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Prodrugs- A Regulatory Prospective

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ABSTRACT

Prodrugs are unique due to special features in contrast to drugs. The primary goal of prodrug design is to conceal harmful drug features, such as low solubility in water or lipid membranes, low target selectivity, chemical instability, undesirable taste, irritation or pain after local administration, presystemic metabolism and toxicity. The prodrug approach emphasizes on the improvements accomplished by developing the prodrug as compared to the free or parent drug. By determining market exclusivity, assessing viability and finding an optimum development pathway such as that offered by the 505(b)(2) process, developers may find that prodrugs present an ideal alternative to new drug development. There is no guidance on the acceptable development path for prodrugs. A clear understanding of what the classification means in terms of the studies required to support clinical development is needed.

Keywords: Prodrugs, regulatory perspective, patent, FDA Approval, regulatory pathways, challenges

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INTRODUCTION

A prodrug is a pharmacological substance that is administered in an inactive form and is subsequently converted to an active pharmacological agent (drug) through normal metabolic processes (bioactivation) with the main aim of improving the pharmacokinetic properties of the parent drug [1, 2]. The immediate objective of using prodrugs is often to create novel molecules with improved effectiveness, selectivity, and minimal toxicity [3]. Prodrugs can thus be viewed as drugs that temporarily change or remove undesired qualities in the parent molecule by adding specific non-toxic protecting groups. Prodrug techniques entail chemical alterations, the synthesis of novel structures and the development of active substance delivery systems for therapeutic purposes, and prodrug-based therapies or treatment. [4]

Prodrugs are either completely inert or much less active than their active counterparts. Other medicines, in contrast, start working immediately as soon as patient utilize them. They can function right away without having to be changed into other compounds. [5]

Various Examples of prodrug medications that are used to treat different health conditions.

- Clopidogrel (Plavix) is a blood thinner used to prevent heart attacks and strokes. [6]
- Enalapril (Vasotec, Epaned) is a prodrug used to treat high blood pressure and heart failure. [7]
- Azathioprine (Imuran) is a prodrug for mercaptopurine. It is used to alter the immune system in people who have rheumatoid arthritis or have an organ transplant. [8]
- Valacyclovir (Valtrex) is a prodrug of acyclovir (Zovirax). Acyclovir can treat and prevent different infections that viruses cause. [9]
- Valganciclovir (Valcyte) is a prodrug of ganciclovir. It is used to treat and prevent cytomegalovirus (CMV). [10]

The prodrugs have two interrelated objectives. The effectiveness of a drug's action must first overcome several obstacles, and then adverse effects must be inhibited. The design of a prodrug is considered as a lead alteration that overcomes the error in a drug molecule. [11,12]

The prodrug approach is used to overcome biopharmaceutic, pharmacokinetic, or pharmacodynamic challenges, such as poor chemical stability, solubility restrictions, lack of site-specificity, extensive drug metabolism, passing through biological barriers, utilizing endogenous metabolic pathways, toxicity, or compliance challenges (unacceptable taste/odor), all in favour of ideal oral bioavailability and ensuing therapeutic effect [13,14]. Prodrugs are expected to play a significant role in the creation of new medications for a very long time. By substituting prodrugs

for parent drug molecules, there are a variety of possible pharmacological advantages that might result in a safer and more effective medicinal product.

Pharmaceutical regulations play an important role in ensuring the safety and efficacy of the approved drugs in every country. They control both the cost and the quality of pharmaceuticals in addition to the price. The regulations are required both for new developments and already existing products, in order to enhance the state of health [15]. Due to the rising regulatory demands of the pharmaceutical industry, the drug evaluation for the control of drug quality and trade has grown extremely complex. While laws offer a legal basis for drug control, regulatory guidelines and industry standards serve as a foundation for their execution. [16]

Over the past decade, at least 33 prodrugs have been approved by the US Food and Drug Administration (FDA) which accounts for more than 12% of all approved small-molecule new chemical entities. [17]

The present paper outlines the information available through the literature regarding the regulatory framework for the approval of the prodrugs for marketing.

Regulatory perspective of prodrugs

There are two FDA's regulatory pathways for how prescription drugs can be approved or authorized and ultimately reach the market. In basic terms, NDA, also called 505 (b)(1), are for new drugs that have not yet been approved and ANDA's are for generic products [18]. However, there is an additional pathway that's a hybrid between these pathways known as 505(b)(2). [19]

A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). An applicant should submit a 505(b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug. This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.

