Introduction:

One of the reasons for the rapid rise in manufacturing productivity in the United States was the presence of a strong patent system. The US patent system has protected the interest of its industries and has motivated innovation within the country. The US patent system has evolved to fit the needs of its economy. The patent system was created to meet the specific needs of the country at specific times.

The primary reason for the inclusion of the study of the US Patent system in this syllabus was to make the students understand the salient features of a strong patent system. We shall be comparing the US Patent system with that of the Indian system and understand the points of difference between the two.

10.1 Salient Features of US Patents:

To better understand the features of the US patent system we have made a comparison of the US system with that of the Indian system.

Basis	US Patent System	Indian Patent System
Patentable Subject Matter	US patent laws provide much broader grounds for patentability, allowing for the patenting of new and useful processes, machines, manufactures or compositions of matter, or new and useful improvements thereof. US Courts have interpreted this provision to allow for the patenting of new life forms, computer software and business methods.	As was mentioned earlier, product protection for pharmaceuticals, Chemicals and food products was provided under the 2005 Act. However, these provisions were tempered by the introduction of Section 3(d) into the Act, which denied protection to new forms, properties or uses of known substances which did not enhance efficacy. Other provisions of the Act deny protection to plants, animals and essentially biological processes of their production or propagations, business methods and computer programs and mental acts or methods.
Qualifications for Inventions – Utility	In the United States, the utility requirement is more liberal, allowing for the patenting of an invention as long as it 'is useful'.	The utility requirement in India corresponds to the requirement for 'industrial application, which, unlike the US requirement for utility, requires that an invention be capable of being made or used in an industry.

Basis	US Patent System	Indian Patent System
Obviousness	The non-obviousness requirement in US law declares that an invention is to be considered obvious if an analysis of the differences between the subject matter and the prior art show that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. The analysis of the obviousness requirement under US patent law has been detailed, and the creation of a number of formal tests and indicators of obviousness have somewhat restricted the scope of usage of this provision.	The obviousness requirement corresponds to the 'inventive step' requirement, which was modified in 2005. The new inventive step clause requires the invention to have a feature that involves a technical advance compared to existing knowledge or economic significance, either or both of which should make the invention non-obvious to a person skilled in the art.
Novelty	A significant difference between US and Indian patent laws lies in the fact that the US novelty requirement requires that the patent not be known or used by others within the US, but only that it not be patented or described in a printed publication in any other country.	The novelty requirement corresponds to the 'new invention' clause in the Act, which requires that the invention has not been anticipated by publication or use anywhere in the world prior to the filing of the patent application.
Administrative Provisions	The patent laws of the United States do not presently offer any provisions for pre-grant oppositions. All oppositions that may be raised by a third party must arise after the grant of the patent.	The Indian patent laws also provide more stringent procedures for the obtaining of a patent. Among the strictest of such procedures are those allowing for pre-grant oppositions, which allow any person to file a petition before the concerned patent office opposing a pending patent application. The grounds for the filing of such an opposition are detailed, and cover patentable subject matter, novelty, obviousness, wrongful

Basis	US Patent System	Indian Patent System
		obtaining of the invention, insufficient disclosure. The representation for a pre-grant opposition may be filed by any person, and is not limited to interested parties, allowing for the representation of public interest groups and other such parties.

10.2 The Hatch Waxman Act with reference to Generic Drugs:

The **Drug Price Competition and Patent Term Restoration Act** informally known as the **Hatch-Waxman Act** was enacted in 1984.The Act encourages the manufacture of generic drugs by the pharmaceutical industry and established the modern system of government generic drug regulation in the United States. Representative Henry Waxman of California sponsored the act.

Hatch-Waxman amended the Federal Food, Drug, and Cosmetic Act. The process for pharmaceutical manufacturers to file an Abbreviated New Drug Application (ANDA) for approval of a generic drug by the Food and Drug Administration (FDA).

According to amendment, the first company to file an ANDA for a particular drug will get 180 days of exclusive rights to market the drug as the generic alternative to the branded drug. The 180 days begins on the first day of marketing the drug under the ANDA.

The Act enables a generic pharmaceutical manufacturer to develop copy of a patented innovator drug without duplicating the clinical and non-clinical studies or risking liability for patent infringement damages. The generic manufacturer must only demonstrate bioequivalence to the innovator.

