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Elements of Regulatory Dissonance: Examining FDA and EMA Product Labeling of New Vaccines (2006–2018)

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Abstract

With the ongoing globalization of the pharmaceutical industry, efforts to harmonize technical requirements of registering drugs and biologics, including vaccines, have produced a number of useful guidelines utilized around the world. However, such efforts have not been extended to the regulatory review process or product labeling. Prescribing information and patient information leaflet are two types of such product labeling documents. This study examined the differences in the languages of these documents between the United States (US) and European Union (EU). The key documents examined were the U.S. Food & Drug Administration’s (FDA) Package Inserts (PIs), U.S. Centers for Disease Control and Prevention’s (CDC) Vaccine Information Statements (VISs), and the European Medicines Agency’s (EMA) Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs). Prescribing information and patient information leaflet languages were subsequently organized into ten and seven categories, respectively. Comparison of FDA PIs to EMA SmPCs showed little harmonization between the two regions, and CDC VISs to EMA PLs revealed even less.

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1. Introduction

Each year, regulatory agencies worldwide review new drugs and biologics, including vaccines, for marketing approval within their respective regions. This process is essential, as it not only assesses the safety and efficacy of products but also oversees the product labeling intended for use by healthcare professionals and patients. However, because approval processes are not globally harmonized, a pharmaceutical company seeking approval for its product in multiple regions must prepare and submit separate applications, which may be different in content and format. Although efforts by the International Council for Harmonization (ICH) to harmonize technical requirements for registering drugs and biologics have produced a number of useful guidelines that are used around the world, such efforts have not been extended to the regulatory review process or product labeling [1]. Currently, the United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA) are considered two of the most prominent regulatory agencies around the world. This study compared vaccine prescribing information and patient information leaflet languages between FDA/Centers for Disease Control and Prevention (CDC) and EMA.

1.1. Vaccine approval

In both the United States (US) and the European Union (EU), vaccines undergo rigorous regulatory approval procedures to ensure their safety, efficacy, and quality. Depending on the product, this process can take anywhere from months to years, where delay in access could pose risks to public health. This is especially important and relevant in the case of vaccines that are developed for highly contagious illnesses or in response to infectious disease outbreaks. In the US, FDA is responsible for all drug approvals. When a company files a Biologics License Application (BLA) for a vaccine, the application is reviewed by the Center for Biologics Evaluation and Research (CBER) [2]. In the EU, all biologics, including vaccines, must be authorized by EMA. There are three available pathways for pharmaceutical product approval in the EU: centralized, decentralized, and mutual recognition [3]. The centralized route allows companies to submit a single Marketing Authorization Application (MAA) to EMA that leads to the product’s approval in all countries within the European Economic Area (i.e., the 27 member states of the EU plus Iceland, Liechtenstein and Norway). Once submitted, it undergoes review by the Committee for Medicinal Products for Human Use (CHMP) [4,5,6,7]. All products
approved by both FDA and EMA during the time frame of this study were approved through the centralized procedure. On the other hand, the decentralized pathway allows companies to apply for simultaneous authorization in more than one, but not all, EU member states, as long as the product for which they are seeking approval has not yet been authorized for marketing in any EU nation [3]. In this process, one country is designated as the reference member state and completes a preliminary assessment. If the other countries are in agreement with the reference state’s assessment, marketing authorization will be granted. Finally, the mutual recognition pathway allows a company whose product has already been authorized in one EU nation (reference state) to apply for approval in other EU countries (target states) [3]. The target states rely on the scientific assessment of the reference state to decide whether to grant a marketing authorization [7].

1.2. Vaccine labeling

The application for approval includes extensive safety and efficacy data collected during the pre-clinical and clinical phases as well as the company’s proposed labeling, which is the ultimate deliverable of the approval process. Based on this information, each agency evaluates the risk–benefit ratio of the vaccine [8,9]. One of the final steps of product approval is the completion of product labeling. Regulatory agencies work with the manufacturers to finalize their proposed language, ensuring that the information is appropriate, sufficient, and accurate [10]. There are two types of product labels – one intended for use by healthcare professionals (prescribing information), and one intended for use by patients (patient information leaflets). Vaccine labeling for medical professionals are technical documents used by physicians, pharmacists, and other qualified medical personnel to obtain information regarding the administration, precautions, safety, potential side effects, and efficacy of a vaccine and evaluate whether it is appropriate to administer to a given patient. On the other hand, the labels for patients present information regarding directions, indication, contraindications, side effects, and dosages in a more patient-friendly manner, allowing the patients to weigh the risks against the benefits and make an informed decision.