The 505 (b)(2) pathway provides manufacturers who have certain types of drugs with an opportunity to acquire FDA approval without performing all the work that's required with an NDA. These drugs are not strictly generics but are often not entirely novel new molecular entities either. 505 (b)(2) can be an option for drugs with a new aspect related to indication, dosage form or regimen, strength, combination with other products, or other unique traits. [20]

505(b)(2) submissions can be advantageous because they can often lead to a faster route to approval when compared to traditional development pathways such as 505(b)(1) NDA, while creating new, differentiated products with commercial value. [21]

Difference Between 505(b)(1) and 505(b)(2) Regulatory Pathways

The 505(b)(1) and 505(b)(2) pathways serve different purposes. The 505(b)(1) pathway is used to obtain FDA approval for new drug whose active ingredient(s) have not been approved by the Agency. This is the traditional NDA regulatory pathway which usually requires substantial resources and is a long process. Meanwhile, the 505(b)(2) pathway is intended for new drugs who have similar active ingredients to something that's already been approved. This process generally requires less resources and is much faster than what sponsors go through with the 505(b)(1) pathway. However, both pathways also have unique requirements so it's beneficial to partner with an expert consultant who can guide you through the process. [22]

In today's market availability of numerous first-rate drugs which is underutilized because of their adverse physicochemical and biological side effects. As synthesis of new drug is costly and time consuming but modification of adverse properties is much easier. Utilization of the 505(b)(2) pathway for a prodrug strategy has the potential to not only lead to better therapeutic options but can be beneficial from a regulatory standpoint as well. The previously conducted studies on the drug may be utilized if it falls under the 505(b)(2) pathway. This can potentially expedite the approval process and reduce costs.

In contrast, drugs using the 505(b)(1) pathway can take far longer to be approved and at significantly greater expense. Therefore, when possible, the 505(b)(2) pathway for prodrugs can remove major barriers that the original, parent drugs faced in the development process. [23] This presents many opportunities for prodrug developers, companies must first fully understand the market exclusivity possible, assess the viability of the candidate and determine the optimum development pathway to approval.

Patents play a distinctively important role in the global pharmaceutical industry today.

Patents for prodrugs

Patents play a distinctively important role in the global pharmaceutical industry today. Usually, a patent is often secured for the actual active moiety, and as such, the prodrug is usually outside the literal scope of the patented invention. [24]

Prodrugs are thought to offer a key to safer, more sophisticated and better targeted drugs. Prodrugs provide a beneficial way to extend the lifecycle of a given drug. There are three possible outcomes when creating patent claims for prodrugs.

1. The usual prodrug case, where the active metabolite is already in the public domain and a first patent application has been filed and published covering the same.
2. These are the cases where the actual prodrug has not been developed. However, the parent patent filing claims not only the compounds of the invention, but also, in generic form.
3. In a third scenario both the metabolite and one or more prodrugs are discovered at the same time and included in a single patent filing. [25]

Benefits of the 505(b)(2) Pathway for Prodrugs

- A prodrug that goes through the 505(b)(2) pathway is eligible for three, five, or even seven years of marketing exclusivity, depending on its level of similarity to a parent compound and/or if it is considered an orphan drug [26].
- A prodrug of a previously approved parent drug or compounds as a result of a modification to an innovator drug would be eligible for a 505(b)(2) development approach. The 505(b)(2) process has many advantages for suitable drug candidates and should be considered by drug developers with prodrug programs.
- The regulatory pathway 505(b)(2) can also eliminate the need for most nonclinical studies and extensive safety and efficacy tests. Specifically, a well-defined 505(b)(2) program can often save one to two years of pre-clinical research and five to ten years of clinical research.
- Developers may be able to rely on studies previously conducted on the drug, to which they typically would not have access. This is particularly advantageous for smaller corporations that do not have either the human or financial resources to conduct extensive studies. [27]
- Businesses can save both time and expense in moving a drug to market. Without time-consuming research studies, a drug can gain faster access to the market. New drugs on the 505(b)(1) pathway can take as long as 15 years and cost more than $800,000 before they progress to the marketplace, whereas 505(b)(2) prodrugs can gain approval within 30 months at a significantly lower cost.
- The FDA standards for the safety and effectiveness of the drug remain the same for 505(b)(1) and 505(b)(2).
- The process is low risk because the drug has already been proven to be safe and effective.

CHALLENGES AND CONSIDERATIONS IN PRODRUG DISCOVERY & DEVELOPMENTS

1. Difficulties in synthesis.
2. Greater analytical complexity profiling.

3. Controlling subsequent metabolism and bioconversion.
4. Studies on pharmacokinetics that must examine both the prodrug and the parent drug.
5. Differences across species in prodrug conversion.
6. Genetic polymorphism and drug interactions regarding prodrug converting enzymes.
7. Concerns over the toxicity of the drug and its precursors as well as the released pro-moieties or byproducts.
8. Navigation of the regulatory environment with prodrugs is far from straightforward, particularly when prodrugs of already marketed active drugs are developed.

