

COMPLEX GENERICS: OPPORTUNITIES & CHALLENGES

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REVIEW ARTICLE

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ABSTRACT

Now a day, big pharmaceutical companies with sustainable revenues are more interested in complex products to minimize competitions. In line with the originator companies, many generic companies are also focusing on complex products, either a specialized dosage form of already approved product or generic version of approved specialized products i.e. complex generics. Inherent 'complexity' involved in such specialized products insulates fierce competition and are considered as potential opportunities with high revenues. U.S FDA approved specialized products with proprietary technologies, such as nanoparticles, microspheres or liposomes are most promising dosage forms. These dosage forms are proven to be safer, while providing better efficacy as compared to historically approved simpler dosage forms, by ensuring targeted delivery of drug towards the infected cells. In the era of recent scientific advances, many generic companies are investing in abundance for the development of complex generics in the segment of targeted delivery systems like liposomes, therapeutic nanoparticles for treatment of various diseases such as cancers, inflammatory disorders, infectious and cardiovascular diseases. Despite potential opportunities reside in developing complex generics in terms of safety, efficacy and high revenue, no authoritative article has enlightened the challenges relating to regulatory, scientific, clinical, intellectual property (IP) and commercialization of complex generics. The present article makes an attempt to address the challenges involved in a regulatory approval of such complex generics involving potential opportunity with low competition.

Keywords: World Health organization (WHO); Low molecular weight heparins (LMWH); Intellectual Property (IP).

INTRODUCTION

Generics

A generic product is a medicine that can be prescribed as a substitute for the originator product because the bioequivalence has been demonstrated. The official WHO definition of generic product, i.e., interchangeable multisource pharmaceutical product, clearly recalls this aspect. To be "generic", a medicinal product must preliminarily exhibit the same qualitative and quantitative composition of active substances and the same dosage form as that of the originator. However, pharmaceutical equivalence is not enough: the generic product must be bioequivalent to the reference product, that is, it must exhibit the same bioavailability³ or the same therapeutic effect. FDA points out that therapeutic equivalence comes out from a demonstrated pharmaceutical equivalence plus bioequivalence³. Only after confirmatory bioavailability studies the generic product can be used as an interchangeable medicine. (1)

Thus, the definition of "generic" implies dosage form sameness; however, in practice exceptions are frequent. For example, the substitution of a product in tablets with a bioequivalent product in hard capsules does not seem illogical. However, an objection might be made by the patient, who, despite the declaration of his centric role in drug administration, is pushed to accept a substitution prescribed for cost reasons. Generic substitutions often create complaints and reconsiderations of approved products, partly because it is not only the originator product that is substituted, but often generic products are substituted with other generic ones.

Complex Generics

A complex generic product is a medicine that can be prescribed as a substitute for the originator specialized product because the bioequivalence has been demonstrated; however it is not as simple as generics to get manufactured. To be "complex generic", a medicinal product must preliminarily exhibit not

only same qualitative and quantitative composition of active substances and the same dosage form as that of the originator, but also lots of various other parameters are considered to prove “sameness”, e.g. physical characterization like particle size distribution, drug entrapment, particle morphology, physical state of entrapped drug, drug release, viscosity, globule size, zeta potential, excipient characterization etc. Along with formulation development challenges, other barriers like strong intellectual property barriers, citizen petitions, facility issues, unavailability of literature, ambiguity in terms of bioequivalence/clinical trial protocol to design, structural characterization, device sameness, stability of formulation according to regulatory guidelines and to establish in-vitro in-vivo equivalence are faced during development of complex generics. Complex generics are classified based on possibility of existing complexity at various stages of product development. In some instances complexity may exist in nature of active itself i.e. LMWH, peptides, complex mixtures, natural source products. It may even exist in formulation such as Liposomes, Nanoparticles and iron colloids. It may even happen to exist in route of delivery i.e. locally acting drugs. In most of the cases, such specialized originator product involves complex IP barrier, which requires strong business support to move forward with costly litigation approach. Other complexity may also exist in drug-device combinations related to DPI, MDI, nasal spray and transdermal delivery systems.

