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# Generic Drug Access In Global Scenario

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**Abstract:**

In the present scenario generic drugs have an important role in pharmaceutical market. Generic drugs are bioequivalent to brand drugs and are much cheaper as compared to brand drugs because of no R&D cost and minimum marketing expenses, hence accelerating competition in pharmaceutical drug market. The applicant has to file ANDA with FDA to get generic drug approval. There are hurdles which delay the timely introduction of generic drugs into the market: use of authorized generics, continued misuse of the Citizen Petition process, the use of Free Trade Agreements and the patent reform. Still there is room for growth, because generic market is undergoing significant change, with intense merger and acquisition activity, a raft of upcoming patent expiries and new legislations being enacted to promote generic prescription in the major markets.

**Key Words:** Generic drug , Hatch-Waxman Act, ANDA, Para IV certification, Authorized generics

## Introduction:

A generic drug is simply a copy of innovator/brand name drug and is bioequivalent to a brand name drug with respect to pharmacokinetic and pharmacodynamic properties. Generic medicines must contain the same active ingredient at the same strength as the innovator drug product and are required to meet the same pharmacopoeial standards, but often have different inactive ingredients. Therefore, generics are assumed be identical in dose, strength, route of administration, safety, efficacy and intended use.[1]

Trademark laws prohibit a generic drug from looking exactly like other drugs on the market.[2] After all; brand-name companies have made distinctive colors, shapes, and sizes part of their sales strategy.

Generic drugs usually cheaper than the innovator drug because of the following reasons:-

1). No cost of identification and isolation of New Chemical Entity (NCE),

2). No cost of research and development,

3). Minimum marketing cost because branded drug is already approved as safe and effective.

A generic drug can be produced for the drugs:

1) Where the patent has expired;

2) Which have never held patent;

3) In countries where a patent(s) is/are not in force;

4) Where the generic companies certify that the branded companies' patents are either invalid, unenforceable or will not be infringed.

Hence, pharmaceutical companies may produce a generic drug when patent expires on the innovator drug. The expiration of a patent removes the monopoly of the patent holder on the drug sale licencing.[1]

**The comparison of generic and brand drug is given in the table 1:** [1, 2, 3, 4, 5]

## History of generic drugs

The generic drug history can be traced back to mid-1960s, when an effort was made by the Government to prove safety and effectiveness of the pharmaceuticals manufactured prior to 1962. In 1962, the National Research Council of the National Academy of Sciences, under the Drug Efficacy Study Implementation (DESI) program reviewed more than 3,000 products. Any new generic had to go through the same investigational trials as any other drug, even if its ingredients were identical to an already approved brand-name drug. Companies also had to wait for the brand name patent to expire before they could even the testing required to produce a generic. *The milestone often acknowledged as the start of the modern generic pharmaceutical industry was the passage of the Drug Price Competition and Patent Restoration Act in 1984, commonly called Hatch-Waxman Act*. This act permitted manufacture to file an Abbreviated New Drug Applications (ANDAs) for generic

version of all post-1962 approved pharmaceutical products (all non-antibiotic drugs).[6] In addition, this act reversed a 1984 ruling and allowed the generic manufacturers to begin the test required FDA approval before the patent in the innovator drug had expired.

Those changes increased the probability that a generic copy would become available after patent expiration and reduced the average delay between patent expiration and generic entry from more than 3 years to less than 3 months. This act also increased the amount of time a company could hold an exclusive patent on a new drug.[7] Thus, brand-name drug companies have tended to litigate aggressively to extend patent protection on their medicines and keep the generic versions off the market, this process referred to by critics as "evergreening".[1]

This new law made it easier and cheaper to bring a new generic drug to the market. Instead of going through lengthy human trials, companies merely had to prove that their drug had the same active ingredients and they were absorbed into the body at a rate within 20% of the rate of the branded drug.[7] Since 1984, the generic industry grown to more than $20 billion in annual sales, representing more than 60% of all prescriptions filled in 2007.

