Available online on 15 June 2018 at http://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Open Access to Pharmaceutical and Medical Research

Review Article

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Differentiation between the Regulatory paths placed on Mouthwashes in the US and EU

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ABSTRACT

Regulating oral rinses has been and still is a topic of debate and confusion. Oral rinses are products that are mainly used for cleaning, perfuming and changing the appearance of the teeth, which in turn improves the individual's external appearance. Adding medicinal ingredients to these rinses, it can then be used for the elimination and/or prevention of some oral diseases, an example being gingivitis. The United States Food and Drug Administration placed guidelines which state that mouthwashes with possible therapeutic properties should be registered as drugs rather than cosmetics. Meanwhile, on a different continent, Germany along with the other members of the European Union decided not to categorize mouthwashes as drugs, but rather as cosmetics, using its sole purpose of cleaning and beautifying the teeth as the excuse. The following research will thoroughly differentiate between the diverse regulatory systems forced upon mouthwashes across the two countries—the United States and Germany.

Keywords: Drugs; Cosmetics; FDA; EMA; EU Cosmetics; Approval process; PIF; CPSR.

Article Info: Received 07April, 2018; Review Completed 23 April 2018; Accepted 30 April 2018

Cite this article as:

Saddik P, Pappan J. Differentiation between the Regulatory paths placed on Mouthwashes in the US and EU. International Journal of Drug Regulatory Affairs [Internet]. 15 Jun.2018 [cited 15 Jun. 2018]; 6(2):8-13. Available from: http://ijdra.com/index.php/journal/article/view/229

DOI:10.22270/ijdra.v6i2.229

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1. Introduction

The United States of America and Europe -lead by Germany- are the two greatest pharmaceutical powers in the world. Their pharmaceutical leadership is earned by them in all the various components of the pharmaceutical field, first being their huge investments in research and development, where the United States lead in 2015 by spending over 50 billion USD, followed by Europe with 33.6 billion USD with Germany leading the pack with 7.7 billion USD (1). According to Hardman &Co. another aspect of the pharmaceutical industry is the sales of pharmaceutical products, in which the United States in 2016 ranked first with about 303 billion USD; this accounted for about 39% of the world's total sales of pharmaceutical products estimated at about 816 billion USD, followed by Europe with 21.9% (2). Germany was the highest in Europe with about 37 billion USD (3).

All these statistics prove the importance of both these markets on the pharmaceutical industry and market worldwide, but what are the factors that lead to the flourishing of these markets? These factors include the adaptability of the pharmaceutical firms to the changes in the industrial and market environments around them, in addition to the implementation of various new regulations and changes introduced to the already present regulations. This involves huge investments by the firms in the department of research and development along with a thorough understanding of the regulatory process of the region where the product is to be marketed. This implies that regulations placed on pharmaceutical products and the importance of proving their safety and efficacy plays a significant role in the development of the pharmaceutical market in a given area. This urges the need to study some of the differences between the regulations placed upon the arguably two most successful pharmaceutical markets in the world, USA and Europe (while placing a special emphasis on Germany) (4).

Although the regulatory bodies of the USA and Europe might be the most successful, both are different, starting with their basic corner stones, which include their definitions of a drug (5). The FDA, which is the federal

US agency that is responsible for regulating the pharmaceutical products defines a drug as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

Meanwhile the EMA (European Medicines Agency), which is the equivalent of the FDA in Europe defines a drug, or rather "a medicinal product" as, "A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action" (6). On the contrary, the Federal Institute for Drugs and Medical Devices in Germany (BfArM), defines a medicinal product as "Medicinal products are used in humans or animals for therapeutic or diagnostic purposes. They are intended to prevent or treat diseases in a first place. These substances can act Both within or on the body. Contrast agents that are used to make anatomic structures are better visible in medical imaging procedures" (7).

This difference in the definition of the same word creates a wide gap between both these regulatory bodies. The EMA, for example, would specify a substance that cures a disease but is not yet recognized by any official pharmacopeia as a drug, while according to the FDA's definition, this substance did not yet complete all the requisites of being called a drug. While a component of a substance that cures a disease might be called a drug by the FDA, it might not be according to the EMA or the BfArM. This implies that a substance that is required to be approved by the FDA through the process of drug approval might not be required to complete a drug approval process elsewhere, but rather as a cosmetic product; an example of such a product is oral rinses, where, according to the FDA, it qualifies as a drug. It then must pass the tough and prolonged process of drug approval as a generic Over-The-Counter (OTC) drug, or even at times as a prescription drug, to be able to be sold in the domestic market of the US. This same product will be considered as a cosmetic product according to the EMA and the BfArM, and therefore requires less time and effort to hit the markets of these respective areas.