Complex generics compete on the basis of their unimaginable cost, since the bioequivalent version receives market authorization using the pharmacological and clinical data produced by the originator. Cost is strictly related to the availability of raw materials, clinical trial to perform in case of local acting drugs, to establish sameness characterization of complex actives.

Complex Delivery System as Strategy

Complex delivery systems are often being called as targeted drug delivery systems (TDDS). TDDS can be parenterally administrable therapeutic nanoparticles; those typically comprise an active ingredient together with organic or inorganic biomaterials, and range

from 50 to 200 nm in diameter. Several classes of therapeutic nanoparticles, commercially available or in development include liposomes, albumin-drug complexes and polymeric nanoparticles.

The earliest specialized formulation approved by U.S. FDA was Doxil® in 1995, for treatment of Kaposi’s sarcoma. Doxil® is a long-circulating unilamellar nano-sized liposome containing doxorubicin. (2) More recently, there has been interest in targeted delivery composed of biodegradable polymers, which offer long circulation characteristic of liposomes together with controllable drug-release kinetics mediated by polymer biodegradation. (3) After parenteral administration, these formulations can selectively accumulate in particular tissues or body locations, thereby enhancing the delivery of the drug payload to the site of disease.

All the targeted delivery systems get access to diseased tissue through the enhanced permeability and retention (EPR) effect. The EPR effect occurs in tumors, sites of inflammation and other diseased body tissues where the blood vessels are either disrupted or not fully formed, and as a result are leakier than normal vessels. The EPR effect allows nanosystems to pass readily from the blood vessels into the tumor or inflamed tissue and to be differentially retained while the drug is released from the particles. It has been demonstrated that, as a result of this effect, therapeutic nanoparticles accumulate in a particular target tissue location and deliver more of the drug to the disease site over a longer period of time than a conventional drug product administered as a solution.

An ideal targeted delivery system must be precisely optimized to prevent its removal from the circulation by the body’s defense systems before it has a chance to reach its target, to maximize trafficking to the desired location and to minimize accumulation at sites where the drug may cause side effects. Like conventional pharmaceutical products, it is necessary to develop a robust and well-controlled manufacturing process that produces desired particle/globule size of uniform quality from batch to batch; however, manufacturing of complex generics has additional complexities

necessitating precise control over critical parameters.

Patenting of former delivery systems is a complex, yet uniformly precise, platform for developing new drugs. Because of the complexity of these delivery systems, opportunities abound for obtaining momentous patent protection. For example, a delivery system success will vary by polymer type, polymer size, active, and mix of polymers, surface characteristics, targeting ligands, content of drug encapsulated, and concentration of dispersion or manufacturing process. Each one of those factors can have a considerable effect on the behaviour of the formulations in a biological system. The combination of many factors leading to many outcomes provides numerous grounds for patentability. As they do for new chemical entities, patenting opportunities exist in the discovery phase of identifying new therapeutic delivery systems. Later in the product development cycle, additional opportunities exist to patent clinical-stage uses and dosing schedules. These patent opportunities can be combined with existing IP to protect a new drug entity or can be the basis of a new patent estate protecting an existing active pharmaceutical ingredient or product.

Proving “sameness” by establishing equivalence in various physical and chemical characteristics of the complex generic product with the originator product is crucial for regulatory approval. Sameness characterization also involves in-vivo performance, such as, drug release kinetics, target tissue accumulation, pharmacokinetics (clearance and volume of distribution). These crucial parameters of complex generic product are dependent on numerous formulation and process parameters. In addition, many aspects of developing and manufacturing complex generic products involve extensive know how to optimize the product. In nutshell in light of all above understandings; it is very difficult to make a generic rather a complex generic equivalent to that of originator in spite of knowing all the formulation related facts of innovator through intellectual property, in addition to this it becomes utmost difficult to overcome the IP related facts & develop the delivery system, just by challenging the grounds on invalidity. (4)

Manufacturing Challenges

Particle size plays key role in all kinds of complex generic formulations. Although various techniques are available for reduction in particle size, adoptability of such techniques should be established based on vast experimental knowledge for the particular drug molecule. In the case of liposomes or nanoparticles, very small changes to the manufacturing process can result profound difference in product characteristics. Changes to the manufacturing process of liposomes/nanoparticles can affect the drug content of the particle and the size and chemical makeup of the polymer component of the particle.

