Generic Drugs & its Regulatory Processes

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Generic Drugs – Definitions and the Law

What is a Generic Drug?

- A drug that is equivalent when compared to the "innovator / patented formulation" in terms of the active pharma ingredient(s), dosage strengths, route of administration, performance (viz. pharmaco-kinetics, & dynamics), labelling, safety and quality
- In most cases, the generic drug has lost patent protection and thus can be duplicated by other pharma companies

In short, the generic equivalent should be an exact replica in all senses when compared to the reference listed drug (the innovator drug)

A GENERIC DRUG, is therefore always shown as an equivalent to a REFERENCE LISTED DRUG

GENERIC DRUG = INNOVATOR DRUG

The Advantage of Generic Drugs

- Since a Generic drug is a copy of an already approved drug, the manufacturer only need to prove bioequivalence to the originator drug ; and
- The process produces purity and consistency of the drug
- There is no need to re-do the expensive and the time consuming process of Clinical Trials
- Generic Drugs, simply make a reference to the Clinical Trials, Efficacy, Safety & other studies, data already done by the Originator;
- Hence Generic Drug Applications are called "ABBREVIATED NEW DRUG APPLICATIONS" or "ANDA"s

BENEFITS OF GENERICS ~

- Generic Drugs development to approval time is only 3 Years (against the time of about 7~8 years for Innovator Drugs)
- The other major benefit is cost savings. Generic drugs significantly reduce healthcare costs for governments. Hence governments in recent times provide more opportunities for growth of generic drugs
- Provide a more competitive environment and ensure accessibility of medicines to all

Types of Marketing Applications & Approvals in the US

In the US, marketing authorisations for a new drug can be filed with the USFDA by the below :

- IND (Investigational New Drug Application)

A new drug approval process begins here, with the IND application to the FDA. This is done once the preclinical studies provide sufficient evidence to suggest the efficacy of the drug to proceed with clinical trial study and data collection

- NDA (New Drug Application)

A new drug application is filed once the drug successfully clears all the three clinical trial stages, including human and animal trials. The safety and the efficacy of the drug has to be established. The new drug is evaluated with respect to the current available drugs for treatment and must have significant advantages over them.

An NDA approval generally takes between 2~3 years.

- ANDA (Abbreviated New Drug Application)

An ANDA application is done for "Generic Drugs". The ANDA application refers to an Approved Drug and claims similarity to the referred innovator product. The FDA waives expensive clinical trials and other safety data for an ANDA application (the reason why it is called as an "Abbreviated" Drug Application)

The ANDA therefore claims reference to data filed in an NDA application.

The ANDA Application

In the US, The Drug Price Competition and Patent Term Restoration Act (better known as the Hatch Waxmann Act) allowed companies to file the Abbreviated New Drug Application (or ANDAs) which allows marketing of Generic Drugs

Section 505(j) of the Act allowed ANDA applications to be filed for Generic Drugs and allowed:

- The applicant to avoid expensive and time consuming human & animal clinical trials to establish safety and efficacy of the active drug or the dosage forms by referring to data submitted by the innovator in his reference listed drug
- The applicant to demostrate that the generic drug is equivalent in all respects to the reference drug
- Applicant to fasten the approval process for drugs already approved by the FDA earlier

Generic Drugs & the ANDA process

ANDA applicants could file a generic drug by citing:

- **Section 505 (b) (2); whereby the applicant refers to data that does not belong to him or has no rights for the same**
- **Section 505 (b) (1) on the other hand refers to data either generated and owned by the applicant or data whose rights have been procured. This is usually referred to in case of NDA applications**

Section 505 (j) (2) (A) (vii) requires that the applicant to certify that the generic formulation either does not infringe any patent, or would be marketed post the expiry of the patent.

This section also provides for the well known Para IV challenges where-in the applicant challenges the validity of a patent.

