Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Current Challenges in Abbreviated New Drug Application (Anda) Approval Process

Mallikarjun V. [*], Babu V. Rajesh [2], Harika A.[1] and Nikhat Syeda Rana [2]

[1]Dept of Pharmaceutics, College of Pharmacy Education & Research, Hanamkonda, T.S.
[2]Dept of Pharmaceutics, MESCO College of Pharmacy, Hyderabad, T.S.

ABSTRACT

Regulatory involvement in the generic drug development hastens the drug approval process which directly/indirectly accelerated the launching of drug into the market. The regulatory documents whether in-house of documents to be submitted to regulatory authorities should be carefully reviewed by the skilled personnel to minimize the queries raised by the regulatory agencies and speed up the approval process. These are few differences in the dossier submission requirements among the three regions i.e., USA, Europe and India which has been clearly represented through succinct comparisons third part of this work. The literature work, the comparison parameters, difference in generic drug approval requirements has been delineated in this work, which gives clear depict where India lies in its generic drug approval process and the challenges that Indian regulatory authority has to overcome in the near future.

KEYWORDS: Exclusivity, Generic product development, Patent, Abbreviated new drug application.

[*]Corresponding Author:

Dr. V. Mallikarjun

Associate Professor

Chaitanya College of Pharmacy Education & Research

Hanamkonda, Telangana State, INDIA

E-Mail: mallikarjunvasam@gmail.com. Mob: 9959202656

INTRODUCTION

A new drug is defined as one that is not generally recognized as safe and effective for the indications proposed. However, this definition has much greater reach than simply a "new" chemical entity. The term "new drug" also refers to a drug product already in existence, though never approved by the FDA for marketing in the United States; new therapeutic indications for an approved drug; a new dosage form; a new route of administration; a new dosing schedule; or, any other significant clinical differences than those approved. A Generic Drug Product is one that is comparable to an Innovator Drug Product in dosage form, strength, and route of administration, quality, performance characteristics and intended use.

How Drugs are Developed and Approved: The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness.CDER is the largest of FDA's five centers. It has responsibility for both prescription and nonprescription or over-the-counter (OTC) drugs. For more information on CDER activities, including performance of drug reviews, post-marketing risk assessment, and other highlights, please see the *CDER Update: Improving Public Health Through Human Drugs*[1] The other four FDA centers have responsibility for medical and radiological devices, food, and cosmetics, biologics, and veterinary drugs.

Types of Applications:

Investigational New Drug (IND): Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

New Drug Application (NDA): When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number.

Abbreviated New Drug Application (ANDA): An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

Over-the-Counter Drugs (OTC): Over-the-counter (OTC) drugs play an increasingly vital role in America's health care system. OTC drug products are those drugs that are available to consumers without a prescription. There are more than 80 therapeutic categories of OTC drugs, ranging from acne drug products to weight control drug products.

Biologic License Application (BLA): Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product.

Abbreviated New Drug Application (ANDA): Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*[1] (*Orange Book*).

North America: Both USA and Canada are the major markets in the pharma industry. The US enjoys the largest player tag in terms of value in the pharma sector. It is valued approximately at USD 300 bn in 2009. The US has evolved from no regulation in the 18th century to one of the highly admired, favorite regulatory authority in the world.

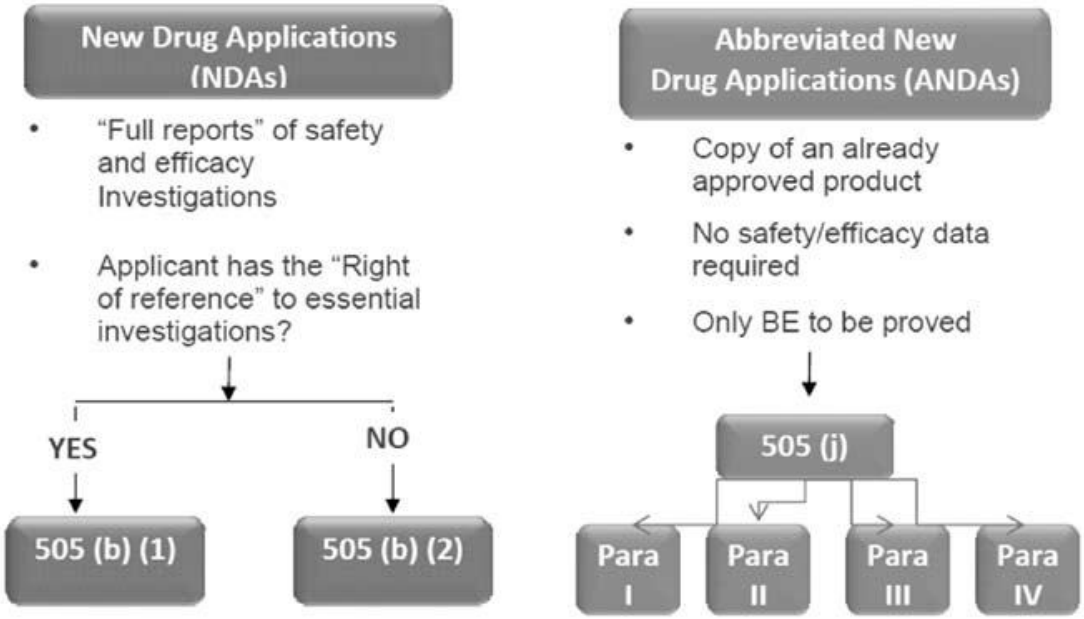

Fig. 1 – Different Applications in USA

Table 1: Different types of ANDA applications in US

Subsection of 505(j)	Products type
Paragraph I	For the products for which no patent information is available in the orange book
Paragraph II	Used for the products for which all the applicable patents are expired
Paragraph III	Used for the products for which the some or all the applicable patents are valid and the applicant confirms that the product will not be placed in the market till such patents are expired
Paragraph IV	Used for the products for which some or all the applicable patents are valid and applicant try to file the product which does not infringe those patents or applicant invalidates the granted patents. That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted On successful outcome, the generic applicant enjoys the six month exclusivity in the market

In Canada, the manufacturer may seek authorization to sell the product in Canada by filing a New Drug Submission with Health Products and Food Branch (HPFB). A New Drug Submission (NDS), typically contains scientific information about the product's safety, efficacy and quality.

Different procedures in Europe: A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued. The marketing authorisation holder must be established within the EEA. European Medicines Agency regulates the medicinal products marketing authorization through various committees.

Japan: Japan is the world's second largest market next to the US. With USD 52 billion drug market, it represents 11% of global sales. The Ministry of Health, Labour, and Welfare (MHLW) is in charge ofpharmaceutical regulatory affairs in Japan and the Pharmaceutical and Medical Devices Agency (PMDA, KIKO) undertakes main duties and functions of the Ministry: it handles clinical studies, approval reviews and post-marketing safety measures i.e. approvals and licensing.

Indian Regulations: India being the leading supplier of API and generic drugs to the world, it is important to understand the Indian requirements and regulations associated with pharmaceuticals. When the applicant intends to develop and export the pharmaceuticals, it is necessary to comply with regulations set forth in the Drugs and Cosmetics Act 1940 and Rules 1945.