Product labeling is often the only vaccine information disseminated to healthcare professionals and patients; hence, it is crucial for it to be accurate and sufficient. Discrepancies between regions can lead to unwarranted differences in the understanding and utilization of the product. In the US, Package Inserts (PI) serve as useful communication tools to healthcare professionals, providing sufficient safety and effectiveness information necessary to administer vaccines appropriately [11,12]. The labels for patients are the Patient Information through FDA and Vaccine Information Statements (VIS) provided by CDC. However, federal law requires that patients receiving any vaccine in the US be given the VIS rather than the Patient Information document [13]. In the EU, the Summary of Product Characteristics (SmPC), required by Directive 2001/83/EC, is the official information source for medical professionals [10,14]. The information in the SmPC is used to draft the Package Leaflet (PL), a document intended for use by patients. It is to be written in clear and understandable language so patients are adequately informed about the safety, effectiveness, and directions for use. With the help of healthcare professionals, patients will use this document to discuss and make decisions about their treatment [15].

1.3. Harmonization efforts

In an effort to develop guidelines for international harmonization, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was created in April 1990 in Brussels, and has since developed quality, safety, efficacy, and multidisciplinary guidelines [16,17,18]. An example includes the Common Technical Document (CTD), which is a harmonized electronic application for new products [18]. The CTD is comprised of Modules 1 through 5, of which Module 1 is region specific, and Modules 2 through 5 are the same for all regions. Included in Module 1 is the prescribing information, such as the proposed product information and labeling, which depicts the essential information on safety, efficacy, and guidelines for use [19,20]. The contents of such approved labeling are an important tool for both healthcare professionals and the general public, because although these products are intended to provide therapeutic benefits, they may also pose harm. This concept is particularly applicable to vaccines, as these products are primarily given to healthy individuals, and their benefits must clearly outweigh their risks. Although product labeling should be tailored to the needs of the local population, the core safety and efficacy information included should be the same across all regions, especially when they are derived from the same set of clinical evidence. The objective of this study was to compare contents of the product labeling and patient leaflets between the US and EU to identify where they harmonize and where they differ.

2. Methods

A retrospective analysis was performed of all vaccines approved by FDA and EMA between January 1, 2006 and June 30, 2018. The regulatory aspects examined for each vaccine were the prescribing information and patient information leaflet languages. Prescribing information was extracted from FDA’s PI and EMA’s SmPC, and the patient information leaflet language from the CDC’s VIS and EMA’s PL. The most recently updated versions (as of August 2018) of all regulatory documents were taken from FDA, CDC, and EMA websites (https://www.accessdata.fda.gov/scripts/cder/daf/, https://www.cdc.gov/vaccines/hcp/vis/index.html, https://www.ema.europa.eu/en/medicines, respectively).

First, the prescribing information and patient information leaflet languages were assessed for the level of harmonization between the two regions. Although the same topics could be found in the documents of both regions, the contents were arranged differently depending on the agency. For example, to describe the intended use of the vaccines, FDA used the term “indications and usage,” while EMA used “Therapeutic Indications.” For analysis, this labeling element was simply referred to as “Indication” (Supplementary Table 1). Ten prescribing information elements and seven patient information leaflet elements were examined (Supplementary Tables 1 and 2). Detailed criteria on the type of information assessed for each element are outlined in Supplementary Tables 1 and 2. These criteria must be the same for the corresponding element to be considered harmonized, ignoring any spelling, punctuation, grammatical, or phrasing differences.

Because the vaccines analyzed in this study were approved over a long period of time (12 years), the possibility of change in the level of harmonization over the years was explored. The number of harmonized prescribing information and patient information leaflet elements were organized by year of approval into three groups: 2006–2009, 2010–2013, and 2014–2018. For vaccines whose approval dates in the US and EU did not fall into the same category, FDA’s approval date was used. The average of the number of elements harmonized was calculated for each time period and analyzed for any trends.