In 1989, federal investigators implicated several generic industry officials in the conduct of fraud, obstruction of justice, and non-compliance with various manufacturing procedures.[8]

The Generic Drug Enforcement Act of 1992 imposes debarment and other penalties for illegal acts involving approval of abbreviated drug applications.[9]

The Food and Drug Administration Modernization Act of 1997 added new provisions to section 505(j) of FFDCA that resulted in a renumbering of the sections.[9]

The Medicare Prescription Drug, Improvement and Modernization Act of 2003 ("Medicare Act") became law in December 2003. This Act includes the title "Access to Affordable Pharmaceuticals," which includes amendments to sections of the Food Drug and Cosmetic Act relating to the filing of generic drug applications. Particularly significant provisions change the way in which marketing exclusivity periods are awarded to generic companies for certain patent challenges, and in which 30 month stays of marketing approval are applied to generic applications.[10]

**Hatch-Waxman Act**

Drug Price Competition and Patent Term Restoration Act of 1984 is commonly called as Hatch-Waxman Act. "The Hatch-Waxman Act is an act dealing with the approval of generic drugs and associated conditions for getting their approval from FDA, market exclusivity, rights of exclusivity, patent term extension and Orange Book Listing."

The act was necessitated by the following observations:

*1. Absence of Generic drug manufacturing*

*2. Cumbersome regulatory procedures*

*3. Patients were denied the option of cheaper drugs*

**General Provisions of the Act**

**1. Maintaining list of patents which would be infringed**:

Each holder of an approved new drug application (NDA) must list pertinent patents it believes would be infringed if a generic drug were marketed before expiration of these patents. The FDA maintains a list of such patents in its publication, Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as Orange Book).

**2. Only Bioavailability studies and not clinical trials needed for approval:**

FDA can only ask for bioavailability studies in respect of an ANDA and not for clinical trials etc. (For bioavailability FDA uses the + 20% test i.e. the amount of active

ingredient in the blood serum over a period of time has to come within + 20% of that which is observed with the patented drug).

**3. Para I, II, III and IV certifications**:

While filing an ANDA, a generic firm must certify any one of the following:

i. Patent information on the drug has not been filed (in the orange book).

ii. Patent has already expired.

iii. Date on which patent will expire, and that the generic drug will not go to the market until that date passes.

iv. Patent is invalid and will not be infringed by the manufacture, use or sale of the generic drug.

The above certifications are also called paragraph I, II, III and IV certifications. In case of certification I and II, approval for manufacture can be granted immediately. In case of III, approval for ANDA can be made effective from the date of patent expiration. In case of IV, it is mandatory for the manufacturer to notify the original patent holder, who can take up to 45 days to bring an infringement suit against the manufacturer, if he feels his IPRs are being violated. However, if no such action is taken within the stipulated period, certification of the ANDA applicant will be accepted by the FDA.

If an infringement action is brought in time, FDA must suspend approval of the ANDA until the date of court's decision. If the court decision goes in favour of the patent owner, FDA will suspend the approval till expiry of the patent. FDA does not wait indefinitely - the maximum time available for coming to a decision is 30 months (2.5 years) after the expiry of 45 days.

The first generic applicant to file paragraph IV certification is awarded a 180 days (6 months) market exclusivity period by the FDA. The six month exclusivity period will start at the earliest of the two dates- the date of commencement of commercial marketing of the generics or the day a court decides that the patent which is the subject matter of Para IV certification, is invalid or not infringed.

**4. Data exclusivity period for New Molecular Entities**:

New molecular entities approved by the FDA will enjoy data exclusivity for a period of 5 years from the date of approval of the NME by the FDA. A generic version cannot be approved during these five years.

**5. Data exclusivity period for supplements**:

Supplements requiring clinical trials will enjoy 3 year data exclusivity period.

**6. Extension of the original patent term:**

Original patent term can be extended by a maximum of five years, if undue delays take place during the regulatory process (FDA approval).

**7**. **The "Bolar" Provision:**

America's Hatch-Waxman legislation included a section, now known as the ""Bolar provision", that allowed the importation of the small amount of raw material required to prepare the compound and test a product before a patent expired. This permitted a generic company to complete its FDA application prior to patent expiration so that the generic version would be available for marketing immediately a patent expired. This provision was a *sine qua non* for generic negotiators of the legislation, since 99% of the raw materials for generic production in the United States are imported.