Structural parameters, including the liposomes/nanoparticles surface properties and sizes, and the spatial arrangement of the polymer, lipid, bioactive and targeting ligand, are determined by the manner in which the particle/vesicle assembles. Changing any of these factors may alter critical properties, such as the distribution of the particles in the body or the rate at which the drug is released from the particle, thereby resulting in a different clinical outcome. Because the analytical tools necessary to characterize these complex delivery systems and their specific biological effects are not yet well established, a generics company may not be able to demonstrate the degree of sameness of a liposomes/nanoparticles product required for FDA or other regulatory approval. As such, the manufacturer of the trade or ‘pioneer’ drug could have great exclusivity advantages by keeping their final manufacturing process a trade secret or by obtaining process patents. If a generics company cannot practice the same manufacturing process, the generic product probably does not have the same therapeutic nanoparticle. Simply put, because the FDA requires that a generic product be the “same,” then without the same process, the generics company will face considerable difficulties producing the same product. (5)

Regulatory with IP challenges

Stringent regulatory requirements exist for the entry of complex generic. **Table 1** lists the currently approved nanoparticle and liposomal products in U.S. market.

Table 1: Current approved nanoparticle, microspheres or liposomal products in USA

Trade Name	Generic Name	Date approved	Patents listed in OB/ Technology Patents	P-IV Filing	Generic équivalent
Doxil®	Doxorubicin-Liposomal	1995	No unexpired Patents	No	Yes
Depocyt®	Cytarabine-Liposomal	1999	US 5, 455,044 (Expiry: May, 2013); US 5, 723,147 (Expiry: March, 2015)	No	No
Ambisome®	Amphotericin B	1997	US 5874104 (Expiry: Feb, 2016); US 5965156 (Expiry: Oct, 2016)	No	No
Abelcet®	Amphotericin B-Liposomal	1995	US 5616334 (Expiry: April, 2014); US 6406713 (Expiry: June, 2019)	No	No
Amphotec®	Amphotericin B-Lipid based	1996	No unexpired Patents	No	No
DepoDur®	Morphine-Liposomal	2004	US 5, 723,147 (Expiry: March, 2015); US 5, 807, 572 (Expiry: Sep, 2015); US 5, 891,467 (Expiry: Jan, 2017); US 5, 931,809 (Expiry: Jul, 2015); US 5, 962, 016 (Expiry: Jan, 2017); US 5, 997,899 (Expiry: Sep, 2016); US 6, 171,613 (Expiry: Oct, 2016); US 6, 193,998 (Expiry: Sep, 2016); US 6, 241,999 (Expiry: Sep, 2016).	No	No
Daunoxome®	Daunorubicin-Liposomal	1996	No unexpired Patents	No	No
Abraxane®	Paclitaxel-Nano-suspension	2005	US 7, 820,788 (Expiry: March, 2024); US 7, 923, 536 (Expiry: Dec, 2023); US 8, 034,375 (Expiry: Aug, 2026); US 8, 138,229 (Expiry : Dec, 2023); US 8, 268,348 (Expiry: Feb, 2026); US 8, 314,156 (Expiry: Dec, 2023); US RE 41,884 (Expiry: Aug, 2016)	No	No
Invega Sustena®	Paliperidone Palmitate-Sub-micron suspension	2009	US 5, 254,556 (Expiry: April 2014); US 6, 077,843 (Expiry: Nov, 2017) ; US 6, 555,544 (Expiry : May, 2019)	No	No
Risperdal Consta®	Risperidone-Microsphère	2003	US 5, 688,801 (Expiry: May, 2015); US 5, 792,477 (Expiry: Nov, 2017); US 5, 916,598 (Expiry: Nov, 2017); US 5, 965, 168 (Expiry: May, 2014); US 6, 110, 921 (Expiry: May,	No	No