Table 2: Type of procedures in Europe

Agencies responsible	Procedure Type	Products Applicable
EMA / CHMP	Centralized Procedure	**Mandatory scope (Article 3(1)) (EC) No 726/2004** Developed by biotechnological processes New active substance for AIDS, Cancer, Diabetes, Neurodegenerative disorder, Autoimmune disease, Viral disease Orphan drugs **Optional Scope (Article 3(2) & 3(3)) (EC) No 726/2004** New chemical, biological or radiopharmaceutical active substance An isomer, mixture of isomers, a complex or derivative or salt Significant therapeutic, scientific or technical innovation Generic/Hybrid of applications (Article 3(2)) Certain medicinal products for pediatric
RMS / CMD(h) /CHMP	Decentralized procedure (DCP) and Mutual Recognition Procedure (MRP)	For drugs which does not fall in the mandatory scope of Centralized procedure
Member States (MS)	National Marketing Authorization	For drugs which does not fall in the mandatory scope of Centralized procedure
EMA - European Medicines Agency; CHMP- Committee for Medicinal Products for Human Use RMS - Reference Member States; CMD(h) – Co-ordination Group for Mutual Recognition and Decentralized Procedure (Human)		

Different legal basis for the applications in Europe:

The eligibility and requirements are set in the commission regulation (EC) No 726/2004 and defined in the Article 8 and 10 are of the Directive 2001/83/EC. The Article 8 (3) and 10 are for full applications (NDA) and other applications respectively as illustrated in Fig. 3.

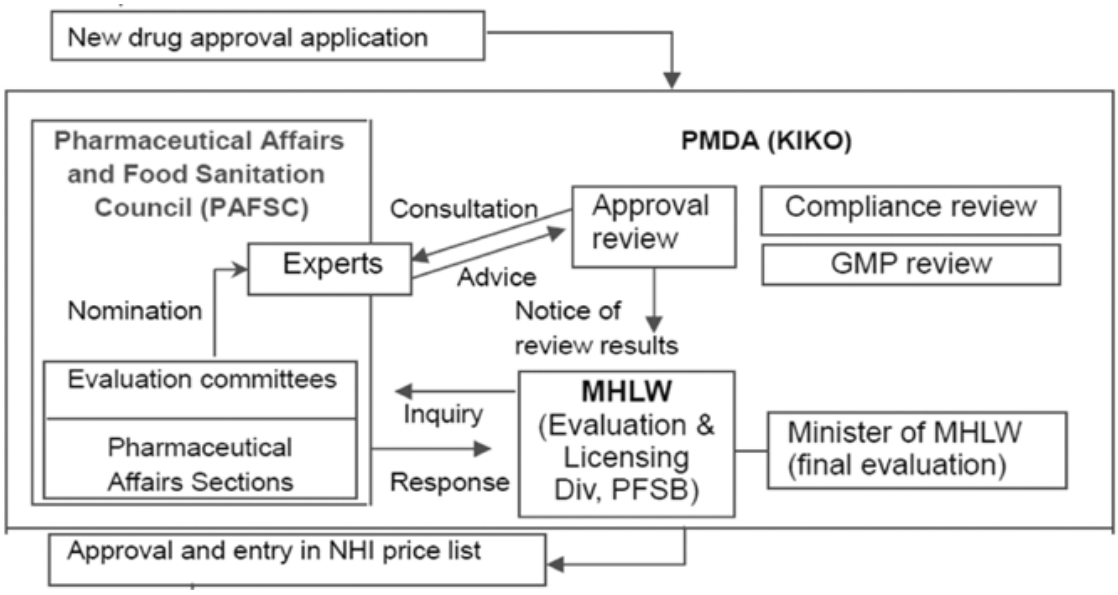

Fig 2: The approval procedures in Japan

Emerging Nations: Rest of the World: This region consists of mainly the countries from Asia pacific, Latin America, Eastern Europe, Africa and Gulf countries. While countries from Asia pacific and Gulf have almost harmonized their regulatory environment through The Association of Southeast Asian Nations (ASEAN) and Gulf Co-operation Council (GCC) organizations, rest of the regions are yet to come up with the harmonized regulations in their respective regions.

Other factors for consideration:

Patents Scenario: All developed nations (US, EU, Japan, ANZ) have established a product patent which runs for 20 years from the date of patent filing. In US, Japan, Australia the original patent term can be extended by a maximum of five years, if undue delays take place during the regulatory approval. In case of Para IV application in US, 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 patents are being violated.

Exclusivities: Data exclusivity is a period granted to the innovator companies in which no other company can file any type of application for that particular molecule. There are other exclusivities

available to promote the company which engages in the innovation or incremental innovations. Table (3) summarizes the various exclusivities available in three major regions.

Table (3): Exclusivities available in major regions

Type of exclusivity	**USA**	**Europe Union**	**Japan**
Data exclusivity	5 years data exclusivity for NCE / 4 years in case of Para IV / 505(b)(2) application	8 years	8 years
Marketing exclusivity	-	2 years	-
Exclusivity for additional indications / changes to existing product	3 years	1 year	years for new delivery routes or for other significant changes / 4 years for new indications and for other relatively insignificant changes
Orphan drug Exclusivity	7 years	10 years	10 years
Pediatric exclusivity	6 months	-	-
Exclusivity for first to file generic application through patent challenge	6 months	-	-

Difference Between patents and exclusivity: Patents and exclusivity work in a similar fashion but are distinctly different from one another. Patents are granted by the patent and trademark office anywhere along the development lifeline of a drug and can encompass a wide range of claims. Exclusivity is exclusive marketing rights granted by the FDA upon approval of a drug and can run concurrently with a patent or not. Exclusivity is a statutory provision and is granted to an NDA applicant if statutory requirements are met. See 21 C.F.R. 314.108. Exclusivity was designed to promote a balance between new drug innovation and generic drug competition.Patents expire 20 years from the date of filing. Many other factors can affect the duration of a patent.

It depends on what type of exclusivity is granted.

Orphan Drug (ODE) - 7 years

New Chemical (NCE)- 5 years

"Other" Exclusivity - 3 years for a "change" if criteria are met

Pediatric Exclusivity (PED) - 6 months added to existing Patents/Exclusivity

Patent Challenge – (PC) – 180 days (this exclusivity is for ANDAs only)

Components of regulatory filing and Data Requirements: The US, EU and Japan are a part of International Conference on Harmonization (ICH), hence the technical requirements for registration of Pharmaceuticals follow the ICH recommendations. These countries require data as per the requirements of Common Technical Document (CTD).