**Recent Changes to the Hatch-Waxman Act**

Under the Medicare Prescription Drug and Modernization Act of 2003, some changes have been made in the existing Hatch-Waxman Act. These are as follows:

**1**. **Non-extension of the 30-month period**:

As per modified rules, only one 30 month stay will be permitted in case of those patents listed in the Orange Book, when an ANDA is filed under paragraph IV

certification. Modifications to the 30 month stay are allowed based on district court judgments. Patent holders included new patents in the Orange Book after receiving notification regarding Para IV certification and thus extended the 30 month period.

**2. *Time limit for informing patent owner***: The company filing ANDA under Para IV must submit full and complete information over and above what is necessary under current law and must notify the patent owner within 20 days.

**3. Provision for allowing declaratory judgment:**

If patent owner does not file infringement proceeding within 45 days of notification issued by ANDA applicant, the applicant may request for a declaratory judgment and thus avoid being sued. If sued, applicant may file a counter claim requiring patent owner to make changes in the orange book listings.

**4. Benefit of exclusivity for several ANDAs filed on same day allowed**:

It is now possible for many generic companies to qualify for the 180 day market exclusivity if several ANDAs are filed on the same day.

**Generic Drug Approval**

*The generic drug approval process has evolved over the past 35 years. In 1970 FDA established the Abbreviated New Drug Application (ANDA) as a mechanism for the review and approval of generic versions of drug products that had been approved between 1938 and 1962. For drugs approved after 1962, manufacturers of generic products were required to submit complete safety and efficacy through clinical trials.* After 1978, however, manufacturers were required to cite published reports of such trials documenting safety and efficacy.

Neither of these approaches was considered satisfactory, as the former was quite expensive and the latter required evidence that was usually unavailable, i.e., data that had not been published. In 1984 the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) focused on modifying and accelerating the ANDA procedure and gave FDA statutory authority to approve generic versions of innovator products approved after 1962 as safe and effective.[11]

Generic drug applications are termed "*abbreviated*" because they are generally not required to include preclinical and clinical data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to innovator product. Because the generic product must be pharmaceutically equivalent and bioequivalent to the innovator product, it is expected that the two products will also be therapeutically equivalent.[1]

To gain FDA approval, a generic drug must:

- Contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have same use/indications
- be bioequivalent
- have same batch requirements for Identity, Safety, Purity and Purity
- follow strict standards of FDA's GMPs

The major components of an ANDA review include bioequivalence evaluation, chemistry/microbiologic evaluation, inspection of the manufacturing facility, and review of the proposed label.[1, 11]

Under Hatch-Waxman Amendments, an ANDA applicant must include in the ANDA a patent certification described in section 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements:

(I) no patent information on the drug product that is the subject of the ANDA has been submitted to FDA;

(II) that such patent has expired;

(III) the date on which such patent expires; or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. This last certification is known as a paragraph IV certification. The applicant filing through para IV certification gets 180-day market exclusivity as reward for challenging innovator company i.e. patent litigation.[12]

**Figure 1 and 2** describes ANDA patent certification options and ANDA approval under Paragraph IV certification respectively.[13]

**Challenges to future growth**

The generic industry remains concerned about acceleration of efforts by some special interest groups that would delay the timely introduction of more affordable generic drugs. Among the major concerns are the need to increase funding for the Food and Drug Administration (FDA) Office of Generic Drugs (OGD), which approves generic applications; attempts by the brand industry to undermine generic patent challenges through the use of authorized generics; continued misuse of the Citizen Petition process to delay generic approvals; and the use of Free Trade Agreements (FTAs) to impose measures that would harm generic industry.

**1. Increased funding for generic drug approvals**

Today, more than 800 generic applications are languishing without approval due to lack of resources at OGD. Funding for OGD has remained relatively flat over the past several years, and the backlog of generic drug applications has continued to grow. OGD's workload has increased by 36 %, and the number of applications awaiting review is expected to increase with more than US $100billion in brand products expected to lose patent protection by 2010. Additional funding would better enable OGD to process these applications more rapidly, and provide consumers with access to affordable generic drugs in a more timely fashion.

Ironically, OGD takes, on average, more than 15 months to approve an 'abbreviated' generic application, while the agency approves priority new drug products in as little as five months and new therapeutic proteins in about seven months.