			2014); US 6, 194,006 (Expiry: June, 2019); US 6, 667,061 (Expiry: Nov, 2020); US 7, 547, 452 (Expiry: May, 2014); US 6403114 (Expiry: Nov, 2017); US 6596316 (Expiry: June, 2019); US 6379703 (Expiry: June, 2019); US 6368632 (Expiry: May, 2014)		
Trilipix®	Choline Fenofibrate-Nanoparticulate	2008	US 7, 259,186 (Expiry: Jan, 2025)	Yes	Yes
Faslodex®	Fulvestrant-intra muscular-micellar	2002	US 6, 774,122 (Expiry: Jul, 2021); US 7, 456,160 (Expiry: Jul,2021); US 8, 329,680 (Expiry: Jul, 2021) ;	Yes (AND A withdr awn)	No
Exparel®	Bupivacaine-Liposomal	2011	US 6, 132,766 (Expiry: Nov, 2013); US 8, 182,835 (Expiry: Sep, 2018)	No	No

*Information available in public domain

Despite the fact that many of these products lack patent protection today and that several generate worldwide sales of \$500–1000 million, most of these products has no generic equivalent. (6) In fact, the FDA has never approved parenterally administered complex generics except in the recent past for liposomal doxorubicin. No generics company has even attempted to seek approval for a generic form of a patent-protected nanoparticle product, and thus there has not been any patent litigation resulting from a generics challenge (that is, a “paragraph IV challenge”). In essence, the technical and manufacturing complexity, difficulties in demonstrating bioequivalence and regulatory challenges result in longer and more expensive development pathways, which are incompatible with most generic drug business models.

The two major regulatory difficulties for the development of Complex generics are (i) showing bioequivalence and (ii) FDA requirements for parenteral drug products. For a generic drug company to avoid doing full clinical trials of safety and effectiveness, they must show that, among other things, the generic product is bioequivalent to the pioneer product that it references and relies on for approval. For typical, oral, small-molecule products, this bioequivalence is easily shown by dosing

healthy volunteers and measuring and comparing the mean area under the plasma concentration curve and maximum plasma nano concentration of the drug and then calculating the 90% confidence interval for the ratio of those mean responses. If that confidence interval is within 80–125% of the pioneer product for those parameters, the generic product is said to be bioequivalent. In the case of Complex generics and other locally acting drugs, the standard approach to the evaluation of bioequivalence is not sufficient to show sameness with respect to rate and extent of absorption of the active pharmaceutical ingredient at the site of action. To directly demonstrate equivalent drug concentration at the site of action, a prospective generic company would have to confront several issues. First, it would need to test the generic product in individuals with the target indication because the EPR effect and the product bio-distribution would be different in healthy individuals. (7)

Moreover, for most anticancer drugs, testing in healthy volunteers is not feasible because of the drugs' toxicity. Second, non-invasive assays for quantifying active pharmaceutical ingredients or complex delivery systems in most tissues do not exist. No assay currently exists to measure the drug release that occurs at the tissue site as

opposed to other areas in the body. In principle, the possibilities exist of sampling the target tissue and analyzing it for the concentration of encapsulated complex generics and active in it. This possibility is only theoretical because the FDA has never accepted this type of data for a generic product; at least not before 2 years or so.

