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Life Cycle Management of Drugs - An Extensive Review

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A B S T R A C T

Lifecycle management refers to extend the market exclusivity period. The exclusivity period is increasing the marketing period by extending the patent life. Patenting is common type of protection in the life cycle management of prodrugs. In the worldwide market 10% of the drugs are categorized as prodrugs, hence it indicates that prodrugs have a potential market. Hence major pharmaceutical industries try to protect the chemical entity by taking patent to the already existing drug molecule by minor changes in the dosing, by using fixed dose combinations and by renaming of a marketed product. The regulatory bodies provide five years marketing exclusivity for a new chemical entity from the date of drug approval, orphan drugs attain an exclusivity period of seven years, new clinical study and pediatric exclusivities attain an exclusivity periods of three years and six months respectively from the date of approval. Patent extension may increase the marketing period of a product, and in some cases the manufacturer may reduce the price of the drug which is beneficial to the patient. Hence the present review elaborates effective life cycle management of drugs.

Keywords: Prodrugs, Lifecycle management, Chemical entity, Patent extension.

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1. Introduction

The term ‘‘life-cycle management’’ refers to the practice of brand-name manufacturers seeking to extend the market exclusivity periods for their drugs. Market exclusivity extensions probably achieved through a number of different strategies. Some evergreening strategies propose scant public health benefits, including slight changes in formulation protected by later issued patents , marketing tools such as drug coupons that reduce patients out-of-pocket spending on brand-name drugs, and negotiating settlements with generic companies to prevent challenges to potentially weak or invalid patents. Other evergreening strategies may provide more measurable advantages to patients, such as developing extended-release versions or combination products older versions, even if they lack evidence of comparative efficiency or safety [1-2].

A prodrug refers to a chemically modified inert drug precursor that is administered in an inactive or less than fully active form and then it becomes converted to its active form through a normal metabolic process, such as hydrolysis of an ester form of the drug. Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the gastrointestinal tract. prodrug used to improve how selectively the drug interacts with cells that are not its intended target. This reduces adverse effects of a drug, mainly important in treatments like chemotherapy, which can have severe accidental and unwanted side effects. During the last two decades, there has been a steady improvement in the physicochemical, biopharmaceutical and/or pharmacokinetic properties of pharmacologically active compounds by the discharge of a prodrug strategy. This is predictable that currently about 10% of worldwide marketed drugs can be classified as prodrugs. Aspirin (acetylsalicylic acid) is an historical example of prodrug, synthesized in 1897 by Felix Hoffman (Bayer, Germany), and introduced into medicine by Dreser in 1899. Still, the prodrug concept was purposely used for the first time in the middle of the 20th century by the Parke Davis Company during studies on modification of chloramphenicol structure in order to improve the antibiotic’s bitter taste and poor solubility in water. Result of this work, two prodrug forms of chloramphenicol was synthesized. Chloramphenicol sodium succinate with a good water solubility, and chloramphenicol palmitate used in the form of suspension in children [3-4].

2. Prodrug concept

The Prodrug concept was first introduced by Adrian Albert in 1958 to describe compounds that undergo biotransformation proceeding to eliciting their pharmacological effect i.e. therapeutic agents that are inactive but can be transformed into one or more active metabolites. Schering first introduced the designed prodrug Methenamine. Methenamine releases 6 Eq of antibacterial formaldehyde along with 4 Eq of ammonium ions in acidic urine. Prodrugs can also improve drug targeting, and the development of a prodrug of an existing drug with improved properties may represent a lifecycle management opportunity [5-7].

Product Life Cycle management [9-10]:

Life-cycle management refers to either expanding or prolonging the life of an already approved drug and still the most successful products express a ticking clock to patent expiration and generic competition. However, from the regulatory point, the regulatory strategy differs, depending on the stage on a product's life. Given the long development process life-cycle management should start long before application for the product is filed. At this early stage development of life-cycle strategies can prolong data and market exclusivity, and as a result improves the return on investment for the product. Life-cycle management may contribute to rising costs at a time when government insurance programs are cutting back on important areas of medical coverage, but their impact on costs or health care delivery is not often subject to empirical analysis. In 2006 publication three brand-name pharmaceutical products such as omeprazole, amoxicillin /clavulanate, and metformin whose market exclusivities were extended through tactics such as lawsuits against generic competitors and patents on peripheral aspects of products. Here identified US$1.5 billion in revenue that Medicaid, the US drug insurance program for low- income patients, could have saved if generic alternatives to these three medications had been available and widely used when the patent on the active ingredient expired. Today Patents play a typically important role in the global pharmaceutical industry. Studies suggest that pharmaceutical firms consider patents critical to their efforts to recoup R&D investments, much more so than firms in other industries. This is believed to reflect the difference between the high cost of discovering and testing new drugs and the low cost of reverse engineering generic copies of existing drugs. The flip side of this is that once drug patents expire, generic competition can reduce prices and promote wider access to medicines.