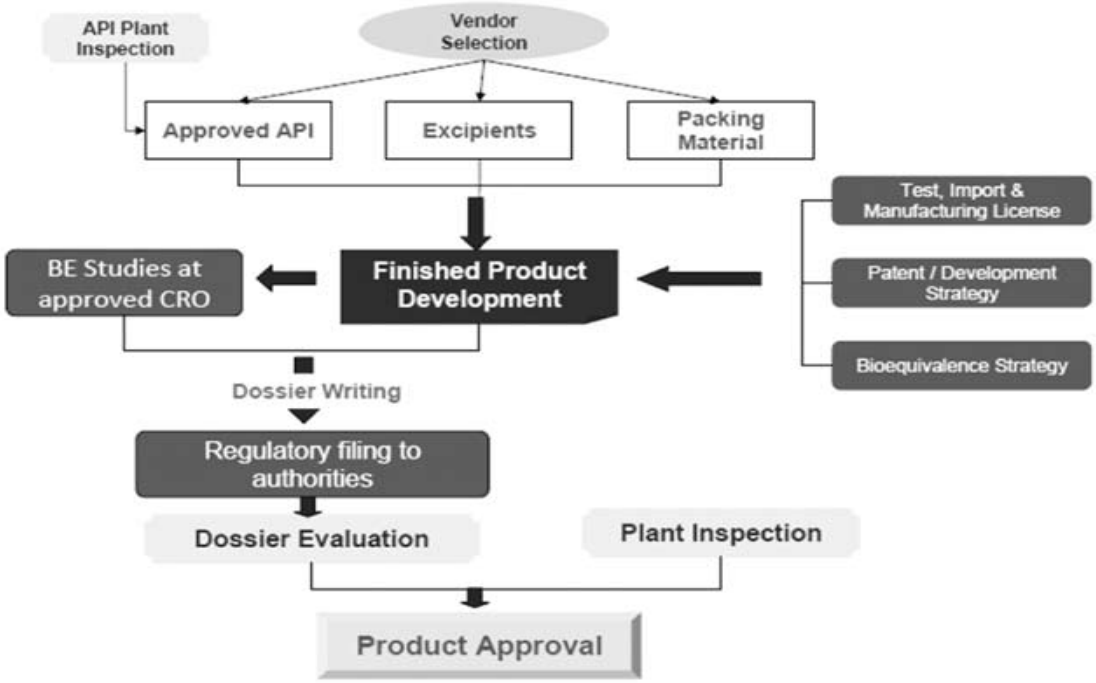

Fig. 3: Components of Regulatory Filing

METHODOLOGY

Patents: A patent is a document issued by the U.S. Patent and Trademark Office located in Arlington, Virginia, that grants to an inventor the legally enforceable right to exclude others from making, selling, distributing or using an invention in the U.S. territory. Congress allows this exclusive right, often considered a limited monopoly, to encourage the public disclosure of technical information and as an incentive for investing in their commercialization.

Types of Patent: There are three primary types of patent: Utility, Design, and Plant.

Utility Patents: A utility patent is the type of patent that is awarded to inventions that perform useful functions. Most of the patents that are issued are of this variety, and in fact most people who simply use the term "patent" are referring to a utility patent. Utility patents can be obtained for a thing, a method for making a thing, and/or a method for using a thing. Many times the news media will report that something that is quite old or well-known has been recently patented.

Design Patents: Design patents can be a useful tool in your intellectual property arsenal, particularly when you are attempting to create overlapping protection, thereby developing a true intellectual property portfolio. Having said this, it is important to know the limitations of design patents. Design patents do NOT protect an idea or an invention, but rather only protect ornamental design of exactly what is pictured.

Plant Patents: Patents to plants which are stable and reproduced by asexual reproduction, and not a potato or other edible tuber reproduced plant, are provided for by Title 35 United States Code, Section 161 which states:

The subject matter of the application would be a plant which developed or discovered by applicant, and which has been found stable by asexual reproduction. To be patentable, it would also be required:

- That the plant was invented or discovered and, if discovered, that the discovery was made in a cultivated area.
- That the plant is not a plant which is excluded by statute, where the part of the plant used for asexual reproduction is not a tuber food part, as with potato or Jerusalem artichoke.
- That the person or persons filing the application are those who actually invented the claimed plant; i.e., discovered or developed and identified or isolated the plant, and asexually reproduced the plant.
- That the plant has not been sold or released in the United States of America more than one year prior to the date of the application.
- That the plant has not been enabled to the public, i.e., by description in a printed publication in this country more than one year before the application for patent with an offer to sale; or by release or sale of the plant more than one year prior to application for patent.
- That the plant be shown to differ from known, related plants by at least one distinguishing characteristic, which is more than a difference caused by growing conditions or fertility levels, etc.

• The invention would not have been obvious to one skilled in the art at the time of invention by applicant.

Kinds of protection are available around a product: A product of interest may enjoy different types of protection, each of which may impact your intellectual property rights and your competitive advantage.

Different types of protection

Different types of protection may be obtained around a product, such as:

- ✓ Product (compound per se/composition of matter)
- ✓ Process (methods for manufacturing the product)
- ✓ Product by process (if the compound is novel)
- ✓ Use of the product or method of use protection (utility of the compound)
- ✓ Formulation of the product (e.g. cosmetic or pharmaceutical formulations)
- ✓ First and second medical use (for compounds found to be useful as a pharmaceutical).

Some specific cases:

Known compounds never used (or anticipated for use) in a medical indication: A compound that is known for use in a non-medical indications may still be patented for any medical indication and for a specific medical indication, in some countries (first medical use) if the inventor finds that it is useful as a pharmaceutical.

"Natural" products: Natural products may still be protected by patent claims framed in such a way as to distinguish the claimed product from the product as found in nature.

Basic patents: A basic patent generally protects a chemical (and eventually salts thereof) or a biological compound per se (composition of matter). It may further protect formulations of this compound, methods of using such a compound and methods of manufacturing it.

Secondary (follow-on) patents: Secondary patents protect "new developments" or "improvements" of the subjectmatter of the basic patent. Depending on when the secondary patent is filed (before or after the publication of the basic patent), the patentability requirements for the subjectmatter of the secondary patent are

(i) Novelty only with respect to the basic patent or
(ii) Both novelty and inventiveness (non-obviousness) with respect to the basic patent.

Secondary patents may be for example directed to:

- Purity/purified form of the compound
- New salts, esters etc…
- Species from the genus or sub-genus (selection invention)
- Metabolites
- Crystalline form
- New formulation
- Combination formulation (with another substance)
- New manufacturing process
- Delivery route
- Dosage regimen
- New therapies/Indications (not predictable).

Patent term extension: Although the legal term of a patent is normally 20 years from filing the "effective patent term", defined as the length of time in which a product (pharmaceutical and agrochemical products) is marketed with the benefit of enforceable patent protection, may be very much shorter due to lengthy regulatory processes. Patent term extensions and the like are available in some countries to compensate for regulatory delays. Deadlines for applying for such patent term extensions are quite short and are triggered by the market approval from the regulatory authorities.

Patent term extensions (PTE): Patent term extension is available in the US, Japan, Israel, Australia, Taïwan, Korea and in some other countries for products subject to a regulatory approval.

Supplementary Protection Certificates (SPCs): In Europe, the possibility of extension of the term of a patent to compensate for regulatory delays is offered by a Supplementary Protection Certificate. The aim of the supplementary protection certificate is to give 15 years of "effective patent protection", defined as being the period during which a product can be sold while benefiting from the protection of either a patent or an SPC. The idea is to ensure that a patent holder can, if desired, market a patented product exclusively for at least 15 years.

Strategies for optimizing patent product life: Complementary strategies to optimize product patent life require good communication, between Intellectual Property professionals, marketing decision makers and regulatory professionals.

Role of the patent attorney: A patent attorney may cast a fresh eye upon your projects and propose possible patenting strategies, making use of a global view of patent life-cycle management. By virtue

of his/her international contacts with foreign patent attorneys, the patent attorney can guide you in building a worldwide patent strategy adapted to your commercial needs.

RESULTS & DISCUSSION:

ANDA Submissions: Procedures for ANDAs submissions are set forth in FDA's regulations in part 314 (21 CFR part 314). An ANDA is usually 3 submitted for a drug product that is the same as an already approved drug or listed drug. A *listed drug* is defined in § 314.3(b) as a new drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness or under section 505 (j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness (§ 314.161). An applicant submits an ANDA based on a listed drug, and the previously approved drug product on which the ANDA relies is officially known as the *reference listed drug* (RLD). A reference listed drug (RLD) is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (§ 314.3(b)). FDA lists approved drugs that may be referenced in an ANDA in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). The Orange Book is updated by a monthly cumulative supplement. On July 9, 2012, GDUFA was signed into law by the President to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. Under GDUFA, FDA agreed to meet certain obligations as laid out in the GDUFA Commitment Letter.5 Among these obligations is FDA's commitment to performance metrics for the review of new ANDAs that are submitted electronically following the electronic CTD (eCTD) format. For example, FDA has committed to review and act on 90 percent of original ANDA submissions within 10 months from the date of submission in Year 5 of the program, which begins on October 1, 2016. To meet these performance goals, FDA is issuing this guidance to assist ANDA applicants in improving the quality of submissions, to increase the number of original ANDAs acknowledged for receipt upon initial submission, and to decrease the number of review cycles. FDA is committed to providing comprehensive assistance in the early stages of the application process so that an original ANDA will contain all information necessary for FDA to complete its review in one review cycle.