According to the FDA, a cosmetic product is defined as, "an article or component intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance". Since a mouthwash cannot be clearly stated as either a drug or a cosmetic product based only on the definitions of the terms, the FDA decided to categorize it based on its intended use, as claimed and labeled by the manufacturer (8). Since it was easy for products incomparable situations to claim drug like indications, while still maintaining its status as a cosmetic product, the FDA created a subcommittee in December 1998to look into the issue, and to recommend a monograph according to which anti plaque and anti-gingivitis OTC drugs can be recognized as safe and efficient. The resulting monograph suggested that these products should pass through the NDA or the ANDA processes described below depending on whether the drug is a brand name or a generic (9).

2. The drug approval process in the US (according to the FDA)

When a new drug is discovered, it must then go through the FDA's drug approval process to be cleared for sale in the US market. The FDA's drug approval process is commonly believed to be the most extensively demanding among its equivalents around the world (10, 11).

The FDA drug approval process is initiated with *Step (I): Pre-Clinical* studies: Before starting the pre-clinical studies a meeting is conducted with members of CDER (The Center for Drug Evaluation and Research) and representatives of the sponsor (the institution or firm responsible for submitting the IND (Investigational New Drug) application), to discuss the studies to be conducted and the requirements needed to state the drug as safe to proceed to the next phase of clinical trials.

These studies include 2 major categories, being (a) In vitro and (b) In vivo. In these studies, the sponsor provides study reports generated from in-vitro tests through cultivated cells and in-vivo by using laboratory animals (traditionally).These tests help to demonstrate the pharmacokinetics of the drug substance to determine the dosage. The reports also highlight the knowledge about the drug's pharmacodynamics to better determine its toxicity factors. The required reports are not based on a "one size fits all" tests, but rather studies tailored to the needs of the specific pharmaceutical substances, their intend use, and the intended path of administration of the drug. These study reports, along with others involving the formulations of the drug substance and its components, are submitted to the FDA in what is called an IND application. This IND application is then reviewed by a team of FDA reviewers from CDER, where experts in each specific field review parts of the IND application related to their expertise. Then, the drug is either stated as safe and ready for the next step of clinical trials or as lacking evidence (where the sponsor is then required to provide additional information about the drug and study reports to support the sponsor's claim of the drug's safety and efficacy) (10, 11).

After the pre-clinical study phase, wherein the drug has been proved to be safe and will not introduce any unreasonable risks on the volunteers, the drug then proceeds to *Step 2: Clinical Trails* (10, 11)*:*

After at least 30 calendar days from the submission of the IND, the IND is reviewed, and the sponsor can commence the clinical trials which are done in 3 phases. All the clinical trials are conducted on volunteers, which may be patients with the targeted disease, or healthy individuals. Phase 1 of the clinical trials are usually small scaled involving fewer than 100 healthy or diseased volunteers (except in cancer drugs, where all the volunteers are required to be patients of the targeted type of cancer, but were unaffected by the previously tried treatments). During this phase, the volunteers are closely observed, monitored and studied to gather more information for the resolve of further strengthening the claims of the drug's safety, and to get a better idea about its effective dosage (i.e. the dosage where the benefits are maximal, and the adverse effects are minimal) needed for the intended use of the drug. Another aspect learnt during phase 1 of clinical trials are the side effects related to the increased dosage. About 70% of the drugs prove to be safe and efficient enough to make it to the next phase of the clinical trials. This phase usually takes several months to be completed (10, 11).

Phase 2 of clinical trials are quite larger in scale than phase 1, usually involving several hundreds of volunteers, with the majority (if not all) being patients with the disease rather than healthy individuals. This phase usually takes several months to a few years for completion. During this phase the scientists aim to improve their understanding of the drug's safety data and its adverse effects. Only about one third of the drugs which enter phase 2 make it through to phase 3 (10, 11).

Phase 3 of the clinical trials is by far the largest in scale of all the phases, as it usually involves a few thousand volunteers. This phase requires at least a few years for completion. During this phase the researchers aim to grow their knowledge regarding the drug's safety, long term and rare adverse effects, and measure the therapeutic potential of the drug. Only 25% to 30% of the drugs make it through this phase.

The last phase of the clinical trials is phase 4, also known as the post-market phase in which the drug is actively monitored by the consumers through active reporting of any earlier unnoticed side effects after it is placed in the market (10, 11).