The United States is the world largest market for pharmaceuticals. Understandably, this country provides the largest number of drug related exclusivities of any industrialized country. Many types of exclusivities are available to innovators, while some are reserved for generic companies. These exclusivities are rooted in the amendments to the Federal Food, Drug, and Cosmetic Act, commonly referred to as the Hatch-Waxman Act, passed by Congress in 1984. With these amendments, the U.S. government tried to reach a compromise between research-based pharmaceutical companies and generic companies.

Exclusivities for Innovators

30-Month Stay under the Hatch-Waxman Act

Under these Federal Food, Drug, and Cosmetic Act, all drug products sold in the United States must be approved on the basis of safety and effectiveness by the Food and Drug Administration. Those approved drugs are identified in Approved Drug Products with Therapeutic Equivalence Evaluations, a publication commonly known as the Orange Book. The Orange Book provides the patent information about the drug it list. So this Orange book is an important resource for innovators. This can be used to delay the approval of generic versions of these drugs.

To obtain the rights to sell a new pharmaceutical products, Within 30 days a drug sponsor must submit a new drug application (NDA), patent information for purposes of listing in the Orange Book must be submitted to the FDA. The patents the FDA regards as being covered by the statutory provisions for submission of patent information are:

a. Patents that claim the active ingredient(s);
b. Drug product patents which include formulation/composition patents;

Use patents for a particular approved indication or method of using the product; and certain other patents as detailed on FDA Form 35426 that is, an approved supplement to change the strength, an approved supplement to change the Formulation, or any other patented changes regarding the drug A company wishing to market a generic version of a listed drug must file an abbreviated new drug application (ANDA). The ANDA must show that the proposed product is bioequivalent to an already approved reference listed drug (RLD) in the Orange Book. The ANDA also include one of the four following certifications:

a. There is no patent information listed;
b. There is a listed patent, but it has expired;
c. The listed patent will expire on a stated date; or
d. The patent is invalid or will not be infringed.

If the ANDA filer makes a paragraph IV certification, the patent holder has 45 days to file suit for patent infringement; otherwise, the FDA will approve the generic product. If a suit is filed, the FDA cannot issue an ANDA to the generic company for a 30-month period. However, the FDA will be free to approve the ANDA in less than 30 months if the court rules the patent is invalid and unenforceable or not in- fringed. On the other hand, the delay may also be lengthened if the court considers it necessary. It is therefore critical for patent holders to list their drug-related patents in the Orange Book because such listing can provide an additional barrier to generic entry.or patented changes for patents issued after drug approval.

New Chemical Entity Exclusivity [11]

The new chemical entity (NCE) exclusivity is granted to any new drug containing a new chemical entity. It offers five years of Data exclusivity and data Marketing from the date of the drug's approval.The marketing exclusivity prevents the FDA from approving an ANDA containing the same NCE for the same approved use for five years. The FDA may, however, approve an NDA for the drug product. The data exclusivity prevents the FDA from accepting the filing of an ANDA until the end of the 5th year unless a patent is listed in the Orange Book; in such case, the FDA will accept the filing one year earlier. In the latter case, the end results are advantageous for the patentee because approval of an ANDA typically takes about 18 months. This protection applies only to the first approval of a drug product in the United States that does not contain an active moiety that has been previously approved by the FDA.

Example: Viviane® (Lisdexamfetamine)

• Dextroamphetamine is a known moiety

• Lisdexamfetamine, once enters the body, undergoes a chemical conversion to produce dextroamphetamine

• Lisdexamfetamine is still considered a new chemical entity entitled to 5 years of exclusivity.