Assuming that the necessary techniques to do this type of work could be developed (as these techniques do not currently exist), the cost and timing to conduct such testing could be prohibitive for most generic manufacturers or create a cost structure for a generic drug that would make it difficult to set the price below the proprietary medicine. A company would have to recruit patients, possibly conduct an invasive procedure on the patients, and develop new and complex analytical methods. A recent draft guidance relating specifically to abbreviated new drug applications for Doxil, a passively targeted nanoparticle, sets a very exacting standard. (8) The guidance states that the generics company should conduct clinical studies in cancer patients and assess bioequivalence based on analysis of both free doxorubicin and liposome-encapsulated doxorubicin. It further states that the pivotal clinical study should use test product produced using the proposed commercial scale manufacturing process - a far more stringent requirement than the 1:10 scale conventionally employed for bioequivalence studies. Moreover, it is recommended that the proposed generic product contain the same lipid excipients produced by the same synthetic route as the reference product, and that the generic product be manufactured using the same process as the reference product. Lastly, the generic product should be equivalent with respect to a broad array of physicochemical characteristics, including liposome composition, physical state of the encapsulated drug, the liposome internal environment, morphology, lipid bilayer fluidity, size distribution, surface chemistry, electrical potential and charge, and *in vitro* drug leakage under a variety of conditions. (4) The FDA will likely review each nano encapsulate products on its own and determine the recommended tests on an individual basis. For nano-concentration particles/globules that localize to a greater extent than Doxil, the FDA may also require a showing of drug and nano encapsulated product

concentration at the site of action. The combination of these factors makes for an uncertain, expensive and daunting development route for complex generic equivalents to originators.

Communication with Regulatory authority

Meeting with FDA is mandatory because pre-ANDA of Complex drugs is not covered by GDUFA. The process needs to be initiated by sending a pre-ANDA meeting request through OGD genericsdrugs@FDA.hhs.gov. Evaluation of the ANDA will start after assigning the project to a reviewer. Information on product necessities can also be done through control correspondence with FDA. Once meeting request is accepted by FDA may happen with schedule meeting of grant or denial. If the meeting request is denial, may be possible with a control correspondence response to specific questions will be provided. If meeting schedule is accepted by FDA, then applicant/or requester needs to prepare the meeting package at least 4 weeks before meeting scheduled and send it to FDA. Final meeting needs to be thoroughly questioned with all kinds of challenges with regard to information needs to be generated in comparison of RLD. (2) That is the reason why procuring information from FDA in order to make the complex generic equivalent that of innovator/RLD is also a challenging task ahead after so many communications with FDA.

Intellectual Property

The Hatch-Waxman Act (1) also created a delicate balance between the rights of generic firms and research-based firms by rewarding exclusivity (Figure 1) to the pioneer company for discovering new drug ingredient and going through the vigorous FDA regulatory process. As a result of Hatch-Waxman Act, the FD&C Act requires that, among other things, one of the following four certifications be made when filing an ANDA or 505(b) (2) purposes:

Para I: That such patent information has not been filed.

Para II: That such patent has expired.

Para III: The generic drug will not go on the market until the patent expiration date passes.

Para IV: The patent in question is invalid, unenforceable, or will not infringe by the manufacture, use, or sale of the generic product.

A Paragraph IV certification is filed on the grounds of either the patent being is invalid only; as no scope exists to non-infringe or overcome the patent by the ANDA or 505(b) (2) filer. (10) FDA approval to market the generic version is automatically postponed for 30 months. The 30-month stay was meant to allow

time for the patent holder to litigate and resolve the PIV issues. In case the pioneer drug company files a lawsuit within the stipulated time period then a lengthy and complicated legal process begins which might delay the generic drug entry for another four to five years on an average, and thereby preventing the access of generic drugs at a lower price.