CTD FORMAT: The CTD format was developed by the International Conference on Harmonisation (ICH) in an attempt to streamline the variability of submission requirements among Japan, the European Union, and the United States. The CTD collects quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. As

previously stated, only ANDA submissions made electronically following the eCTD format on the date of submission will be subject to the review metric goals described in the GDUFA Commitment Letter.Section 745A (a) of the FD&C Act, added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), requires that submissions under section 505(b), (i), or (j) of the FD&C Act and section 351(a) or (k) of the Public Health Service Act (42 85 U.S.C. 262(a) or (k)) be submitted in electronic format specified by FDA, beginning no earlier than 24 months after FDA issues a final guidance specifying an electronic submission format.

The CTD is comprised of the following modules:

• Module 1: Administrative information;

• Module 2: CTD Summaries;

• Module 3: Quality;

• Module 4: Nonclinical study reports; and

• Module 5: Clinical study reports.

The sections that follow in this guidance detail the information to be submitted in the applicable Modules, sections, and subsections.

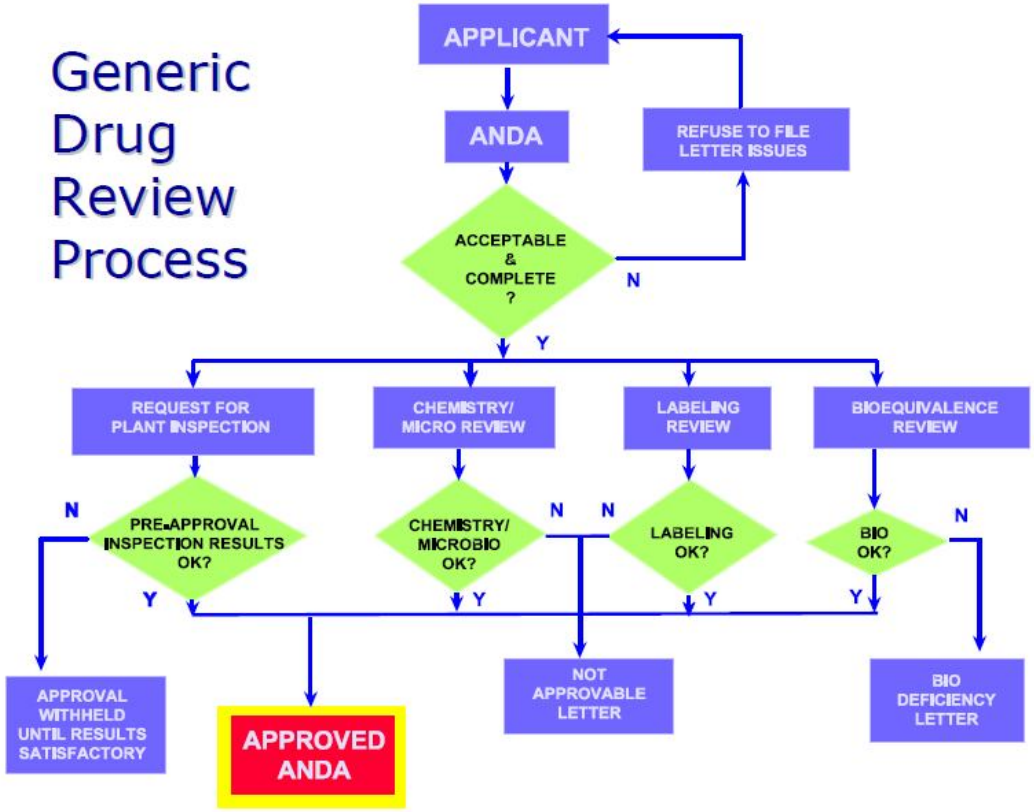

Fig 4: Generic drug review process

Generic drug approval process in USA

Hatch-Waxman Act: Intended to balance interests of consumers, the brand name pharmaceutical industry (innovator) and the generic drug industry to "make available more low cost generic drugs and to create a new incentive for increased expenditures for research and development of certain products which are subject to pre-market approval. In fewer than 20 years since enactment of the statute, generic drugs increased from 19% to 47% of prescriptions[4].

Title I of Hatch-Waxman Act: Authorized marketing of generic drugs upon approval of Abbreviated New Drug Application (ANDA). Under this ANDA can be approved upon submission of evidence that the active ingredient of the generic drug is the "bioequivalent" of a drug previously approved by USFDA after submission of a full NDA without having to submit studies establishing the safety and efficacy of drug.

Title II of Hatch-Waxman Act: This section provided specific extensions of patents covering drugs and other products subject to "regulatory review" by the FDA and government agencies. This provision was intended to balance the benefits of ANDA practice by providing brand name drug companies with the restoration of portions of the terms of their drug patents lost during the testing period required for the approval of the drugs. These patent term adjustments as well as patent extensions implemented 10 years after the enactment of Hatch-Waxman Act.

Abbreviated New Drug Applications (ANDA): Under section 505 (j) of Hatch-Waxman Act, an ANDA may be filed for a generic version of any "listed drug".

Listed Drug: Any drug for which an NDA has previously been approved is deemed to be a listed drug and is listed by FDA in the orange book. Drugs previously approved under ANDA's and Antibiotics are also regarded as listed drugs. An ANDA must include all information required in an NDA except full reports of investigations demonstrating that the drug is safe and effective in use.

ANDA additionally must show: Labelling of the drug for which ANDA is sought is same as the approved labelling for the listed drug. b) Its route of administration, dosage form and strength are the same as the listed drug or supply such information respecting any differences as FDA may require bioequivalence reports c) Status of orange book listed patents on the approved drug.

TYPES OF CERTIFICATIONS

An applicant for ANDA must certify to FDA that in its opinion and to the best of its knowledge, with respect to each listed patent that claims the drug or use of the drug for which the

applicant seeking approvals are: Paragraph I; Paragraph II; Paragraph III; Paragraph IV. The Hatch-Waxman act has undertaken necessary considerations to prevent litigations between generics and NDA applicants[6]. The act is successful in making a pathway for approval of generics without infringing the original patent. The pathway for approval of generics by the Hatch-Waxman begins with the certification procedures. Hatch-Waxman proposed four options for application for generic approval. The first three options avoid litigation.

PARAGRAPH I	:	That the patent information relating to innovator patent has not been filed
PARAGRAPH II	:	That relevant patent has already expired
PARAGRAPH III	:	That the generic will not market the drug until after the patent expires
PARAGRAPH IV	:	The generic manufacturer should certify that an applicable patent is invalid or will not be infringed by the generic product.

ANDA approval process in USA: Initially, an ANDA filer must show that the conditions of use identified in its proposed labelling have been previously approved for the listed drug on which the ANDA is based. According to this statute, ANDA must incorporate the same labelling as that of previously approved for the listed drug except for any changes required because of the differences are approved on the basis of a suitability petition.

Withdrawal of Approval of an ANDA: FDA may withdraw/suspend approval of an ANDA when the approval of the listed drug on which the ANDA relies is either withdrawn or suspended. Further, an approval of an ANDA or 505 (b)(2) application may be withdrawn on the basis of evidence showing that the drug is unsafe for use or ineffective or that the ANDA or 505 (b)(2) application contains any untrue statement of material fact. FDA must withdraw approval of an ANDA if it finds that the approval "was obtained, expedited or otherwise facilitated through bribery, payment of an illegal gratuity, or fraud or material false statement", or may withdraw approval of an ANDA if it finds that the applicant has "repeatedly demonstrated a lack of ability to produce drug, and has introduced or attempted to introduce, such adulterated or misbranded drug into commerce".