**2. Authorized generics**

"An authorized generic is defined by the FDA as "*any marketing by an NDA holder or authorized by an NDA holder, including through a third-party distributor, of the drug product approved under the NDA in a manner equivalent to the marketing practices of holders of an approved ANDA for that drug*."[14]

Authorized generics — brand products masquerading as generics — are an increasingly common brand tactic aimed at discouraging generic companies from challenging questionable brand patents. Determined to maintain their market shares at all costs, brand companies recognized that by simply changing the labels of their products, they could compete directly against the generic during the 180-day exclusivity period. Because FDA considers authorized generics to be brand products, the authorized generic is not subject to the 180-day marketing exclusivity provision. Although the practice might sound relatively benign, these products take advantage of an unintended loophole in federal law that, if left unchecked, could result in fewer affordable medicines coming to market.[15]

Brand companies argue that authorized generics merely foster competition and lower prices. Yet authorized generics tend to appear on the market only immediately at the start of the 180-day period and some are even removed from the market as soon as the 180-day period expires, when other true generics are allowed to compete.

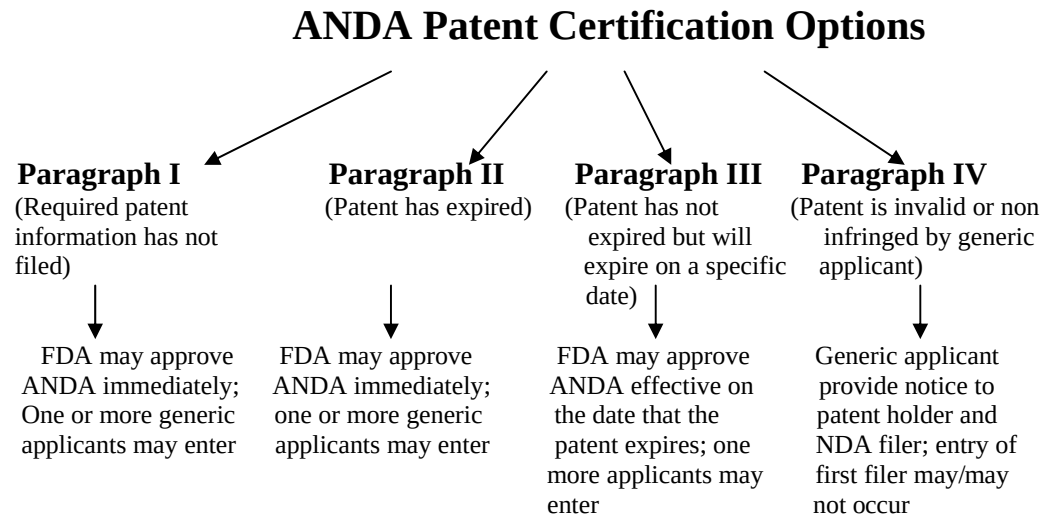


**Figure 1**: ANDA Patent Certification Options

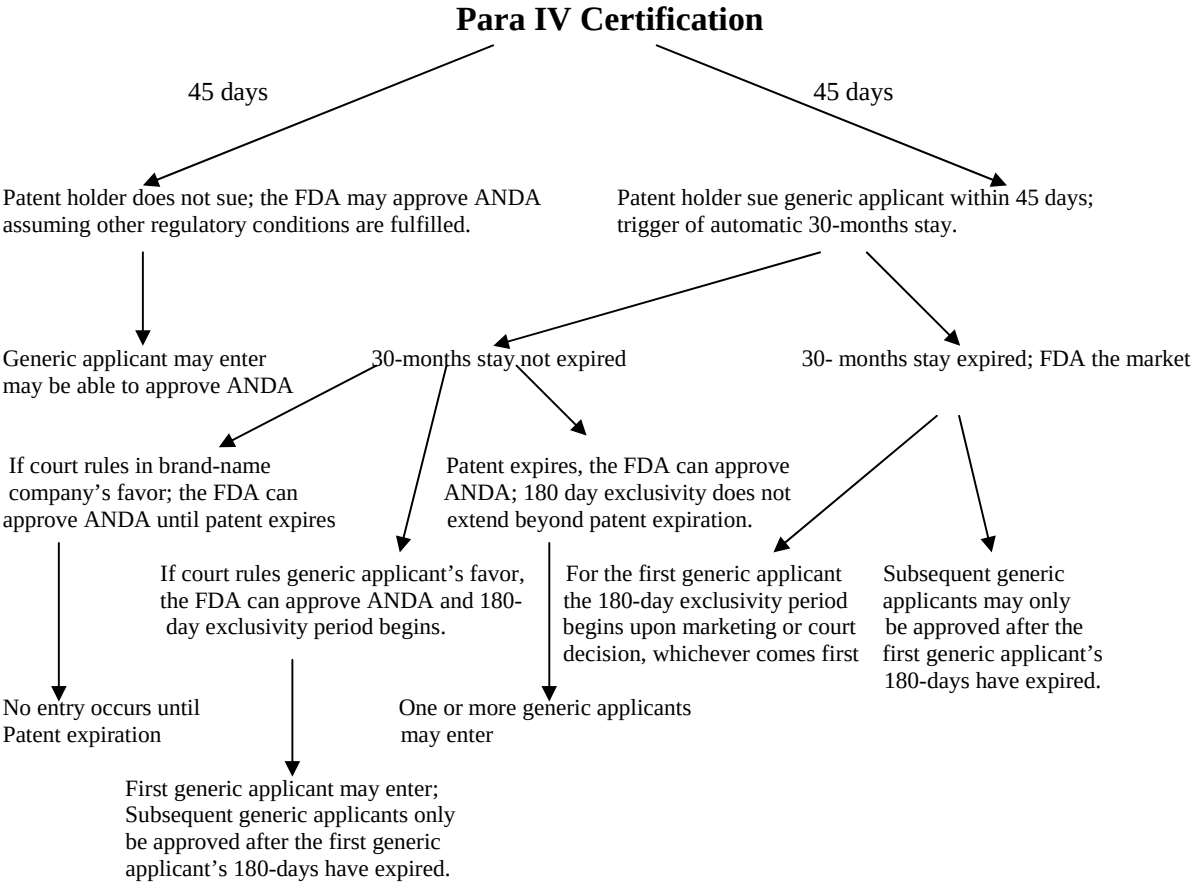


**Figure 2**: Para IV certification

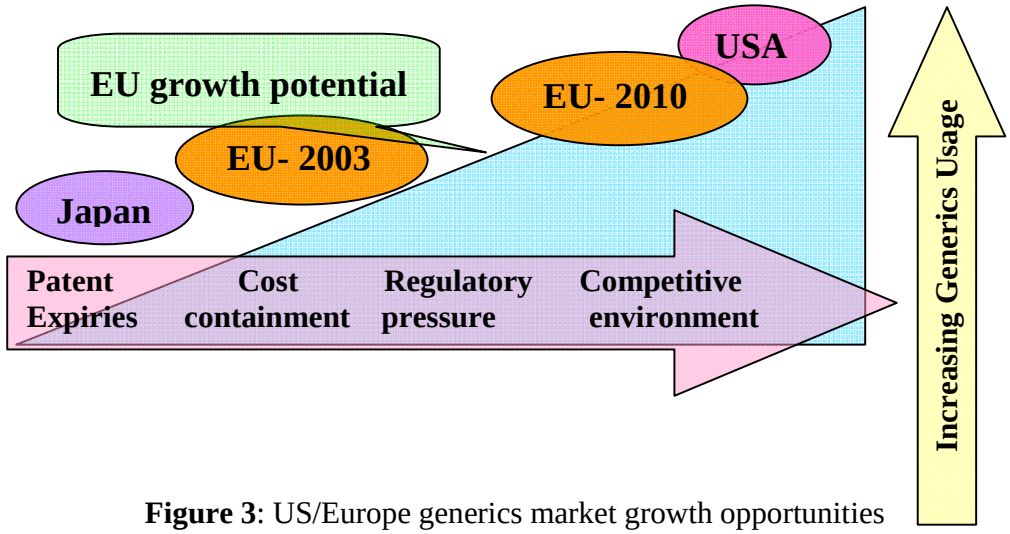


**Figure 3**: US/Europe generics market growth opportunities

**Table 1:** Comparison of Innovator and Generic Drugs

| S.N. | PARAMETERS | INNOVATOR DRUG | GENERIC DRUG |
|---|---|---|---|
| 1. | Active ingredients | Same | Same |
| 2. | Safety & efficacy | Same | Same |
| 3. | Quality & strength | Same | Same |
| 4. | Performance and standards | Same | Same |
| 5. | Costs/prescription | Highly expensive | Less expensive |
| 6. | FDA inspection of manufacturing facilities | Yes | Yes |
| 7. | FDA reviews reports of adverse reactions | Yes | Yes |
| 8 | FDA reviews drug labeling | Yes | No |
| 9. | Extensive research and development investments | Yes | No |
| 10 | Expensive marketing & advertising | Yes | No |
| 11. | Patent protection | Yes | No |
| 12. | FDA review to show active ingredient is equivalent to original | --- | Yes |
| 13. | Product Development Time | ~ 12 yrs | 2- 4 yrs |