Background of Act:

Prior to 1962, drugs were approved for safety only. In 1962, the consequences of the discovery that the use of a drug called thalidomide by pregnant women (mostly in Europe) had caused severe birth defects, Congress added a requirement that drug manufacturers also prove the effectiveness of the products before FDA could approve them for marketing. Thus, under these amendments to the Federal Food, Drug, and Cosmetic Act, new drugs had to be proven both safe and effective before they could be legally marketed. It is also important to note that for drugs approved prior to approval of Hatch Waxman, generic versions could be approved with a "paper" new drug application (NDA). This "abbreviated" NDA was based solely on published scientific or medical literature. Therefore, a generic manufacturer could get its drug approved by presenting academic articles about the chemical demonstrating that it was safe and effective. Despite this fact, it was found that in the years after 1962 there were 150 drugs that were off-patent, but for which there were no generics because generic companies simply would not spend the time and money doing the clinical trials to get to market, and that there were only fifteen "paper NDAs," for post-1962 generics.

10.3 Objectives of Hatch-Waxman Act:

1. **Reducing the cost associated with approval of generic drug:** for getting the marketing approval for generic drug, the generic drug companies were no longer required to conduct costly and time consuming clinical trial studies of their own. The generic drug companies were allowed to relay on clinical studies done by branded drug manufacturer. The generic drug manufacturers only have to prove that the generic version is bioequivalent to the drug.
2. **Permission for Early Experimental Use:** before Hatch-Waxman Act even the experimental use of patented drug considered to be infringement. The generic drug manufacturers had to wait until the expiry of innovator drug patents before starting to prepare for marketing approval of generic version of that innovator drug. This result in undue prolongation of patent protection for the innovator drug. Due to this the approval for the generic version would take another 2-3 years to enter in market. Hence it was an objective of the Hatch-Waxman act to allow the early experimental use of the patented drug and not to consider as infringement.
3. **Motivating generic drug manufacturer:** the Hatch-Waxman Act establishes the concept of "Market Exclusively" in Federal Food, Drugs and Cosmetic Act. Under this provision exclusive marketing rights for 180 days were granted to generic drug manufacturer who was the first one to file application for marketing of generic version of innovator drug. This provision provided incentive for generic drug manufacturer to file Abbreviated New Drug Application (ANDA) and promote healthy competition. The drug could be available to public at relatively lower prices.
4. **Patent term Extension:** The branded drug manufacturer lost time from patent term because of regulatory approval formality. To compensate this time lost in regulatory approvals branded drug manufacturer were allowed a patent term extension (Maximum of 5 years).

10.3.1 General provisions of Hatch-Waxman Act:

1. **Creation of section 505(j):** Hatch-Waxman Amendments amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) and created a required 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 previously approved NDA (the "listed drug") and relies on the Agency's finding of safety and effectiveness for the listed drug product.
2. The timing of an ANDA approval depends in part on patent protections for the innovator drug. Innovator drug applicants must include, in an NDA, information about patents relating to the drug product that is the subject of the NDA. FDA is required to publish

the patent information submitted once the drug is approved. The regulation or law establishes a process that requires that ANDA applicants certify to the patents listed, provide notice to the NDA holder and patent owner, and, if patent infringement litigation is filed, it imposes a 30-month stay on the approval of an ANDA.

Conclusions:

1. The Hatch-Waxman act provides an expedited USFDA drug approval program for speedy generic entry and Market Exclusively as an incentive for continues innovation.
2. Pre Hatch-Waxman Act those seeking to market a generic version of branded drug also had to carry out their own safety and efficacy studies much like the branded drug companies.
3. Post Hatch-Waxman Act for getting marketing approval the generic drug companies are not required to conduct the costly and time consuming clinical trials studies.
4. The generic drug companies are allowed to relay on clinical studies done by the branded drug manufacturer.
5. Before Hatch-Waxman Act there was unethical patent extension due to unavailability of generic drugs as soon as the patent term of patented product is over.
6. After Hatch-Waxman Act this unethical patent extension was stopped.
7. The Hatch-Waxman Act has a provision for generic drug manufacturer that the generic version will not infringe the branded drug patent.
8. The Hatch-Waxman Act also allows for patent term extension of maximum five years for the branded drug manufacturer to compensate for the time lost during the New Drug Application (NDA) approved by USFDA