Generic drug approval process in EU: As for all medicines, generic medicines must obtain marketing authorisation before they can be marketed. Marketing authorisations are granted after a regulatory authority, such as the European Medicines Agency, has conducted a scientific evaluation of the medicine's efficacy (how well it works as measured in clinical studies), safety and quality. Applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can

demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product.

Centralised Procedure: Generic/Hybrid medicinal product applications of the medicinal products authorized via the centralised procedure have automatic access to the centralised procedure under article 3(3) of the regulation (EC) number 726/2004. For generic/hybrid applications of a centrally authorised product, the application should state in their "Letter of intent to submit" that they have automatic access to the centralised procedure under article 3(3).

Letter of intent to submit: Before submission of the dossier, applicants should notify the agency of their intention to submit an application, preferably 6-18 months in advance and indicate that the application is generic/ hybrid medicinal product application of a medicinal product authorized via centralised procedure. EMA (European Medicines Agency) will inform the applicant on the outcome of the eligibility request.

Generic Medicinal Product: A medicinal product that has; the same qualitative and quantitative composition in active substances as the reference product. The same pharmaceutical form as the reference medicinal product. And whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Hybrid Medicinal Product: Hybrid applications differ from the generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following 3 circumstances: Where strict definition of a "generic medicinal product" is not met, Where the bioavailability studies cannot be used to demonstrate bioequivalence, Where the changes in active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

Generic Drug Entry Prior to Patent Expiration: The Drug Price Competition and Patent Term Restoration Act of 1984, otherwise known as the *Hatch-Waxman Act,* have been quite successful in increasing the availability of generic drugs to consumers. By 1996, forty-three percent of the prescription drugs sold in the United States was generic compared to just nineteen percent in 1984[1], and at present it is 70% of prescription drugs. Despite the Act's overall success in promoting increased availability of generic drugs, the Act's provisions relating to patent certification actually delayed approval of generic drugs. The Hatch-Waxman Amendments were intended to balance two important public policy goals. First, Congress wanted to ensure that brand-name (also known as innovator) drug manufacturers would have meaningful patent protection and a period of marketing

exclusivity to enable them to recoup their investments in the development of valuable new drugs. Second, Congress sought to ensure that, once the statutory patent protection and marketing exclusivity for these new drugs has expired, consumers would benefit from the rapid availability of lower priced generic versions of innovator drugs.

Hatch Waxman Act: The Drug Price Competition and Patent Term Restoration Act of popularly known as the Hatch-Waxman Act. The act is codified in various sections of Titles 15, 21, 28, and 35 of U.S.C. The informal name comes from two sponsors of this Act, Henry Waxman, representative of California and Senator Orrin Hatch of Utah.

Primary Objective behind this act:

- To encourage greater public access to generic drugs (in favor of generic drug manufacturers)
- To spur new pharmaceutical development (in favor of branded drug manufacturers)

In order to reach its objective, Congress used this Act to create a delicate balance between the rights of research-based firms and generic firms, a balance crucial to the American pharmaceutical industry and the public alike.

- Prior to Hatch-Waxman Act 1984, generic manufacturers had to file their own "New Drug Application" (NDA) for regulatory approval, either relying on already published scientific literature or with the support of clinical data, to demonstrate the safety and efficacy of their product, even though it was identical to that of previously approved drug. Such generic versions were known as "paper" NDA.
- Thus approval of a generic drug was a costly, duplicative and time-consuming process.
- Congressional testimony prior to Hatch-Waxman reported that there were 150 off-patent drugs for which no generic existed because the cost of FDA approval was too high.
- In 1984, Court of Appeals for the Federal Circuit, in *Roche v. Bolar,* concluded that experimental use i.e. formulation development to obtain stability data, dissolution profile and bioequivalence data for regulatory submission, during the patent term, is an act of infringement.
- This decision created a situation of de facto patent term extension which was not supported by Food, Drug and Cosmetic Act, 1938 and Patent Act, 1952.

STATUTORY PROVISIONS: The Hatch-Waxman Amendments amended the Federal Food, Drug, and Cosmetic (FD&C) Act and created a statutory generic drug approval process with section 505(j). Section 505(j) established the abbreviated new drug application (ANDA) approval process,

which permits generic versions of previously approved innovator drugs to be approved without submitting a full new drug application (NDA). An ANDA refers to the clinical research and data in a previously approved NDA (the "listed drug") and relies on the Agency's finding of safety and effectiveness for the listed drug product.

Principle provisions of Hatch-Waxman Act: To overcome the above mentioned problems as well as to address the inadequacies in the pharmaceutical regulatory system, on September 24, 1984, President Ronald Reagan signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act") having three titles:

Title I: Abbreviated New Drug Application Provisions

Title II: Patent Term Restoration Provisions

Title III: Amendments to the Textile Fiber Products Identification Act and the Wool Products Labeling Act of 1939

Generic Drug Approval Process:

- ANDA process was created to encourage greater access to lower-priced drug products, and to shorten the time it took for generics to reach the market.
- The ANDA process does not require the generic manufacturer to repeat costly animal (preclinical) and human (clinical) research on ingredients or dosage forms already approved for safety and effectiveness.
- Drug companies must submit an ANDA for approval to the FDA's Office of Generic Drugs in the Center for Drug Evaluation and Research, wherein, a generic drug must meet the following criteria:

- ✓ Contain the same active ingredient(s) as the innovator drug (inactive ingredients may vary).
- ✓ Be identical in strength, dosage form, and route of administration.
- ✓ Have the same indications.
- ✓ Be bioequivalent (performs in the same manner as the innovator drug).

Generic Drug Competition Provisions

- **Orange Book :** Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book," is compiled by the USFDA and lists all approved drugs.

Each holder of an approved NDA must list patents, which he believes would be infringed if a generic drug were marketed before the expiration of these patents. NDA holder should list patent(s) in OB, within 30 days of NDA approval or within 30 days of patent grant.

The statute requires the NDA applicant to:

(a) Submit patents, by patent number, expiration date, and use codes; and

(b) The submitted patent must claim the drug that is the subject of the NDA or must claim a method of using such drug.FDA also publishes a list of exclusivity(s) pertaining to the specific product in OB.Once approved by the FDA, all products, both innovator as well as generic, are listed in OB.

ANDA STAY PROVISION AND PRELIMINARY INJUNCTION PRACTICE:

The scope of exclusivity granted by the FDA's thirty month stay provision under 21 C.F.R. § 314.107 (b) (3) (i) (A) has the same effect as a preliminary injunction because the provision prevents the ANDA applicant from producing, selling, or using its applied for drug product until a trial decision is made in the ANDA applicant's favor. Because of the statute has a similar result to a preliminary injunction, it is useful to compare the differences in how these to results are obtained.

A patent holder seeking a preliminary injunction against an alleged infringer must demonstrate:

- ✓ a reasonable likelihood of success on the merits;
- ✓ irreparable harm if an injunction is not granted
- ✓ a balance of hardships tipping in its favor
- ✓ the injunction's favorable impact on the public interest.The factors taken individually are not dispositive; instead, a district court in its discretion "must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested.

Showing the first two factors, likelihood of success and irreparable harm, are essential if a preliminary injunction is to be granted.[16] The preliminary injunction should not issue if the alleged infringer raises an infringement or invalidity defense that the plaintiff cannot prove "lacks substantial merit.In contrast to the requirements for issuance of a preliminary injunction, the FDA's thirty-month stay provision under 21 C.F.R. § 314.107 takes effect regardless of likelihood of success or irreparable harm. If a NDA holder files suit, the ANDA applicant's entry into the market is delayed for thirty months or until the ANDA applicant receives a favorable verdict even where the NDA holder has a very small chance of success on the merits of the suit. The ANDA applicant's barrier to entry remains absolute even where the ANDA holder presents powerful defenses that either tend to show non-infringement or presents serious challenges to validity of the NDA holder's patents.