This Section requires that the applicant issue a certification from one of the below lists:

- **Para I Certification – No Patent information exists on the formulation or is not submitted to the FDA**
- **Para II Certification – Patents that exist have expired`**
- **Para III Certification – The Product is to be marketed only after the expiry of the listed patents**
- **Para IV Certification – The Patent(s) are either invalid or would not be infringed by the product**

ANDA – Para IV Generic Challenges

ANDAs with Para I & II Filings are immediately approved by the USFDA

ANDAs with Para III may be approved upon expiration of the patents

For ANDAs with Para IV citations, need to determine, if:

a. patent is **valid / invalid**, or
b. patents are **infringed / not infringed**

(may be decided by the courts)

Para IV approval process:

ANDA applicant with Para IV citation, **informs the patent holder** and NDA holder of the patent challenge

→ NDA holder or **patent holder may file a suit** against the ANDA applicant (within 45 days of receipt of notice)

→ Suit filed by the originator triggers a **30 month stay** on the ANDA application. FDA will not grant final approval

→ 30 month stay applies unless **court reaches a decision** earlier to this period

Para IV approval process (Contd.)

FDA may give a **final approval** to the Para IV-ANDA, either
a. at the completion of the 30-month stay, or
b. a favorable decision by the court upholding the non-infringement or the non-validity of the patent (s)

If upon completion of 30-month stay, & the FDA grants an approval,
- the ANDA applicant may commercially launch the generic, **under risk, pending the court's final decision on the patents law suit**

The applicant gets a **180-day marketing exclusivity** for being the first to make a Para-IV challenge
180-day exclusivity starts from date of commercial launch or the date of the court's final decision, whichever is earlier

However, if upon commercial launch, the ANDA applicant loses the patent suit, he would be liable to pay damages / compensation to the originator

Drug Approval Processes in EU

Generics Approval Process in EU

The EU member states allow the following options for approval of a new drug including Generic approvals:

- Centralised Procedure for approval
- National Authorization Procedure
- Decentralised Procedure, &
- Mutual Recognition Procedure

The Centralised Procedure for Approvals

Drugs approved by the Centralised procedure is examined & qualified by the EMA (European Medicines Agency)

Drugs approved by this route is granted an Marketing Authorization for all EU member states & all EEA countries

The procedure is mandatory for all biological agents, HIV/AIDS drugs, Cancer, Diabetes, Neurogenerative, Immunomodulating & immune related drugs, Antivirals, & Orphan drugs

The Centralised procedure can also be used for new / innovative drugs not earlier approved in EU

The National Approval Procedure

Under the National Procedure, drugs in EU are approved by the relevant authorities in each member state

Approvals are granted on a country-to-country basis and by separate applications to individual authorities in each country.

Such approvals allow the MA holder to market the drug only within the state where the drug has been approved

The Mutual Recognition Procedure

The Mutual Recognition Procedure allows the MA Holder to seek approvals in EU Member States based upon an approval already granted by a Member State

In this case, the state which has approved the product is taken as the 'Reference Member State' (RMS); Applications for approvals are made on the basis of this approval to the 'Concerned Member States' (CMS)

The procedure cuts down the time required for parallel national applications and seeks members to respond & approve within a given time-frame.

The procedure sometimes gets complex when Member States disagree on certain issues and delays occur

The Decentralised Procedure

The Decentralised procedure is similar to the Mutual Recognition route but differs in that ‘it allows applications to several Member States for products not yet approved in any state’

The applicant selects a Member state as a reference state (RMS). The RMS then asseses & co-ordinates within the CMS for a simultaeneous review & approval

The process was introduced in 2005 & significantly reduces approval times, & has a single MA licence issues across Member states.

Also the MA holder can look to launch in several states at the same time with simultaeneous approvals.

Generics in US, EU & the World

- The US & the EU through various laws and regulations are promoting generic launches to benefit healthcare costs and accessibility to medicines to all
- The world generic market is estimated to be about US$ 145 Billion
- The US is the biggest generic market known, with US$ 45 Billion. EU markets follow closely with US$ 26 Billion
- Drugs with about US$ 250 billion, are estimated to lose patent protection before 2015
- The Generic pharma market therefore would grow multifolds in the period between 2010 & 2020!!

Thank you, Folks!