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REVIEW ARTICLE

REGULATORY PERSPECTIVE OF GENERIC ANTI CANCER DRUG DEVELOPMENT PROCESS IN EUROPE AND USA

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ABSTRACT

The aim of the present study discuss about the generic anti-cancer drug development process in the Europe and USA. It deals with the classification of the anti-cancer drugs and the criteria for selection of the anti-cancer drugs, GMP specific requirements for cytotoxic drugs in EU and USA, its bioavailability and bioequivalence study and the oncology drug product market approval process and its comparison its data exclusivity and market protection and entry of oncology drugs into the market.
Keywords: Oncology, EU, USFDA

INTRODUCTION

The health care system counts on drug regulatory affairs for availability of good and safe effective medicines are available to the patients. The Drug Regulatory Affairs is responsible for ensuring the efficacy, safety and quality of medicines in the entire product life cycle, and is expected to carry out its tasks by applying the best available scientific knowledge and skills without bias. Regulatory authorities are continually challenged by the rapid development and sophistication of medicinal product, new technologies and health care techniques. Any strategy to improve anything in pharmaceutical or any problem encountered in the area of pharmaceuticals needs up port from drug regulatory authorities. Such development poses a heavy demand on proper regulatory control system. In drug regulation, the government sets legal requirements relating to drugs and specifies the activities that must be under taken before and after a drug is placed in the market. Regulation of drugs encompasses a variety of functions. Key functions include licensing, inspection of manufacturing facilities and distribution channels, product assessment and registration, adverse drug reaction(ADR) monitoring, Quality control and control of clinical drug trials. Each of these functions targets a different aspect of pharmaceutical activity [1].

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Table 1: Classification of anti- cancer drugs

CYTOTOXIC DRUGS				HARMONAL DRUGS	MISCELLANEOUS DRUGS
ALKALYTING AGENTS	**ANTI METABOLITES**	**ANTIBIOTICS**	**PLANT DERIVATIVES**	Glucocorticoids	Crisantapase
Nitrosourea	Folate antagonists	Anthracyclines	Vinka Alkaloids	Oestrogens	Amsacrine
Busulfan	Pyrimidine analogues	Dactomycin	Taxanes	Progestogens	Imatinib
Platinum compounds	Purine Analogues	Bleomycin	Etoposide	GH analogues	Monoclonal antibodies

CRITERIA FOR SELECTION OF ANTICANCER DRUGS The Regulatory perspective of anticancer drug development is a sequential process, four parameters are selected for the understanding and studying the regulatory requirements.

Part-I: Study about the Oncology: Anticancer drugs are mainly Cytotoxic drugs i.e. this treatment destroys the body's normal cells in addition to cancerous cells. Due to nature of cytotoxic many of the side effects are associated with Antineoplastic agents.

Part-II: Specific Regulations for anticancer Drugs:

a) Specific Regulations at manufacturing site: Good Manufacturing practice guidelines and WHO Bio safety guidelines indicated some specific regulations for manufacturing and handling of anticancer (Cyto toxic) drugs.

B) Bioequivalence study information: Anticancer drugs mainly cytotoxic drugs and have a many of side effects are associated with it, so that for safety concerns Bioequivalence study should be conducted on Patients instead of Healthy Volunteers.

Part-III: Bioavailability and Bioequivalence study information: During conducting Bioequivalence study, it should be conducted in according to the irrational regulatory legislations and the various differences like statistic application, study population, the fasting and fed conditions, etc. in the study pattern of the Bioequivalence study of US and Europe country .

Part-IV: the compilation of dossier included about the parentral and solid dosage forms according to USFDA and EMA. And the study about the fast track applications for new drugs and ANDA and Europe application procedure for generic drug application.