TACTICAL USE OF THE THIRTY-MONTH STAY PROVISION: Because the thirty-month stay provision takes effect automatically, NDA holders have a very significant incentive to file suit against ANDA applicants even where the merits of the case are weak. Additionally, the power of the thirty-month stay provision provides incentive for NDA holders to list as many patents as possible in the Orange Book in order to ensure that competitors will need to make a paragraph IV certification even after a primary patent covering the NDA product has expired. The practice of prosecuting and listing secondary patents is referred to as "evergreening" or "trip wire" listing of patents.

Generic Drug Competition Provisions:

Statutory 30 months stay on ANDA approval: Generic applicant, who files paragraph IV in its ANDA, has to notify the patent holder and NDA filer about the ANDA submission with PIV certification, when FDA accepts his ANDA for filing.If the patent holder files an infringement suit against the generic applicant within 45 days of the PIV notification, 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.The district court dismissed Abbott's case pursuant to FRCP 12(b)(6) on March 16, 1996, and the Federal Circuit affirmed this dismissal in a succinct January 14, 1997 opinion[23], Here, the ANDA applicants had a clear cut case (clear enough to win the case on a motion to dismiss), but the barest legal argument as to why Abbott's patent should have expired in January 21, 1997 allowed Abbott to trigger the thirty-month stay provision and perpetuate the monopoly on its NDA product for over a year past the expiration date of their patent. The problem is exacerbated by the FDA's apparent lack of review or understanding of the patent laws in that it blindly accepted for the Orange Book Abbott's assertion that its patent would expire in 1997 and used this assertion to deny ANDA approval to two competitors. The Federal Circuit upheld summary judgment in favor Elan and found that Bayer's patent could not possibly cover Élan's product literally or under the doctrine of equivalents because Bayer had "made statements of clear and unmistakable surrender of subject matter outside the claimed SSA range of 1.0 to 4 m^2/g.[26] Despite the fact that Bayer's patent clearly did not cover Elan's product, Bayer's strained argument for a broad scope of its claims triggered the thirty-month stay provision and delayed Elan's ANDA application at least until March 16, 1999 when the district court granted summary judgment in Elan's favor.

The possible scenarios and tactical litigation moves that can arise are further complicated by the fact that the first ANDA applicant to make a paragraph IV certification is granted 180 days of

exclusive production before a second ANDA applicant can gain approval for its application *Mova Pharmaceuticals v. Shalala* illustrates the kind of situation that may arise Mova filed an ANDA application to produce a generic diabetes drug in December 1994.

A paragraph IV certification, however, begins a process in which the question of whether the listed patent is valid or will be infringed by the proposed generic product may be answered by the courts before the expiration of the patent. The submission of an ANDA for a drug product claimed in a patent is an infringing act if the generic product is intended to be marketed before expiration of the patent. This 30-month stay will delay approval of the generic drug product unless the court reaches a decision earlier in the patent infringement case or otherwise orders a longer or shorter period for the stay. Under FDA's traditional interpretation of the Hatch-Waxman Amendments, multiple 30-month stays have been possible. Submission of newly issued patents after an ANDA application has been filed with FDA has required the appropriate certification and notice to the NDA holder and patent owner with the possibility of a 30-month stay if patent infringement litigation resulted. As a result, there have been a number of instances in which delays in ANDA approval have exceeded 30-months.

A recent review of FDA's records indicates that of the 442 active ANDAs that contained paragraph IV certifications, only 17 have had multiple 30-month stays, representing 3.8 percent of all applications with patent challenges. However, we note that a significant number of these products have high dollar value annual sales, and we are aware of some instances where multiple stays have resulted in the delay of a generic drug approval for a number of years.

180-Day Exclusivity: The Hatch-Waxman Amendments provide an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification and thereby runs the risk of having to defend a patent infringement suit. The statute provides that the first applicant to file a substantially complete ANDA containing a paragraph IV certification to a listed patent will be eligible for a 180-day period of exclusivity beginning either from the date it begins commercial marketing of the generic drug product, or from the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first. These two events -- first commercial marketing and a court decision favorable to the generic are often called "triggering" events, because under the statute they can trigger the beginning of the 180-day exclusivity period. Only an ANDA containing a paragraph IV certification may be eligible for exclusivity. If an applicant changes from a paragraph IV certification to a paragraph III certification, for example, upon losing its patent infringement litigation, the ANDA will no longer be eligible for exclusivity. The 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years, as the courts, industry, and FDA have sought to interpret it in a

way that is consistent both with the statutory text and with the legislative goals underlying the Hatch-Waxman Amendments. A series of Federal court decisions beginning with the 1998 Mova[2] case describe acceptable interpretations of the 180-day exclusivity provision, identify potential problems in implementing the statute, and establish certain principles to be used by the Agency in interpreting the statute. As described in a June 1998 guidance for industry, FDA currently is addressing on a case-by-case basis those 180-day exclusivity issues not addressed by existing regulations.One of the most fundamental changes to the 180-day exclusivity program, resulting from the legal challenges to FDA's regulations, is the determination by the courts of the meaning of the phrase "court decision." The courts have determined that the "court decision" that can begin the running of the 180-day exclusivity period may be the decision of the district court, if it finds that the patent at issue is invalid, unenforceable, or will not be infringed by the generic drug product. FDA had previously interpreted the "court decision" that could begin the running of 180-day exclusivity (and the approval of the ANDA) as the final decision of a court from which no appeal can be or has been taken - generally a decision of the Federal Circuit. FDA had taken this position so that the generic manufacturer would not have to run the risk of being subject to potential treble damages for marketing the drug, if the appeals court ruled in favor of the patent holder.

Generic Drug Competition Provisions: The 180-day exclusivity is the so-called incentive for generic companies to step forward and challenge patents. The first applicant to submit a paragraph IV certification ANDA to the FDA has the exclusive right to market the generic drug for 180 days."First applicant—As used in this subsection, the term 'first applicant' means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug."

The 180-day market exclusivity period begins on earlier of two dates:

(i) Date of first commercial marketing of approved ANDA; and

(ii) Date of court decision holding that the patent which is the subject of the certification is invalid or not infringed.

The FDA granted the one hundred eighty day exclusivity period to Mylan instead of Mova since Mylan had not yet "successfully defended" itself against Upjohn.[34]Mova challenged this decision and ultimately prevailed in April 1998 when the D.C. Circuit held that the FDA's successful defense requirement was unsustainable based on Congress's statutory language.The complicated

statutory construction issues surrounding the 180-day exclusivity period addressed by the D.C. Circuit obscures the overall picture of what happened in this case. Upjohn sued Mylan in February 1997, and the trial court ruled that Upjohn's patent was *invalid* and not infringed on March 31, 1998.The problematic interaction between the thirty-month stay provision and 180-day exclusivity period is illustrated by a footnote in the *Mova*case.[37] An *amicus* brief by Biovail Corporation reveals that it was the second applicant to file a paragraph IV certification for a heart medication.The incentive of NDA holders to list as many patents in the Orange Book as possible ("land mine" patents) exacerbates thirty-month stay provision problems. Regulations allow "drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents" to be listed in the Orange Book.[41] Thus, pharmaceutical companies often list "unapproved uses, special crystalline forms of the active ingredient, specific formulations, tablet shape or other subject matter.