3. Results

From January 2006 to June 2018, 39 vaccines were approved by FDA and 34 by EMA. Of these, a total of 12 vaccines were approved by both FDA and EMA (Supplementary Table 3).
3.1. Prescribing information elements

Of the twelve common vaccines across FDA and EMA, none had harmonized prescribing information across all ten elements (Table 1). The greatest level of harmonization across the elements was six out of ten. The labeling elements with the greatest level of harmonization were Pregnancy Assessment and Pediatric Assessment, both of which were harmonized across seven out of twelve vaccines. Conversely, Warnings & Precautions, Adverse Events, and Patient Counseling Information were not harmonized for any vaccine (Tables 1 and 2).

3.2. Patient information leaflet elements

Similar to the prescribing information, none of the twelve vaccines demonstrated harmonized patient information across all seven elements (Table 1). For all vaccines, harmonization occurred across only one or two out of seven elements. The element that was most harmonized (observed across all 12 vaccines) was Side Effects Reporting, as both CDC and EMA have established national reporting systems. The element Use During Pregnancy was harmonized in four out of twelve vaccines. The elements Disease Information, Contraindications, Side Effects, and What to Look Out For were not harmonized in any products across the two regions (Table 3).

3.3. Changes over time

No pattern was observed in the number of prescribing information and patient information leaflet elements harmonized over time (Fig. 1).

4. Discussion

This analysis of prescribing information and patient information leaflet languages demonstrated that certain differences exist between the labeling languages of the US and EU. Despite the same clinical data submitted for market authorization application, it is evident that the resulting labeling language is different. For example, same products assessed by each regulatory agency with the same set of pre-clinical and clinical trial data may result in labels with different therapeutic goals [21,22]. Hence EMA’s SmPC for a shingles vaccine may state that it is for the prevention of herpes zoster (shingles) and post-herpetic neuralgia, while FDA’s PI states that it should be used for the prevention of herpes zoster only and explicitly indicates the vaccine is not to be used for the treatment of postherpetic neuralgia.

These observed differences indicate the lack of a harmonized process to translate the information in the marketing application to the prescribing information and patient information leaflet. Although ICH provides guidelines on a harmonized method of application submission, there are currently no harmonized guidelines on the content of labels; hence different agencies around the world may be submitted the same set of pre-clinical and clinical trial data but use different assessment criteria that ultimately lead to divergent labeling language.

4.1. Implications of dissonance

Given the findings of this study, the question arises as to what implications these differences could have for medical professionals and patients. For instance, differences in indication, dosing, and recommended ages for use may lead to inconsistencies in not only
the number of doses but also whether individuals receive the vaccine at all. An example of differences in the recommended age range for use is demonstrated by the meningococcal vaccine. In the US, FDA sets the age range to 2 months to 55 years of age, while EMA’s age range is from 2 years of age. Moreover, the age ranges for use may be complicated by the recommended vaccine schedules set by the public health authorities of each country. Within the age ranges set by EMA, each country in the EU can have different recommendations based on the epidemiology and culture of the respective region [23]. In the US, children 2 to 23 months are able to receive the vaccine if they have certain conditions, including complement deficiency or human immunodeficiency virus (HIV). However, in the EU countries, these children cannot be vaccinated due to the restrictions set by the indication statement. What are the implications of this difference? One of the reasons for EMA’s decision not to include children ages 2 to 23 months was that antibody persistence was decreased in clinical trial participants who received the vaccine in those age ranges [24]. In this case, the children in the US who receive the vaccine may be placed at unnecessary risk of injection-related side effects. On the other hand, even this temporary protection provided by the vaccine may be beneficial for children who are at especially high risk of contracting the disease; in this case, the children in the EU who do not receive this vaccine may be faced with greater risk of harm. As such, although the implications of these differences may not be clear, they could be clinically significant.

Furthermore, an important patient information leaflet element that supplements the patient’s understanding of the therapeutic indication is Disease Information, which describes the disease that the vaccine is designed to prevent. With this information, patients can understand what the disease is, the dangers of contracting the disease, and why it is important to be vaccinated against it. However, there were notable differences in the level of detail for this element between the US and EU. Although patients may consult other sources as well, the Disease Information section of the patient information leaflet remains the primary document to learn about the disease that the vaccine protects against. If this section is not sufficient, patients will not be able to properly make an informed decision as to whether they should be immunized. The dangers of having limited information on the populations at risk is that individuals within this population may not know that they are especially vulnerable to contracting the disease. As such, they may not be fully equipped with the information necessary to make an educated decision.