10.4 Orange Book:

For a generic drug to be approved by FDA, it must:

- contain the same active ingredients as the innovator drug
- come in the same dosage form
- be administered in the same way.
- be identical in strength
- have the same conditions of use
- be bioequivalent (the generic product gets to the relevant part of the body at the same rate as the innovator)
- meet the same standards for identity, strength, purity and quality
- be manufactured under the same standards that FDA requires for the manufacture of brand products

The publication of ***Approved Drug Products with Therapeutic Equivalence Evaluation,*** the list of the generic drugs is commonly known as 'Orange Book.'

Orange book contains list of drug products approved as 'Safe' and 'Effective' under section 505(c) of the Federal Food, Drug, and Cosmetic Act

The List is composed of four parts:

(1) Approved prescription drug products with therapeutic equivalence evaluations;

(2) Approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs, because they are not covered under existing OTC monographs;

(3) Drug products with approval under Section 505 of the FD&C Act administered by the Center for Biologics Evaluation and Research; and

(4) A cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn for safety or effectiveness reasons, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing

This publication also includes indices of prescription and OTC drug products by trade or established name (if no trade name exists). All established names for active ingredients generally conform to official compendia names or *United States Adopted Names* (USAN).

An *Addendum* contains drug patent and exclusivity information for the Prescription, OTC, Discontinued Drug Product Lists, and for the Drug Products with Approval under Section 505 of the FD&C Act Administered by the Center for Biologics Evaluation and Research. The publication may include additional information that the Agency deems appropriate to disseminate.

The 1984 Amendments required the Agency to begin publishing an up-to-date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required.

Under the FD&C Act, some drug products are given tentative approvals. The Agency will not include drug products with tentative approvals in the List. Tentative approval lists are available on FDA's website at Drug Approval Reports. When the tentative approval becomes a full approval through a subsequent action letter to the applicant, the Agency will list the drug product and the final approval date in the appropriate approved drug product list.

The industries, consumers and health care professionals can utilize orange book.

Orange Book is available on the internet**: http://www.fda.gov/cder/ob/default.htm**

In Conclusion:

- Generic drugs now represent 88 percent of drugs dispensed in the United States.
- The *Orange Book* is particularly critical in determining when generic drug versions can be substituted for the brand name product.

Although some outside users repackage the information, the only definitive source for Therapeutic Equivalence (TE) and brand-name ("innovator") drug data, as well as Patent and Exclusivity data, is the *Orange Book*.

10.5 Contents of ANDA and Bioequivalence:

- An Abbreviated New Drug Application (ANDA) contains data submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, for review and ultimate approval of a generic drug product.
- Once ANDA is approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public.
- A generic drug product is the 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 (Orange Book).
- Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One of the ways that scientists use to demonstrate bioequivalence is to measure the time taken by the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This will gives them the rate of absorption or bioavailability of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.
- Use of bioequivalence as the base for approving generic drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the HATCH WAXMAN- ACT. It is because of this Act that there is the availability of less costly generic drugs into the market without conducting costly and duplicative clinical trials. At the same time, the brand-name companies (innovators) can apply for up to five additional years longer patent protection for the new medicines that they developed to make up the time lost while their products were going through FDA's approval process.
- Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.
- Pharmaceutical Equivalents: Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules).

- Therapeutic Equivalents: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labelling.

10.5.1 Guidelines Available For ANDA:

Various guidelines have been developed to assist applicants in preparing and filing ANDAs. These guidelines describe:

Format & content for the following sections:

a. Application summary
b. Chemistry, Manufacturing and controls section
c. Non clinical pharmacology and toxicology section
d. Human pharmacokinetics & bioavailability section
e. Clinical and statically section
f. Microbiology section

Various guidelines available for ANDA includes:

1. Organization of ANDA
2. Electronic submission of data for ANDA
3. Submission of archival copy of application in Microfiche
4. Guideline for impurities in drug substances
5. Guideline for submitting supporting documentation for the Manufacture of Drug substance.
6. Guideline for submitting supporting documentation for the Manufacture of finished dosage forms.
7. Guideline for submitting supporting documentation for stability studies of Human drugs and Biologics.
8. Guideline for packaging
9. Guidelines for changes in approved ANDA and NDA
10. 180 days exclusivity under Hatch Waxman amendment
11. Guidelines for alternate source of API in pending ANDAs
12. Post marketing reporting of Adverse Drug reactions

10.5.2 Filing of ANDA:

- In order to file ANDA all required items should be in proper order (organization).
- Office of Generic Drug (OGD) strongly encourages submission of the bioequivalence, chemistry and labeling portions of an application in electronic format.