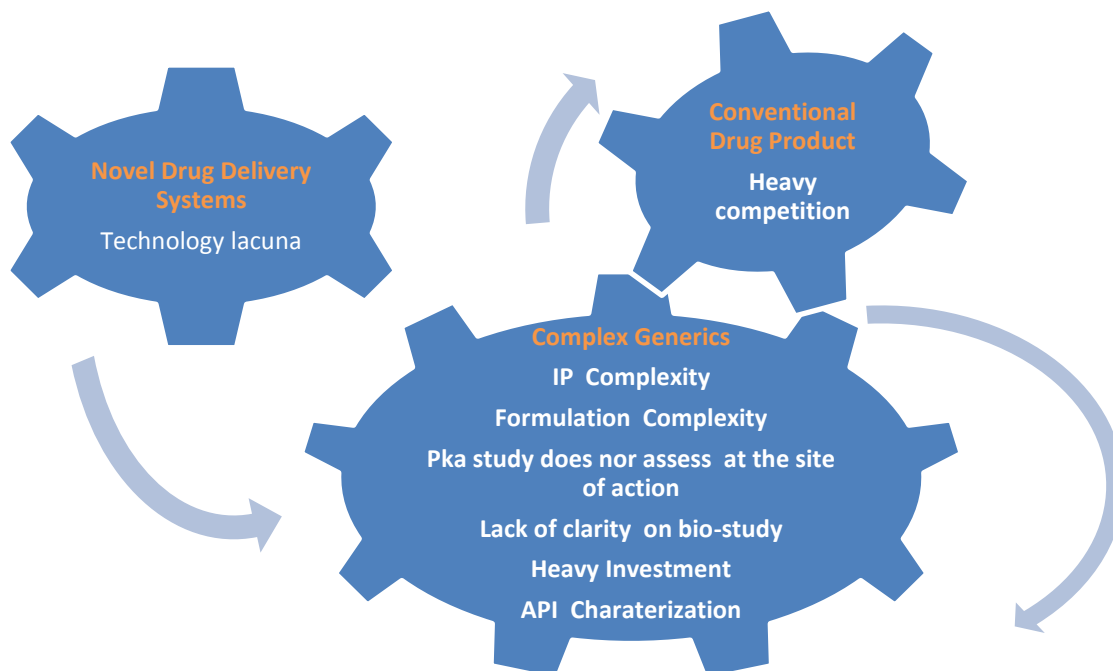


Figure 1: Market exclusivity: complex formulations versus conventional drug product.

A generics company could attempt to circumvent the FDA's requirements for parenteral drug products by filing a Section 505(b)(2) new drug application (NDA). Such a filing would not require the 'same' formulation. In the case of complex generics a 505(b)(2) applicant would need to conduct new effectiveness trials in order to ensure that the new formulation would deliver the same quantity of drug to disease sites over the same time course, or produce the same drug exposure to non-diseased tissues. Because conducting effectiveness trials is the most expensive part of product development, this 505(b)(2) regulatory route is unlikely to be economically viable for the generics drug industry. It is also other way around; suppose if it is successful in conducting the trials & getting the product approval will definitely lead to at least 80 % of market share. In addition, products approved through the

505(b) (2) route are not directly substitutable in the pharmacy for the branded product. Hence, a 505(b) (2) generic product would need to be marketed and sold by a sales force, which most generics companies do not have. (10)

However to make or develop complex generics becomes uphill task due to presence of various aspects of complexities existed at various stages of product development starting from active pharmaceutical ingredient characterization to bio-analytical development is protected by intellectual property or some other way of block through citizen petition. Thereby the only possibility to have early launch of complex generics lies within the secret fact of how strong we could be able to challenge the patents listed in orange book on invalidity grounds (Table 1: shows various aspects of intellectual property).

Opportunities

A complex generic formulation will also have to meet the FDA's stringent requirements for drug products intended for administration. The FDA regulations state: Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. (4) Essentially, this requirement means that a generic company seeking to make a drug product for parenteral use, such as a liposome or nano system, must develop the same formulation, both qualitatively and quantitatively, as that of the pioneer drug; that is, with certain exceptions, it must contain precisely the same ingredients in precisely the same amounts. The recent guidance from the FDA on liposomal doxorubicin suggests that even changes in preservative, buffer or antioxidant may not be accepted for generic liposomes.