Options Available To Anda Applicants: An ANDA applicant who wants to avoid the thirty-month stay provision and faces patents listed in the Orange Book which do not cover the NDA drug itself but instead cover narrow forms of the drug or irrelevant uses for the drug (unapproved uses) has a very limited number of undesirable legal options available to it. The applicant either must argue to the FDA or to a court that paragraph IV certification should not be required or must certify against all the patents listed in the Orange Book and hope to have the inevitable lawsuit by the NDA holder dismissed on the merits as soon as possible to end the thirty-month stay. The ANDA regulations require that certifications be made only against patents "which claims the reference [Orange Book] listed drug or that claims a use of such listed drug.[47] To "claim" the drug, according to the patent law definition of "claim," a patent's claim section would have to include every element directed at the drug and no other elements. For example, a patent having claims that include elements of the drug and elements of packaging does not "claim" the drug.[48] The code suggests that the term "drug" includes only drug products (dosage forms) and drug substances (active ingredients).FDA regulation interpretations indicate that, in the FDA's view, an ANDA applicant must certify against every patent listed in the Orange Book. The FDA has "determined that 'Congress intended that an ANDA applicant need only consult the Orange Book to determine the existence of an applicable patent claiming the listed drug or use of the listed drug.The FDA's view is supported by the regulations' mechanism for challenging disputed patent. Existence of a formal procedure for disputing an Orange Book listing implies that third parties would have a reason, such as required certification, to dispute a listing.

Incentives of Patent Law: Exclusive rights granted for the originator of an invention or creative work, intellectual property rights, are well recognized in the modern laws of nearly every nation.64 In fact, the Constitution specifically allows Congress "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries. A number of principle philosophical foundations for privileging intellectual property rights exist. The foundations can help inform policy makers on what extent of intellectual property rights should be granted. Specifically, the ANDA thirty-month stay provision can be evaluated on the basis of how well the provision furthers the goals addressed by these philosophical foundations. The United States patent law regime, according to most courts, is primarily concerned with providing an economic incentive for invention. The U.S. Supreme Court has stated that, "The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. People are more likely to invent new products if they get an award in the form of the exclusive right to sell the product because the exclusive right to sell often translates into the ability to charge significant royalties for the invention compared to the price that would be charged if competition existed.The ability of the patent law to encourage development of knowledge through incentives must be weighed against the harm caused by the "patent monopoly. Ultimately, the inventor's royalty results in higher prices for consumers of the invention and perhaps a reduced output of production of the invention. Applying a utilitarian or economic standard to drug patents is an especially delicate balance. Obviously, for utilitarian and humanitarian reasons, the development of promising new drugs should remain a very high priority, and the government should maximize incentives for developing these new drugs. On the other hand, the costs of one inventor maintaining a monopoly on a drug are also quite high. Patient demand for a much needed drug is relatively inelastic, so the royalty on a drug monopoly can be very costly to consumers.The ANDA thirty-month stay provision is problematic from an economic or utilitarian perspective for several reasons. First, an NDA holder may sue an applicant based on any patent listed in the Orange Book for which it can make even the most strained argument for infringement. Many of these patents cover "unapproved uses, special crystalline forms of the active ingredient, specific formulations, tablet shape or other subject matter" which may or may not be truly useful or practical in a real world setting.Thus, the thirty-month stay provision extends the patent monopoly on a drug sold by the NDA holder while potentially only encouraging the NDA holder to prosecute and file suit on patents that disclose inventions that really do not help society at all. In these cases, the stay provision clearly is not supported by an economic or utility maximizing approach to patent law since the provision does nothing to encourage useful

drug development while society suffers all the costs of the patent monopoly. Secondly, the thirty-month stay provision encourages drug companies to file suit against an ANDA applicant based on unsustainably broad interpretations of their patent claims. For example, Bayer was able to utilize the thirty-month stay provision to prevent Elan from selling a drug with a measured SSA of 6.15 m^2/g on the basis of a Bayer patent listed in the Orange Book which only claimed a range of 1.0 to 4 m^2/g.[72] Bayer's patent is the only legal instrument which documents what Bayer has invented and what knowledge Bayer has contributed to the world in exchange for a patent monopoly, and according to this document, Bayer did not invent any variant of the drug having a SSA greater than 4 m2/g. Third, the thirty-month stay provision does not particularly encourage patents on the core commercial drug invention but instead encourages the practice of listing "evergreening" and "trip wire" patents.[73] In order to promote maximum utility and economic efficiency in society, it would be far better to encourage development on useful core drug inventions instead of encouraging drug companies to spend resources devising and identifying non-useful sub-inventions that may act as "trip wire" patents. A fourth problem with the thirty-month stay provision from an economic or utility maximizing perspective is that it encourages drug company emphasis on profits through patents in general. One problem with patents is that their power to encourage invention is limited by the ability of consumers to pay monopoly rents. The most economically efficient system would encourage that drugs be developed that will help society the most for the minimum research costs, rather than encouraging development of drugs that help the wealthy segment of the population slightly at greater research expense. To reach greater efficiency than the patent system allows, the public could, for example, divert funds from monopoly rents paid to patent holders toward direct government subsidies for drug researchers developing drugs which attack the most devastating diseases that affect the greatest number of people. The thirty-month stay provision enhances the value of patents in a vague way by allowing the patent to be used to significantly delay ANDA approval regardless of whether the patent actually covers the ANDA drug as long as some argument for infringement can be made. By enhancing the value of patents, the stay provision encourages drug companies to focus on the kind of drugs that are made most valuable by patents, namely those drugs which are marketable to people have the money to pay monopoly rents. A fifth problem with the thirty-month stay provision is that any gains it may provide to a company are too unpredictable and speculative to be substantial incentive for research and development. The drug company's primary patent on a new drug protects the company's monopoly on the NDA product for at least twenty years from the date the patent is filed. "Evergreening" or "trip wire" patents which might trigger the thirty-month stay of ANDA approval would not have value until after the primary patent which prevents others from

manufacturing and selling the drug has expired. During the twenty-year life of the primary patent, a better drug or treatment technology could potentially be developed thus making the potentiality of a thirty-month stay of competing ANDAs worthless. The thirty-month stay provision could be rescinded or reinterpreted not to be triggered upon suits based on "trip wire" patents again making the stay provision worthless. After twenty years, there may be no need to exclude ANDA competitors as it could be that no significant competitor exists. Since, ex ante, a drug company or inventor is likely to consider the potential gains from the thirty-month stay provision merely speculative rather than significant, the stay provision provides very little incentive for new drug manufacture.

There more efficient possibilities for encouraging research and development of new drugs rather than allowing new drug applicants to block ANDA applications based on patents which would not meet a preliminary injunction standard. One possibility, mentioned above, is that the public's payments toward patent monopoly rents could be shifted towards direct research for the most needed drugs. In this scenario, the thirty-month stay provision would decrease in importance as drug patents in general decrease in importance to drug companies.

Federal Trade Commission Study: In response to reports of brand-name and generic drug companies engaging in anti-competitive behavior, the FTC conducted a study to determine if the 180-day exclusivity and the 30-month stay provisions of the Hatch-Waxman Amendments have been used strategically to delay consumer access to generic drugs. In July 2002, FTC published the findings of their study and provided two primary recommendations. FTC recommended that only one automatic 30-month stay per drug product per ANDA be permitted to resolve infringement disputes over patents listed in the "Orange Book" prior to the filing date of the generic applicant's ANDA. FDA agrees with FTC's conclusion that recently, more ANDAs have been subject to 30-month stays, and more multiple 30-month stays, than in years past, and more patents on average are now being litigated per generic drug application than in the past.FTC's second recommendation was to pass legislation to require brand-name companies and first generic applicants to provide copies of certain agreements to FTC. This is a response to FTC's finding that brand-name companies and first generic applicants have on occasion entered into agreements to delay generic competition. FDA has no objection to this recommendation. FDA agrees with many of the conclusions of the FTC study and has found the factual information provided in the report to be extremely valuable in our own deliberations regarding the generic drug approval process. One example of this is the compilation of information on the disposition of litigation surrounding patents filed after NDA approval. Finally, we

note that FTC's report recognized that FDA does not have the capacity to review the appropriateness of patent listings.