10.5.3 Difference between Submission of NDA and ANDA:

In contrast to NDA, ANDA requires the submission of:

NDA	ANDA
A New Drug Application (NDA) requires the submission of : 1. Well-controlled clinical studies to demonstrate effectiveness 2. Preclinical and clinical data to show safety 3. Detailed descriptions of manufacturing and packaging procedures 4. Proposed annotated labeling referencing all studies from which statements contained in the package insert has been derived.	A Abbreviated New Drug Application (ANDA) requires the submission of 1. Detailed descriptions of the components 2. Manufacturing, controls, packaging, and labeling (which can be in final, printed form), data sufficient to assure the bioavailability or bioequivalence of the drug to be marketed. The labeling should be prepared in accordance with that specified in DESI (Drug efficacy study implementation) Notice or other Federal Register

10.6 Patent Certification:

A valuable provision of the Hatch-Waxman Act requires that ANDA-applicants make one of four "certifications" with respect to each patent listed in the Orange Book for the particular drug to which the ANDA is directed. And if there are no patents listed, ANDA-applicants must so certify.

1. **Paragraph I certification:** The patent information has not been submitted for listing in the Orange Book.
2. **Paragraph II certification:** The patent has expired.
3. **Paragraph III certification:** The patent will expire on a given date.
4. **Paragraph IV certification:** The patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted.

If an applicant makes a paragraph I or paragraph II certification, the FDA may approve the ANDA "immediately." If a paragraph III certification is made, the ANDA-approval is effective on the date the patent expires. If, however, an applicant wishes to obtain FDA approval during the term of a listed patent, it must make a paragraph IV certification.

The Hatch-Waxman Act requires that when an applicant makes a paragraph IV certification, the applicant must provide notice of such certification to the patent owner and holder of the NDA for the branded drug to which the ANDA applies.

In particular, the statutorily required notice must include a "detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid [or unenforceable] or will not be infringed."

The purpose of the notice is to alert the patent owner of the challenge to its patent(s) and to give the owner time to decide whether to bring an action for patent infringement. The patent owner has a special 45-day window in which to decide whether to file suit.

If the owner does not file suit within 45 days, the FDA may approve the ANDA immediately. If, however, the patent owner files suit within 45 days, the FDA is prohibited from approving the ANDA for 30 months, unless the ANDA-applicant prevails in the ensuing litigation before the 30-month period.

Review Questions

Q. 1 Differentiate between NDA and ANDA. Write a note on 'The Orange Book'. **(April 2010; 10 Marks)**

Q. 2 Explain certification for ANDA. **(April 2016; 5 Marks)**

Q. 3 Write significance of Hatch Waxman Act. **(April 2013; 3 Marks)**

Q. 4 Define generic drug and branded drug? **(April 2016; 3 Marks)**

Q. 5 What is Hatch Waxman Act with reference to generic drugs, add note on ANDA and bioequivalence.**(April 2011; 10 Marks)**

Q. 6 What is Hatch Waxman Act ? **(April 2012; 3marks)**

Q. 7 Discuss in detail Hatch Waxman Act with reference to NDA and ANDA. **(10 Marks)**

Q. 8 Write significance of Hatch Waxman Act, **(3 Marks)**

Q. 9 Discuss in detail Hatch Waxman Act with reference to ANDA.**(April 2014; 5 Marks)**

Q. 10 What is therapeutic equivalence book? **(April 2014;3 Marks)**

Q. 11 Write a note on 'Orange Book' **(October 2011; 5 Marks)**

Q. 12 Why generic drugs are cost lesser than innovator drug. **(October 2012; 3 Marks)**

Q. 13 Define generic drug and branded drugs. **(April 2016; 3 Marks)**

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