The safety profile for vaccines is especially important and must be clearly established, as these products are generally given to healthy individuals. Included in the safety profile is the element Contraindications. An example of differences in this element is demonstrated by the shingles vaccine. In particular, one of the contraindications listed by EMA is “active untreated TB.” However, the US documents do not include this contraindication. If the vaccine administration to individuals with active untreated TB causes harm, then those in the US may not be adequately informed about this risk. On the other hand, if it is generally satisfactory for TB patients to receive the vaccine, these individuals in the EU may be placed at a disadvantage, as they would be at increased risk of contracting shingles without this vaccine.

4.2. Benefits and risks of harmonization

If vaccine labels were harmonized, everyone, regardless of region, would receive the same comprehensive information necessary to make an informed decision regarding each vaccine. Moreover, having harmonized schedules and administration would lead to simplified vaccine delivery. This is particularly relevant for individuals traveling or re-locating from one region to another, as their vaccine needs would remain the same anywhere. However, differences in culture, local terminology, and/or epidemiology may result in labeling language differences. As such, the set of vaccines necessary in one country may not be important in another due to a low disease prevalence, and cultural and terminology disparities may mean that the best labeling language is not identical across all countries.

Harmonized vaccine approval and administration would be valuable for diseases that impact the global community, as it would lead to faster access to potentially beneficial vaccines. For example, the rapid expansion of the 2019-nCoV (COVID-19) pandemic demonstrates that a swift global response is necessary, and the development of a safe and effective vaccine is crucial to control such outbreaks. As infectious agents can readily cross national boundaries and regulatory jurisdictions, a globally harmonized approach to vaccine approval and administration would be valuable to protect the health of the populations around the world.

The lack of harmonization among global regulatory agencies means that each country implements its own system of review. These differences lead to redundancy and decreased efficiency, as several approaches are taken to demonstrate the same concept. This redundancy may lead to increased cost for drug manufacturers that is passed down to consumers as increased drug prices. Having a harmonized approach to vaccine approval would lead to lower cost of vaccines and ultimately greater affordability and access. However, different approaches to regulatory decisions are not necessarily a problem. Although redundancy may decrease efficiency, it could increase reliability, as repeated results will confirm the same concept [25]. Moreover, the best approach to a product approval or public health matter is not always obvious. When presented with the same set of evidence, different agencies can have differing opinions and draw different conclusions. Ultimately, by presenting divergent opinions, the agencies as a whole are able to explore a variety of different paths and contribute to a more thorough assessment of the issue at hand.

5. Limitations

One limitation of the study is the small sample size, which limits the ability to detect clear trends. The limited sample size was determined by the number of vaccines approved by the two agencies during the 12-year period.

Another limitation is the subjective interpretation of the language and approach used by the two agencies required to identify and align the labeling elements. For example, the US PI may state that the vaccine should not be administered to anyone who experienced a “severe allergic reaction... after a previous dose... or any component” of the vaccine, while the EU SmPC states that “hypersensitivity to the active substance or to any of the excipients” is a contraindication to receiving the vaccine. In this case, a severe allergic reaction and hypersensitivity were considered equivalent, as they refer to the same immunological reaction against the vaccine.

6. Conclusion

Overall, this analysis compared clinical labeling languages for several vaccines approved by FDA and EMA. Some of the observed differences have clinically significant implications that could affect downstream patient care. Future research could investigate differences between the two regions in vaccination completion rates, disease rates, and vaccination-related injuries. Moreover, future work could also evaluate what regulatory processes were implemented by the two agencies and whether they led to the observed language differences. Moving forward, the US and EU, as well as...
other countries, should work together to create uniform prescribing information and patient information leaflet content so that all individuals, regardless of region, could have access to the same clinical information.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**ICMJE Authorship**

All authors attest they meet the ICMJE criteria for authorship.

**Appendix A. Supplementary material**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.09.067.

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