This level of sameness contrasts with typical oral formulations. For generic oral products, a generics company can substitute a wide variety of excipients and change their concentrations as compared to the pioneer product in light of IP related facts on that product. Generics companies also often change the excipients in a formulation because the manufacturer of the pioneer drug has a formulation patent and the generics company is looking to circumvent this patent. A generics company's ability to switch excipients in oral products often limits the value of formulation patents for oral products. The issue for the pioneer drug company is typically that broad formulation claims can be challenged on invalidity grounds and narrow formulation claims are often circumventable. In contrast, because of the FDA's requirements for complex formulation, patents for complex products have a much greater value than formulation patents for an oral product. For example, a pioneer drug company could have a patent claim narrowly

covering a nanoparticle formulation, which a generics company could not circumvent. Importantly, however, if this claim covered FDA-approved complex formulations, a generics company would have to develop an identical product with the exact same polymers and the exact same drug, all in the exact same proportions. Based on the FDA guidance on liposomal doxorubicin, it is now apparent that, at a minimum, the generic liposome would also have to match the pioneer product in state of encapsulated drug, internal environment, particle/globule morphology, particle/globule size distribution, polymer orientation, electrical surface potential and drug release. (4) Regulations for more complex delivery systems could have even more rigorous regulatory requirements including clinical outcome data. An attempt to circumvent the claim by substituting a different polymer or slightly reducing the concentration of a particular polymer would not be allowed for a complex generic. Thus, the combination of even a very narrow composition or process patent claim with the FDA's general requirements for parenteral drug products and the heightened requirements for advanced or complex delivery systems can result in a significant and long exclusivity period. Even broader patent claims could also be obtained for additional market protection, as described above.

Notes

1. Hatch-Waxman Act is nothing but called as The Drug Price Competition and Patent Term Restoration Act of 1984, usually referred to as the Hatch-Waxman Act. The informal name comes from the Act's two sponsors, representative Henry Waxman of California and Senator Orrin Hatch of Utah. It was designed to promote generics while leaving intact a financial incentive for research and development. It allows generics to win FDA marketing approval by submitting bioequivalence studies (as opposed to clinical data, which is costlier to compile). This act provides the process by which would-be marketers of generic drugs can file Abbreviated New Drug Applications (ANDAs) to seek FDA approval of the generic by allowing 180 day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts. It

also grants a period of additional marketing exclusivity to make up for the time a patented pipeline drug remains in development. This extension cannot exceed five years, and it is in addition to the 20 years exclusivity granted by the issuance of a patent. Another provision of the Hatch-Waxman grants a 30-month stay to drug companies that file suit against generic manufacturers that challenge their patents.

2. A reference listed drug (RLD) under (21 CFR 314.94(a) (3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. It is a reference standard to which all generic versions must be shown to be bioequivalent.

3. Bioavailability (BA) is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation. Bioequivalence (BE) refers to pharmaceutically equivalent drug products where the rates/extents of bioavailability of the actives are not significantly different under suitable test conditions. In other words, this is a comparison of two or more products with respect to their bioavailability.