ANTICANCER DRUGS :

Anti-neoplastics and anticancer drugs are used to prevent or inhibit the maturation and proliferation of neoplasms and also destroy cancer cells in addition to body's normal cells also. this causes many side effects like Bone marrow depression, Lymphocytopenia, GIT **EU AND US SPECIFIC REQUIREMENTSFOR ANTICANCER DRUGS :**

Personnel training:

Personnel working in handling and preparation of cytotoxic drugs should be given specific training for control and protecting from hazardous environment. Premises and Equipment: The Production area should be minimizing the risk of a serious medical hazard due to cross

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contamination. In this dedicated and self-contained facilities must be available for the production of particular medicinal, such as highly sensitizing materials. The production of cytotoxic drugs and certain highly active drugs should not be conducted in the same facilities and it should be in separate area. For these products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made

Containment ofcytotoxic drugs:

Dedicated production areas should also be considered when materials of highly pharmacological or toxicity is involved i.e. certain steroids or cytotoxic anticancer agents, unless validated inactivation and/or cleaning procedures are established and maintained [2].

Cytotoxic drug safety specifications:

Class II biological safety cabinets are used to prevent harmful exposure to cytotoxic agents during their compounding or preparation for parenteral use. Biological safety cabinets may be used to control harmful exposure to aerosols and particulate matter provided the presence of the substance in the biological safety cabinet does not present a risk off explosion. When biological safety cabinets are used to control exposure to these hazards they shall meet the requirements of this section.

NOTE: The U.S. Department of Labor recommends the use of externally vented biological safety cabinets for the preparation of cytotoxic drugs in its work practice guidelines for cytotoxic drugs, OSHA Instruction PUB8-1.1, January29, 1986[3].

Biosafety Level 2 Criteria (BSL-2):

Biosafety Level 2:

BSL-2 is suitable for work involving agents that poses moderate hazards to personnel and the environment. It differs from BSL-1 in that

1) Laboratory personnel have specific training in handling pathogenic agents and are scientists competent in handling toxic agents and associated procedures;

2) Access to the laboratory is restricted when work is being conducted;

3)All procedures in which toxic aerosols or splashes may be created are conducted in BSCs or other physical containment equipment.

The following standard and special practices, safety equipment, and facility requirements apply to BSL-2:

A. Standard Practices

B. Special Practices

C. Safety Equipment (Primary Barriers and Personal Protective Equipment)

D. Laboratory facilities (secondary barriers)

A. Standard Practices

- The laboratory supervisor must enforce the institutional policies that control access to the laboratory.
- Persons must wash their hands after working with potentially hazardous materials and before leaving the laboratory.

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- Eating, drinking, smoking, handling contact lenses and storing food for human consumption must not be permitted in laboratory areas.
- Instead of mouth pipetting, mechanical pipetting devices must be used.
- .Policies for the safe handling of sharps, such as needles, pipettes and broken glass ware must be and implemented.
- Perform all procedures to minimize the creation of splashes and/or aerosols. Decontaminate work surfaces after completion of work and after any spiller splash of potentially toxic material with appropriate disinfectant.
- Decontaminate all stocks, and other potentially toxic materials before disposal using an effective method.
- Depending on where the decontamination will be performed, the following methods should be used prior to transport B. Special Practices
- All People entering the laboratory must be advised of the potential hazards and meet specific entry/exit requirements.
- Laboratory personnel must be provided medical surveillance and offered appropriate immunizations
- for agents handled or potentially present in the laboratory.
- A laboratory-specific biosafety manual must be prepared and adopted as policy.
- The biosafety manual must be available and accessible to the employers.
- The laboratory supervisor must ensure that laboratory personnel demonstrate proficiency in standard and special microbiological practices before working with BSL-2 agents. Potentially toxic (toxic)materials must be placed in a durable, leak proof container during collection, handling, processing, storage, or transport with in a facility.
- Laboratory equipment should be routinely decontaminated, as well as, afters pills , splashes, or other potential contamination.
- C. Safety equipments : (Primary barriers)
- Properly maintained BSC's, other appropriate personal protective equipment or other physical containment devices must be used whenever work with toxic agents involve
- aerosols, large volumes, high concentrations.
- Protective laboratory coats , gowns , socks or uniforms designed for laboratory use must be worn while working with hazardous materials
- Eye and face protection must be disposed of with contaminated laboratory waste or decontaminated before reuse

