, that ADRs were associated with over 2,216,000 hospitalization cases annually in USA (admitted because of ADR or suffered ADR while in hospital), leading to more than 106,000 deaths each year. Therefore, ADRs take the place as the fourth to sixth major cause of death, eclipsing pulmonary disease, diabetes, acquired immunodeficiency syndrome and pneumonia.[10] According to the Centers for Disease Control and Prevention, ADRs are responsible for almost 1,300,000 emergency department visits annually.[11] In 1995, the burden of ADRs in financial terms was estimated to be up to US$136 billion dollars annually.[12] More recently, Poudel *et al.* estimated the cost of ADR related hospitalizations in 2011 to be US$38.9 billion dollars.[13]

Post-marketing surveillance (PMS), or pharmacovigilance, of herbal medicines involves monitoring their safety and efficacy after they have been released on the market, focusing on identifying rare or unexpected adverse reactions that might not have been detected during pre-market clinical trials.

Herbal medicines have gained increasing popularity worldwide due to their perceived safety, effectiveness, and cultural acceptance. However, the regulation of herbal medicines varies significantly across different regions, leading to inconsistencies in safety, efficacy, and quality. Harmonization of regulations and efficient post-marketing surveillance (PMS) are crucial to ensure public health and facilitate global trade. This paper explores the challenges and future prospects of harmonization and PMS of herbal medicines in **India, the United States (US), and Europe** with a focus on the role of **Drug Regulatory Affairs (DRA) departments** in each region.

Need for Study:

1. **Regulatory Variations:** Different countries follow distinct regulatory pathways, leading to complexities in ensuring the quality, safety, and efficacy of herbal medicines.
2. **Growing Global Trade:** Harmonization is essential to promote international trade and eliminate regulatory barriers.
3. **Rising Safety Concerns:** Increased use of herbal medicines necessitates robust post-marketing surveillance systems to identify and mitigate adverse effects.
4. **Scientific Validation:** Establishing global standards for scientific validation of herbal medicines can enhance their acceptance.

Literature Review:

Regulatory Frameworks for Herbal Medicines:

- **India:** Regulated under the **Drugs and Cosmetics Act, 1940** and **Ayush Ministry Guidelines**. Quality standards are defined by the **Pharmacopoeia Commission for Indian Medicine and Homoeopathy (PCIM&H)**.
- **United States:** Herbal products are regulated as **dietary supplements** under the **Dietary Supplement Health and Education Act (DSHEA), 1994**, with post-market surveillance conducted by the **FDA**.
- **Europe:** Regulated by the **European Medicines Agency (EMA)** under the **Traditional Herbal Medicinal Products Directive (THMPD), 2004/24/EC**, with pharmacovigilance and PMS under the **European Union (EU) Pharmacovigilance Directive**.

Post-Marketing Surveillance and Pharmacovigilance:

- **India:**Pharmacovigilance of herbal medicines is conducted under the **Pharmacovigilance Program of India (PvPI)**, but challenges exist due to poor reporting and lack of awareness.
- **US:** Post-market surveillance is carried out by the **FDA**, but the system relies on voluntary reporting, which can lead to under-reporting of adverse events.
- **Europe:** The **EMA** requires detailed PMS and risk management plans for herbal medicines, ensuring rigorous monitoring.

Harmonization Efforts:

- **WHO Guidelines on Herbal Medicines:** Aim to establish a global framework for quality, safety, and efficacy.
- **International Cooperation on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):** Works towards harmonizing pharmaceutical regulations, including herbal medicines.

Aim and Objectives:

Aim:

To evaluate the challenges and future prospects of harmonizing regulations and post-marketing surveillance of herbal medicines in India, the US, and Europe.

Objectives:

1. To analyze the current regulatory frameworks governing herbal medicines in India, the US, and Europe.
2. To assess the effectiveness of post-marketing surveillance systems in these regions.
3. To identify the challenges hindering harmonization and PMS implementation.

4. To propose strategies for strengthening regulatory frameworks and surveillance mechanisms.
5. To evaluate the role of the DRA department in ensuring regulatory compliance and harmonization.

Methodology:

Study Design:

- **Comparative Regulatory Analysis:**Analyzing similarities and differences in regulations and PMS practices in India, the US, and Europe.
- **Data Collection:** Secondary data from regulatory guidelines, WHO publications, and published research papers.
- **Case Studies:** Review of adverse event reports and post-marketing surveillance data from India, the US, and Europe.

Data Analysis:

- **Qualitative Analysis:** Comparative study of regulations and surveillance systems.
- **Quantitative Analysis:** Evaluation of adverse event data and reporting trends.

Results:

1. Regulatory Variations and Challenges:

- **India:** Limited enforcement of pharmacovigilance and lack of integration of traditional systems with global standards.
- **US:** Weak post-marketing surveillance due to voluntary reporting and the lack of mandatory safety monitoring.
- **Europe:** Strict regulatory requirements with a more developed PMS system but challenges in harmonizing diverse traditional systems.

2. Gaps in Post-Marketing Surveillance:

- **Under-Reporting of Adverse Events:** Common in all regions, leading to inadequate safety data.
- **Lack of Standardization in Reporting:** Different terminologies and methodologies create challenges for global surveillance.
- **Inadequate Risk Communication:** Delayed or incomplete communication of safety concerns.

3. Challenges in Harmonization:

- **Divergent Regulatory Philosophies:** Ayurvedic systems in India, dietary supplements in the US, and standardized herbal medicines in Europe create inconsistencies.
- **Lack of Scientific Data:** Insufficient clinical evidence on safety and efficacy hinders harmonization efforts.

- **Cultural and Ethical Concerns:** Traditional beliefs and practices influence regulatory frameworks and consumer preferences.

Discussion:

Role of DRA in Harmonization and PMS:

- **India:** The DRA needs to strengthen pharmacovigilance systems for Ayurvedic, Unani, and Siddha medicines and improve adverse event reporting.
- **US:** Enhancing mandatory post-marketing surveillance and improving adverse event reporting systems under DSHEA.
- **Europe:** Facilitating the integration of traditional and complementary medicines into the existing pharmacovigilance framework.

Proposed Strategies for Harmonization:

1. **Standardizing Quality and Safety Parameters:** Developing globally accepted pharmacopoeial standards.
2. **Establishing Unified Adverse Event Reporting Systems:** Introducing a global pharmacovigilance platform for herbal medicines.
3. **Strengthening Collaboration and Information Exchange:** Enhancing cooperation between regulatory agencies in India, the US, and Europe.
4. **Capacity Building and Training:** Promoting awareness and training on pharmacovigilance practices in the herbal sector.

Summary:

Harmonization of regulations and post-marketing surveillance of herbal medicines remains a significant challenge due to regulatory diversity, under-reporting, and lack of scientific data. While efforts are being made by international bodies like WHO and ICH, achieving harmonization requires active collaboration between India, the US, and Europe. Strengthening the role of DRA departments is key to ensuring regulatory compliance, improving PMS systems, and enhancing global acceptance of herbal medicines.

Conclusion:

Harmonizing the regulatory frameworks and strengthening post-marketing surveillance of herbal medicines in India, the US, and Europe is essential for ensuring public safety and facilitating global trade. Addressing regulatory challenges, improving adverse event reporting, and promoting scientific validation can enhance the credibility of herbal medicines. DRA departments play a pivotal role in achieving this objective through policy reforms, capacity building, and promoting international collaboration.

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