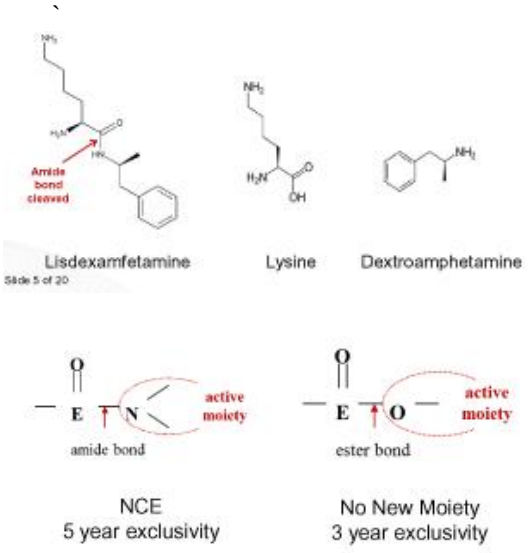

Figure 1

3. Orphan Drug Exclusivity

The orphan drug exclusivity having seven years marketing exclusivity period. This only to drugs proposed for treatment of a "rare disease or condition" or in instances where there is no reasonable expectation of recovering development costs of such a drug in the United States. If two sponsors are pursuing the same drug for the same medical indication, the first one to be approved will obtain the exclusivity. The orphan drug exclusivity prevents the FDA from approving a third-party NDA, a biologic licence application (BLA), or an ANDA for the same drug used for the treatment of the same disease. This exclusivity prevents FDA approval of the same active drug for the same medical indication. However, it will not block approval of the same drug for a different indication, approval of a clinically superior drug, or approval of a drug with a greater safety profile. Furthermore in contrast to NCE exclusivity, there is no restriction on filing an NDA or ANDA on the orphan drug before the expiration of the seven-year marketing exclusivity. In addition to marketing exclusivity, rewards such as research grants, fee waivers for regulatory approval, and tax credits may be provided through the Orphan Drug Act. In order to benefit from these tax incentives, the sponsor must have in- come from sales or royalties from commercial distribution of other products.

Example: Abraxane is a Orphan drug it's having the seven years marketing exclusivity period.

New Clinical Study Exclusivity

This protection provides three years of marketing exclusivity for drug products that depend on new clinical investigations to support new therapeutic claims, even though they do not feature a new active ingredient. After successful submissions of results of new clinical investigations this exclusivity will be granted. It seeks to protect new formulations, new indications (even if same dosage), or other labelling changes of an old drug. Only changes implemented through an NDA or a supplement may benefit from the three-year exclusivity and the three

year period starts from the date of approval from the NDA. Generic companies can also benefit from this protection if they submit their own data in support of their application.

Pediatric Exclusivity

The pediatric exclusivity adds a six-month marketing exclusivity to any existing exclusivity. It operates as a general exclusivity extension added to the end of non-patent exclusivities and it adds six months to the life of patented drug products listed in the Orange Book containing the same active moiety. This additional six-month marketing exclusivity applies only to unexpired patents and exclusivities still in place at the time the pediatric exclusivity is granted. Because the exclusivity is awarded for a given active drug moiety, already approved related drug products containing the same active moiety will also be awarded the protection. Although patent protection is not extended per the FDA acts as if the exclusivity actually had a later expiration date and will not approve ANDAs until the extended date is met.

To be granted the pediatric exclusivity an applicant must successfully complete FDA-requested clinical trials of a drug product in a pediatric population. The clinical study has to be done in accordance with the instructions given by the FDA and the exclusivity will only be possible if the FDA makes the request for such studies in children. However, granting of the exclusivity is not dependent on the success of the study.[14-17]

Example: Adrafinil

a. Adrafinil is a prodrug of modafinil; it is a modafinil family of drug. It's having the standard dose 300mg.
b. Adrafinil once enter the body its converted to Modafinil when metabolized.
c. Adrafinil considered entitled to Six months added to all regulatory and patent exclusivities.

Patent extension

Strategies for patent extension

a. Minor changes in dosing
b. Fixed-dose combinations
c. Metabolites, prodrugs, analogs
d. Renaming

1) Minor changes in dosing [18-19]

Very good example of this type was Aricept used for treating Alzheimer's disease. To extend patent life on Aricept, the manufacturer developed a 23 mg version. Aricept 23 mg failed to show a statistically significant improvement over the previously approved Aricept 10 mg formulation in both primary and secondary outcome measures. Aricept 23 mg demonstrated a higher incidence of adverse events such as nausea, vomiting, diarrhea, anorexia, and fatigue. Aricept 23 mg was approved, despite a lack in superiority over Aricept 10 mg and recommendations of non-approval by two FDA medical reviewers.