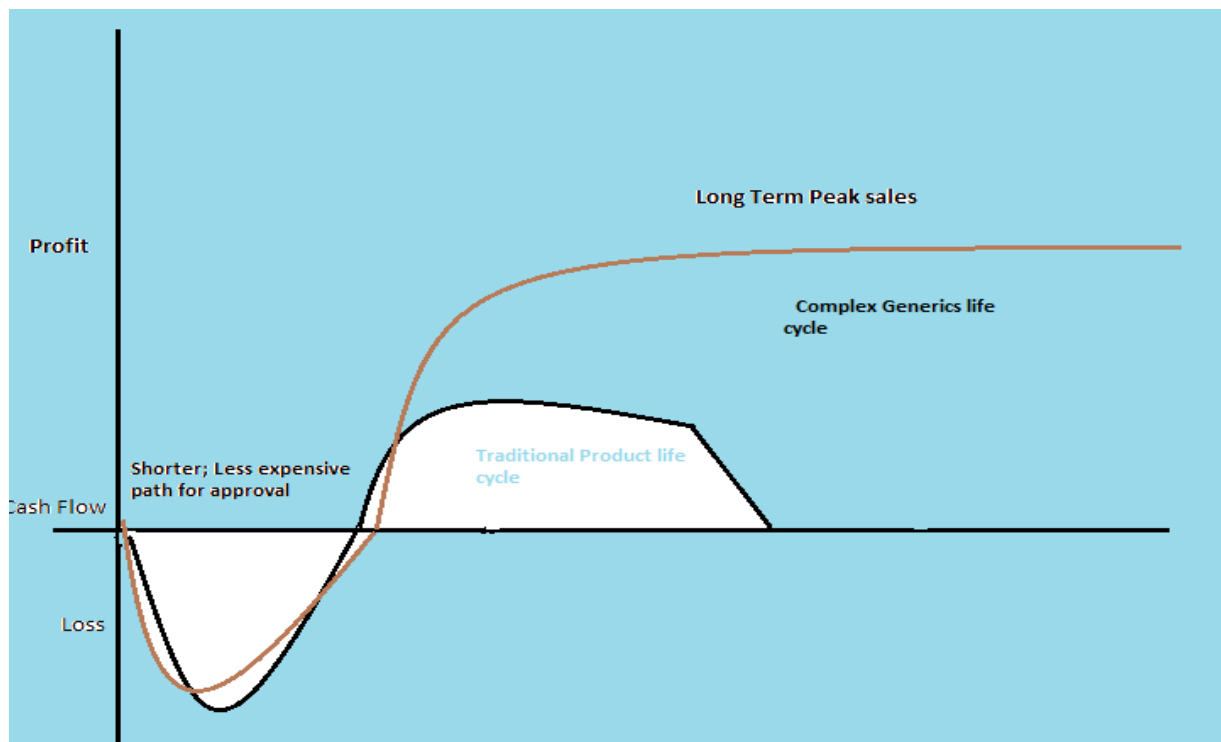


Figure 2: Drug development economics: traditional versus therapeutic complex formulations

CONCLUSION

In order to maximize and sustain the revenues from their products, pharmaceuticals companies work out strategies to extend patents and stifle generic competition at the outset of product life cycles. This kind of life-cycle management is not limited to patent strategies, but also extends to an entire range of practices aimed at limiting or delaying the entry of a generic product onto the market leading to anti-competitive consequences. Marketing of generic products can be delayed through various means in which

generic companies and innovator drug makers are either pitted against each other or work hand in hand or kind of adopting the development of proprietary products such as complex delivery systems.

The stockpiling of patents include, but are not limited to, patenting of methods of treatment, delivery profiles, packaging, dosage regimen, dosing range, dosing route, combinations, method of reducing side effects etc. The list for which pioneer companies rush for obtaining a patent to thwart the generic entry is quite

exhaustive. (11) Complex generics such as liposomes, nanoparticles, targeted delivery systems offer the potential to dramatically improve the effectiveness and side-effect profile of new and existing drugs. In addition, this new drug class presents equivalent or possibly greater challenges for generic drug entry than other types of pharmaceutical products, including biologics. The combination of scientific, patent, know-how and regulatory issues makes the development of a generic more complex, very difficult and inconsistent with the generics business model.

Pioneer drug companies have the opportunity to obtain strong patent protection, which can maintain market exclusivity for the full patent term and potentially beyond patent expiration due to the scientific, manufacturing and regulatory hurdles confronting the development of novel complex delivery systems. If successful, this opportunity will fundamentally change the pharmaceutical business model by reducing or avoiding the sudden revenue fall-off for successful proprietary drugs that confronts the industry today (Figure 2).

The same will also be applicable to all generic followers to adopt this strategy & have targeted for sustainable business using development of complex generics strategy.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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