FDA Rulemaking: On June 12, 2003, President Bush, HHS Secretary Thompson and FDA Commissioner McClellan announced a new regulation to be effective in 60 days that will streamline the process for making safe, effective generic drugs available to consumers. This rule was first proposed on October 24, 2002, in response, in part, to the FTC recommendations and other changes the Agency identified as being useful in improving generic competition. The new rule will limit an innovator drug company to only one 30-month stay of a generic drug applicant's entry into the market for resolution of a patent challenge. The rule provides a full opportunity for only one 30-month stay per ANDA or 505(b)(2) application; prohibits the submission of patents claiming packaging, intermediates, or metabolites; requires the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA; adds a requirement that, for submission of polymorph patents, the NDA holder must have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA; makes changes to the patent information required to be submitted and provides declaration forms for submitting that information to FDA, both with the NDA and after NDA approval; and does not require claim-by-claim listing on the declaration form except for method-of-use patents claiming approved methods of use.

30-Month Stay Provisions: The final rule limits brand-name companies to only one 30-month stay. The rule accomplishes this by establishing when generic companies must provide notice of a paragraph IV patent challenge to a brand-name sponsor and the patent owner (which initiates the 30-month stay process). Notice of a paragraph IV certification must be provided with an initial paragraph IV certification and when a previous certification and notice did not result in a full opportunity for a single 30-month stay. If an ANDA or 505(b)(2) application is amended to include a paragraph IV certification, notice must be provided to the NDA holder and patent owner only if the application did not already contain a paragraph IV certification or there was not a full opportunity for a 30-month stay. If an ANDA or 505(b)(2) applicant changes its paragraph IV certification before the 45-day period after notice to the NDA holder and patent owner has expired, and the NDA holder or patent owner has not initiated patent litigation, such paragraph IV certification and related notice are not considered to have satisfied the requirement of providing one notice of a paragraph IV certification and a full opportunity for a 30-month stay. Generic drug applicants will still have to file paragraph IV certifications to FDA, and the ability of brand-name firms to obtain patents and to

challenge alleged infringement in court is undiminished. They will not, however, be able to forestall approval of a generic version of a drug by engaging in submitting later-issued patents or repeated patent filings. These later submissions will no longer result in multiple 30-month stays.

Requirements for Drug Patent Submissions: Under the final rule, drug manufacturers will not be allowed to submit patent information for listing in the Orange Book for drug packaging, drug metabolites, and intermediate forms of a drug. Permitted submissions include patent information on drug product (active ingredients), drug substance (formulation/composition), and approved uses of a drug. In addition, patent submission declarations will be more detailed. There are mandatory forms that must be used to submit patent information to FDA. The forms include a series of questions with check-off boxes to be completed that provide details on the type of patent information submitted. The questions request information on whether the patent is one of the type permitted or not under the regulations, whether the patent is a product-by-process patent and the product claimed is novel, whether the method of use is an approved method of use and the relevant indication included in the approved labeling, and other relevant information. The declarations must be filed with the NDA, amendment, or supplement, and for patent information submitted after NDA approval. The check-off questions are designed so that FDA does not have to do anything more than quickly reviews the form to determine whether the patent information is eligible for listing. A signed attestation is required on the declaration form that requires that the submitter attest to the familiarity with the regulations and the information submitted.

Initiative on Improving Access to Generic Drugs: Concurrent with FDA's June 12, 2003, announcement on publication of its final rule, President Bush announced an initiative on Improving Access to Generic Drugs, which includes the following components:

- A proposed increase of $13 million in Fiscal Year 2004 in FDA resources devoted to improving access to generic drugs.

The proposed addition in the President's fiscal year 2004 budget of an additional $13 million in spending for FDA's generic drug programs would be the largest annual infusion of resources into the generic drug program ever, increasing the program's size by about one-third. FDA will be able to hire about 40 additional staff in generic drugs and expand the new chemistry review division in the Office of Generic Drugs. This expansion should help reduce the average review time by at least two months, increase the percentage of reviews that are completed within 180 days, approach the goal of reviewing 100 percent within 180 days and further reduce the time it takes FDA to review. Beginning in the next fiscal year, FDA will make significant changes in its processes for approving

generic drugs. In particular, the FDA will implement early communications with generic drug manufacturers to discuss their applications.

Recent Senate Action on Generics Legislation: We are pleased to note that in addition to our actions designed to speed access to generic drugs, last week the Senate Committee on Health, Education, Labor and Pensions by unanimous consent ordered reported legislation on generic drug access. This agreement is an important step forward. We recognize and appreciate Chairman Gregg's leadership in achieving a bipartisan agreement with the other original sponsors of the bill.

SUMMARY AND CONCLUSION

The statutory thirty-month stay of approval triggered by paragraph IV certification and subsequent patent infringement suit by the NDA holder is not efficient when evaluated under any of the prevalent norms justifying intellectual property regimes. The thirty-month stay provision allows NDA applicants to prevent generic drugs from entering the marketplace on the basis of expired patents, unsustainably broad readings of core patents on the NDA product, and "trip wire" or "evergreening" patents which do not reflect substantial change or improvement over an original patent but are prosecuted for the sole purpose of triggering the stay provision. The problems created by Hatch-Waxman Act's creation of the thirty-month stay provision should be addressed at many levels. First and most obviously, Congress should repeal the certification requirement for ANDA applicants. The FDA should interpret Hatch-Waxman Act within statutory constraints in order to minimize the stay provision's effect. The FDA could reasonably interpret the Hatch-Waxman Act to only allow core patents directly covering the NDA product to be listed in the Orange Book, and rigorously review all patents submitted for inclusion in the Orange Book for suitability. Courts should more freely exercise their discretion under the Hatch-Waxman Act to modify the length of the stay based on the plaintiff or defendant's failure "to cooperate reasonably in expediting the action. The FTC and parties excluded from the generic drug market because of the thirty-month stay provision may seek remedies through antitrust laws in some cases.Finally, individual attorneys should refuse to pursue patent prosecution or litigation that has little merit even if the client desires to trigger the thirty-month stay provision.

REFERENCES:

1. Markman V. West view Instruments holding that the judge must determine the scope of patent claims as a matter of law Inc. 1996; 1384-96.

2. Roberts v. Sears, Roebuck. Drug approval process in the European region, 18th edition, 2002; 6(2): 1321-35.
3. Bayer AG. Elan Pharmaceutical Research Corp., 212 F.3d 1241, 1248. http:// openjurist.org/ 212/ f3d/ 1241/ 2000.
4. Hayes TA. The Food and Drug Administration's regulation of drug labeling, advertising, and promotion: looking back and looking ahead. Clin Pharmacol Ther. 1998; 63(6): 607-616.
5. Derbis J, Evelyn B, McMeekin J. FDA aims to remove unapproved drugs from market: Risk-based enforcement program focuses on removing potentially harmful products. Pharmacy Today. 2008; 21-22.
6. David A Donohoe and Maiysha R Branch Akin, Orphan Drug Act. US Food and Drug Administration. 2011; 178-192.
7. Georgetown L.J, Justin Hughes. The Philosophy of Intellectual Property. 1988; 287-297.