Justification of FDA approval:

The 23 mg dose is clearly superior to the 10 mg dose on the cognitive measure. 23 mg dose is very likely to have an effect on overall functioning, despite this not having been demonstrated directly in this study. This is only useful for the manufacturer.At what time generic products become obtainable, the market competition leads to substantially lower prices for both the original brand name product and the generic forms. The time it takes a generic drug to appear on the market varies. Most countries of the world, patents give 20 years of protection. However, many countries or regions, e.g. the European Union and the USA may grant up to 5 years of additional protection for drugs. Generic drugs are generally sold for extensively lower prices than their branded equivalents. Because of one reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents. Companies incur fewer costs in creating generic drugs and are therefore able to maintain profitability at a lower price. The prices are low enough for users in many less-prosperous countries to afford them. Thailand has imported millions of doses of a generic version of the blood-thinning drug Plavix (used to help prevent heart attacks), at a cost of 3 US cents per dose, from India, the leading manufacturer of generic drugs so that Thai peoples benefited.

2) Fixed Dose combination [20-23]

Fixed dose combinations are two or more drugs combined together in one pill. Fixed dose combinations are frequently more expensive than their components and it provide less flexibility in dosing options.

Example:

Fosamax plus D (Vitamin D), a bisphosphonate is patent-protected and costs six times as much as its generic, alendronate. Bisphosphonates must be taken with a calcium supplement. However, calcium supplements are often formulated with Vitamin D.Since a patient must still take additional calcium with Fosamax plus D, the total tablet burden remains the same. Therefore, the "plus D" component is of no use beyond marketing the product. In February 2013 meeting the PBAC's Drug Utilisation Sub-Committee (DUSC) spoken it concern about emerging trends with fixed-dose combination (FDC) products, including a higher proportion of patients starting on FDCs before trialling individual components, and increased use of FDCs without a comparable decline in prescribing of indivisual components. The profit of FDC products have been promoted by sponsors as improved adherence, convenience and reduced cost to the consumer. Whereas evidence to support adherence benefits of FDC products. Some examples of fixed dose combinations are Caduet (atorvastatin/amlodipine) or Exforge (amlodipine/valsartan)

Figure 2

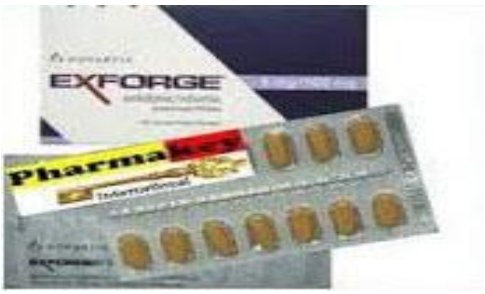

Figure 3

3) Metabolites, prodrugs, analogs

Prodrugs, when metabolised in the human body, result in an active ingredient. Metabolites are often patented along with the compounds containing the metabolite. Tamoxifen (Nolvodex 20 mg) tablet an estrogen receptor antagonist in breast tissue via its active metabolite, 4-hydroxy tamoxifen. Tamoxifen is standard endocrine therapy for hormone receptor breast cancer in pre menopausal women, and is also standard in post menopausal women even if aromatase inhibitors are also frequntly used that setting. Patients with alternate forms of the gene CYP2D6 (also called simply 2D6) may not receive full benefit from tamoxifen because of too slow metabolism of the tamoxifen prodrug into its active metabolite 4-hydroxytamoxifen [24-27].

4) Renaming

A new indication can extend the patent life of a drug. Some drugs are renamed upon approval for a new indication, allowing for patent extension. Fluoxetine is the generic version of both Prozac and Sarafem. After Prozac lost patent exclusivity, Sarafem provided new life to the patent. Fluoxetine could only be substituted for Prozac, NOT Sarafem, because the indications for which the drugs were approved were different. Now that Sarafem has lost patent exclusivity, both drugs are available as generics.

4. Conclusion

Before expiration of marketing exclusivity period, manufacturer will further extend the patent life by using patent extension strategies. The patent extension may increase the marketing period of a product, and in some cases the manufacturer may reduce the price of the drug which is beneficial to the patient.

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