Generic Pharmaceutical Association will continue to work with Congress to close loopholes in the Hatch-Waxman Act and preserve this important incentive, before irreparable damage is done to the patent challenge process.

**3. Citizen petition issues** [16]

Citizen petitions are a growing concern not only for the generic industry, but for FDA as well. Every US citizen has a constitutionally protected right to petition the federal government. However, some brand pharmaceutical companies, their lawyers, or other representatives routinely file citizen petitions against pending generic drug applications on the eve of product approval.

Upon receipt of a citizen petition, regardless of its merits, FDA typically delays approval of the generic drug application until the issue underlying the citizen petition can be reviewed and addressed. The vast majority of such petitions are without merit and do not result in any modification of the drug application approval requirements as they are ultimately denied, but not before they have their intended effect of extending brand companies' product monopolies.

Both FDA and Congress have recognized the inherent issues related to delaying generic competition through the abuse of the citizen petition process, and GPhA will continue to work with congressional and administrative leaders to ensure that this process does not delay generic competition.

**4. Free trade agreements (FTAs)**

Recent FTAs contain unlimited patent extensions, greater market exclusivity, and elimination of the requirement that a brand company disclose the best mode of practicing its invention: all dramatic divergences from US law.[17]

For example, in Canada, the brand industry is promoting eight years of market exclusivity, which is three years longer than the market exclusivity provision in the North American Free Trade Agreement. In Chile, the brand industry continues to try to impede implementation of a robust generic approval process by pressuring the Government to adopt a complex patent linkage system that lacks generic access provisions.

In response, the generic pharmaceutical industry has become even more active on International issues, heading off attempts by the brand industry to make changes in US patent and exclusivity laws under the guise of harmonization with trade agreements. For example, the generic industry has called for clarification of provisions of the Central American Free Trade Agreement (CAFTA) that would have made it more difficult for Central American countries to obtain access to affordable medicines.

**5. Other threats to generic competition**

Another potential threat to consumers' timely access to affordable medicines is patent reform. Congress has for some time been considering legislation that could make sweeping changes to the way patents are filed and how questionable patents are challenged. Some proposals could weaken the integrity of the US patent system by increasing the length of patent monopolies on expensive, branded drugs by eliminating several defenses to patent infringement currently available to generic competitors.

Reform proposals might also eliminate the 'best mode' requirement, under which the inventor must disclose in the patent application the most efficient known method for producing the invention. Elimination of this requirement would amount to *de facto* patent extensions, unduly prolonging the brand's monopoly.

GPhA has cautioned Congress on moving too quickly on patent reform and called for careful analysis to ensure that the legislation does not unintentionally harm the healthcare system.

**Conclusion:**

The generic drug access is increasing continuously in the international market. The generics industry is facing a period of unprecedented growth, with $82 billion worth of global blockbusters set to face US patent expiry by 2007.[18] Today, the global

generic market accounts for about US$70 billion.[19]

**Figure 3,** shows that US generics market approaching saturation, while Europe provides growth opportunities.

The generic drug market is undergoing significant change, with intense merger and acquisition activity, a raft of upcoming patent expiries and new legislations being enacted to promote generic prescription in the major markets. In addition, key issues, such as authorized generics, the first biosimilars approvals and increasing competition within the market are also affecting growth dynamics. [20]

- There is still room for growth in the more mature generics markets, with Governments examining methods of increasing generic usage even further. However, pricing pressures may result in this growth not being translated into positive returns for the generics industry.
- Competition in the generics market is becoming increasingly intense, with low cost producers expanding globally and branded Pharma becoming involved through subsidiaries or via authorized generic agreements. The wave of consolidation that swept through the generics market has been spurred on by this competition and is unlikely to end any time soon.
- Rapidly changing global scenario necessitates urgent need for complete harmonization in the present day regulatory environment.

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