FDA Approved Prodrugs

Table 1: FDA Approved prodrugs

S.No	Date of approval	Name of Prodrug	Marketed as	Manufacturer
1	25 Jan 2008	*Fosaprepitant (fosaprepitant dimeglumine)*	*Emend [28]*	*Merck Sharp & Dohme Corp*
2	31 Oct 2008	Fesoterodine (fesoterodine fumarate)	Toviaz [29]	*Pfizer Inc*
3	12 Dec 2008	Fospropofol (fospropofol disodium)	Lusedra [30]	Yichang Human well Pharmaceutical Co., Ltd., Hubei, P. R. China
4	7 Oct 2009	Prasugrel (prasugrel hydrochloride)	Effient [31]	*Daiichi Sankyo Co and* Eli Lilly and Company
5	5 Nov 2009	Romidepsin	Istodax [32]	Ben Venue Laboratories, Inc
6	21 Sept 2010	Fingolimod (fingolimod hydrochloride)	Gilenya [33]	*Novartis*
7	19 Oct 2010	Dabigatran etexilate (dabigatran etexilate mesylate)	Pradaxa [34]	Boehringer Ingelheim Pharmaceuticals, Inc.
8	29 Oct 2010	Ceftaroline fosamil (ceftaroline fosamil monoacetate monohydrate)	Teflaro [35]	*Forest Pharmaceuticals, Inc*
9	25 Feb 2011	Azilsartan medoxomil (azilsartan medoxomil monopotassium)	Edarbi [36]	Takeda Pharmaceutical Company Limited and Arbor Pharmaceuticals, LLC
10	6 Apr 2011	Gabapentin enacarbil	Horizant [37]	*GlaxoSmithKline and XenoPort, Inc*
11	28 Apr 2011	Abiraterone acetate	Zytiga [38]	*Janssen biotech*
12	10 Feb 2012; first approval in Germany on 1 Mar 2008	Tafluprost	Zioptan [39]	Thea pharma
13	27 Mar 2013	Dimethyl fumarate	Tecfidera [40]	*Biogen inc*
14	8 Nov 2013	Eslicarbazepine acetate	Aptiom [41]	Sunovion Pharmaceuticals Inc
15	6 Dec 2013	Sofosbuvir	Sovaldi [42]	Gilead Sciences, Inc.
16	18 Feb 2014	Droxidopa	Northera [43]	Camber Pharmaceuticals
17	20 Jun 2014	Tedizolid phosphate	Sivextro [44]	*Cubist Pharmaceuticals, Inc*.
18	6 Mar 2015	Isavuconazonium (isavuconazonium sulfate)	Cresemba [45]	Astellas Pharma US, Inc
19	7 Jul 2015	Sacubitril sodium	Entresto [46]	Novartis
20	4 Sept 2015	Uridine triacetate	Vistogard [47]	Wellstat Therapeutics Corporation.
21	6 Oct 2015	Aripiprazole lauroxil	Aristada [48]	Alkermes Pharma Ireland Limited
22	5 Nov 2015	Tenofovir alafenamide	Genvoya [49]	Gilead Sciences, Inc.
23	20 Nov 2015	Ixazomib citrate	Ninlaro [50]	Takeda Pharmaceuticals U.S.A., Inc.

24	22 Dec 2015	Selexipag	Uptravi [51]	Actelion Pharmaceuticals
25	9 Feb 2017	Deflazacort	Emflaza [52]	PTC Therapeutics
26	28 Feb 2017	Telotristat etiprate	Xermelo [53]	Lexicon Pharmaceuticals, Inc.
27	11 Apr 2017	Valbenazine (valbenazine tosylate)	Ingrezza [54]	*Neurocrine Biosciences, Inc*
28	29 Aug 2017	Benznidazole	Benznidazole [55]	*Roche*
29	15 Sept 2017	Secnidazole	Solosec [56]	Lupin Pharmaceuticals
30	2 Nov 2017	Latanoprostene bunod	Vyzulta [57]	Valeant Pharmaceuticals
31	23 Feb 2018	Benzhydrocodone	Apadaz [58]	KemPharm, Inc.
32	9 Dec 2020	Tozinameran	Comirnaty [59]	BioNTech Manufacturing GmbH
33	4 June 2021	Brincidofovir	Tembexa [60]	Chimerix, Inc.

CONCLUSION

Drugs are either discovered or designed. They are characterized by their biological and physiochemical properties. Some drugs have undesirable properties that can result in an inefficient delivery and unwanted side effects. Prodrug concept is justified because it enables the active drug to overcome the barrier that would impede it from reaching the site of action to exert the required pharmacological activity. Regulatory pathway is discussed in the paper to examine the success of prodrug approach by measuring the number of prodrugs that are currently available in the market for various diseases. But still there is not much documented regulations for the prodrugs.

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