After the end of phase 3 of the clinical trials, the sponsor then moves to file what is called an NDA (New Drug Application), which contains all the information about the drug. The NDA contains information from research and development of the drug through the preclinical studies plus the results of the clinical trials, in addition to the proposed labelling information, list of adverse effects, directions of use, along with all the information collected about the drug inside and outside the United States. Then a review team from the FDA decides whether the NDA is complete or is lacking (where the sponsor is requested to provide additional information about the drug concerning a specific detail or field of study). If it is stated as complete, the review team takes 6 to 10 months to review the NDA to decide whether the drug is to be approved or the NDA is still lacking information or is to be placed on hold (rare as stated by the FDA). If approved the drug can then be legally mass produced in FDA registered establishments, and then distributed inside the US market.

If a firm's patent of a new drug expires, other manufacturers can produce the drug as a generic drug after filing an ANDA (Abbreviated New Drug Application) showing that the drug to be produced is bio-equivalent to the brand name drug, with the same intended use, dosage form, performance, safety and efficacy. The ANDA path is the path required by all the OTC therapeutic products in the United States (including most of the mouthwashes) (10, 11).

Meanwhile, in Europe, a cosmetic product (according to the European Union Cosmetics Directive) is defined as (12):

Any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odors and/or protecting them or keeping them in good condition.

This clearly matches the description of mouthwashes and places them on the list of cosmetic products in the European market. Being a cosmetic product means that the product is allowed to hit the market without going through any kind of complicated approval process, but that does not mean that the product is free from regulations. As a matter of fact, it is exactly on the contrary; cosmetic products in Europe are subjected to regulations placed by the local law of all the 24 member countries of the European Union through the "EU Cosmetic Regulations" which came into force in 2009.

3. Cosmetic Product Regulations in Europe

To understand the regulations placed on the cosmetic products in the European Union (EU), one must first understand the concept of "single market", which states that, since cosmetic products in the EU move freely between the markets of the member countries, the legislation placed on these products must be compatible with the legislations of the local authorities in the member countries. To achieve this, seven major amendments were introduced to the 1976 EU Cosmetic Directive, which was renamed the "EU Cosmetics Regulation" in 2009 when it was enforced (13, 14).

Another aspect that is essential to understand the EU Cosmetic Regulations is the concept of the so called "responsible person" which states that, the entity that brings forward the cosmetic product into the European market is responsible for the product. Most commonly, the responsible person is the manufacturer of the product or the product's importer if the product is imported from outside the EU. And since the term "manufacturer" or "importer" might involve more than a single individual or company, one person or company must be responsible for ensuring the safety of the product (13, 14).

In order to provide products with immediate access to the market, no pre-market registration is required for

cosmetic products in the EU. Rather than use pre-market approval processes, European authorities prefer in-market surveillance to monitor these products. When a cosmetic product is placed on the shelves of distributors in the EU market, it is assumed that the product has already undergone all the tests required to prove that the product is "safe for human health when used under normal or reasonably foreseeable conditions of use" (article 3 of EU Cosmetic Regulations) and complies with the rest of the regulations (13, 14).

After the placement of the products on the shelves for public use, investigators appointed on the national level can pick it up from the shelves and start investigating these products in official laboratories, where if the necessity arrives, the responsible person must be able to show proof of compliance to all the regulations. To do so, the EU Cosmetic Regulations placed a standardized format for the report compiled for each product. This standardized format was first introduced as a part of the 6th amendment of the EU Cosmetic Directive back in 1993 and was named the Product Information File (PIF), then was modified to include additional information about the safety of the product namely the Cosmetic Product Safety Report (CPSR). The PIF is at the heart of the EU Cosmetic Regulations, and understanding the PIF and especially the CPSR and its components is a huge step in understanding the EU Cosmetic Regulations (13, 14).

The PIF starts with a description about the product, which plays a very important role because this description provides the basis on which this product is perceived as a cosmetic product. The description must also include unique characteristic information about the product such as the product's name, code name, market code or any identification information to relate the PIF to its respective product.

After that, the PIF must include the CPSR (Cosmetic Product Safety Report). The CPSR is divided into two portions. The first portion of the CPSR, namely Part A, contains the cosmetic product safety information. Meanwhile, the second part of the CPSR (Part B) includes the cosmetic product safety assessment.

Part A: This part of the CPSR has information about (13, 14):

1. The Quantitative and Qualitative Composition of the Cosmetic Product: this includes the ingredients from which the cosmetic product is composed and the function of each ingredient and additional information about the source of these ingredients.

2. The physical, chemical and stability information of the product: Under this heading, information about the physical and chemical status of the product is to be mentioned along with the product's stability under the expected circumstances of storage and transport.

3. Microbiological Quality: This is where knowledge about the ability of the product to increase or decrease the microbiological population and in-depth information is included. This information is of immense value especially in cases of products applied in close proximity to the eyes or mucus membranes and even more importantly in cases of products that are expected to be used by children under the age of three and patients/people complaining from a compromised immune system.

4. Impurities, traces, information about packaging: under this heading, the purity of the product is discussed to prove the absence of any prohibited substances as a part of the product, and if any traces of such substances exist, the inevitability of their existence is to be explained along with a report of their ignorable harm if any happens to exist. Along with that, information about the changes of the product due to the packaging material is to be mentioned.

5. Normal and foreseeable use: this part includes the intended use of the product in light of the directions and instructions that are placed on the labelling of the product.

6. Exposure to the cosmetic product: This report includes information about the site and surface area, which will be exposed to the product and the quantity of the product used as well as the duration of exposure along with the frequency of use in addition to the expected population to which the product is targeted.

7.Effect of exposure: information about the effect of exposure of the product and its relevance to the previous set of information is listed.

8. Toxicological profile of the product: An account about the toxicological effects of the product must be submitted, focusing mainly on the toxicological effects related to the skin and the eyes. When noting the toxicological profile of a product, its effects must be studied in relation to all its paths of absorption and determining its Margin of Safety (MoS) so that the product is used without any apparent adverse effects. The source of the information must be mentioned to set aside any concerns.

9. Undesirable effects and serious undesirable effects: In this section, a list of adverse or undesirable effects is to be submitted highlighting extensive adverse effects. Statistical data is preferable to predict the population in risk of developing these effects.

10. Additional Information about the product: Any additional information about the product is to be submitted including but not limited to clinical and non-clinical studies about the product.

Part B:This portion has information about the "Cosmetic Product Safety Assessment" which includes (13, 14):

1.Assessment conclusion: This is a statement that states whether the product is safe or not in relation to article 3 of the EU Cosmetic Regulation depending on all the information already presented in Part A of the CPSR.

2.Labelled warnings and instructions of use: this is where all the warnings about the product is carefully revised, as not to leave any unmentioned on the actual labelling along with checking the accuracy of the directions of use, all according to article 19 of the Regulation.

3.Reasoning: This is where all the reasons used to reach the assessment conclusion are listed, including the studies conducted by the responsible person or by other organizations proving its safety along with information mentioned in Part A of the CPSR.

4. Assessor's Credentials and Approval of Part B: A safety assessor is a person or a team of people who work for the responsible person as an employee or a consultant and is responsible for collecting all the information of the CPSR while ensuring the information is credential and can be used as a reference to prove the safety of the product. The safety assessor must also meet a minimum requirement to qualify as a safety assessor. These qualifications are:

The cosmetic product safety assessment, as set out in Part B of Annex I shall be carried out by a person in possession of a diploma or other evidence of formal qualifications awarded on completion of a university course of theoretical and practical study in pharmacy, toxicology, medicine or a similar discipline, or a course recognized as equivalent by a Member State.(Article 10 of the Regulations) (10, 11).

After the CPSR, the PIF should include information about the ways of manufacturing along with the establishments where such processes are carried out. Also proof of compliance with the Good Manufacturing Practices must be provided.

After that, additional information which supports the claim of the effects capable to be achieved by the product must be provided to ensure that the product is not mislabeled and meets the expectations of the consumers relating to the product's labeling. This can be done through testing the products on humans, especially to the targeted population.

Any information about animal testing for the product or any of its ingredients must be submitted. These tests can be conducted inside or outside of the EU. Animal testing was already banned since 2009 but in 2013, marketing ban was also implemented. If any of the ingredients are proved to be produced after animal testing, the ingredient along with the product is banned from testing and marketing inside the EU. This concludes the PIF (13, 14).

4. Conclusion

So, who is right and who is wrong? Are mouthwashes dangerous enough–If inappropriately used– to be considered a drug and therefore required to go through a lengthy and tedious process of drug approval? Or are they safe enough to be considered a cosmetic product that can be placed instantly in the market and might be later a subject of question? My answer would be "There is no wrong answer." It only depends on the perspective from where you view the issue. Mouthwashes are considered safe and so should be considered a cosmetic product. Meanwhile, mouthwashes can falsely claim drug like indications and so should be a subject of in-depth studies to prove these claims.

Acknowledgments

The authors are thankful to college management for providing the equipment and the facility and IJDRA journal for publishing the article.

Conflict of interest

The authors declare no conflicts of interest.

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