- **D. Laboratory facilities**
- Laboratories should have self-closing doors Laboratories should have a facility of sink for hand washing and it may be manually, hands- free, or automatically operated.
- The laboratory should be designed for easily cleaned and decontaminated.
- Windows that open to the exterior are not recommended. If it has windows then it should be fitted with screens.
- BSCs must be properly installed so that fluctuations of the room air supply and exhaust do not interfere with proper operations.
- Vacuum lines should be protected with High Efficiency Particulate Air (HEPA) filters, or their equivalent.

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- Filters should be properly maintained.
- An eyewash station must be readily available.
- HEPA filtered exhaust air from a Class II BSC can be safely re-circulated back into the laboratory environment if the cabinet is tested and certified at least annually and operated according to manufacturer‘s recommendations

Bioavailability and bioequivalence

- **Bioavailability** is defined as–the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action‖.
- **Bioequivalence** is defined as–the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Specific requirements for anticancer drugs for bioequivalence studies :

For conducting Bioequivalence studies for cytotoxic drugs, the studies should conducted on patients instead of healthy volunteers because of safety concerns or safety profile of the cytotoxic drugs.

- According to USFDA 21CFR part 320.31, to conduct Bioequivalence studies for cytotoxic drugs, the applicant shall submitan— Investigational New Drug Application‖ to the authority and it is called as — Bio-IND‖[4].
- But according to EMEA, for conducting Bioequivalence studies for cytotoxic, drugs there is no specific regulation like USFDA.
- **Investigational New Drug Application :**
- An IND (investigational new drug application) is a submission to the U.S. Food and Drug Administration (FDA) requesting permission to initial preclinical study of a new drug product in the United States.
- An IND is a request for authorization from the Food and Drug Administration(FDA) to administer an investigational drug or biological product to humans.
- **Bio-IND:**
- The requirements for submission of a Bio-IND in support of an abbreviated new drug application(ANDA) were revised when FDA published the Title I regulations.
- The revisions made the requirements for the submission of a Bio-IND consistent with the Office of Generic Drug (OGD) practice at that time.
- The regulations state specifically when a Bio-IND must be submitted for an invivo bioavailability or bioequivalence study involving a cytotoxic drugin humans.
- The applicant (Sponsor) has to complete the form FDA 1571 to assume the responsibility of Investigation of study.

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The Bio– IND application requirements:

Type of IND (Basis) FDA Form 1571- Completed/Original Signature

- Table of Content.
- Introductory Statement
- General Investigational Plan
- Protocol.
- Components &Composition.
- Manufacturing Controls for Active Ingredient DMF.
- Specification and tests for Active Ingredient
- .Source of Active Ingredient.
- COA (Certificate of Analysis) from Manufacturer of Active Ingredients.
- Specification and Tests for Inactive Ingredients
- Source of Inactive Ingredients.
- COA for Inactive Ingredients.
- COA for Finished Dosage Form
- Manufacturing Controls (Method and Equipment).
- Address of Manufacturing. site
- Manufacturing Procedure (Batch Records)Batch/Lot
- Stability Profile Including Stability Data.
- 3 Months Accelerated Stability Data
- Batch/Lot #Listed on Stability Records.
- Container/Closure Information
- Environmental Assessment or Claim for Exclusion
- Compliance Statement Additional Information[15]

U/US CTD MODULE3 QUALITY SECTION DOSSIER REQUIREMENTS FOR SOLID DOSAGE FORMS AND PARENTERAL DOSAGE FORMS [5-8]

Table 2: Dossier Requirements for Solid Dosage Forms

Module No	Solid Dosage Form	Parentral Dosage Form
3.2.P.1. Description and Composition of Drug Product		
Dwscription of the dosage form	**Required**	**Required**
Composition	**Required**	**Required**
Description of diluents	**Required**	**Required**
Type of container closure	**Required**	**Required**
3.2.P.2pharmaceutical development		
P.2.1components of drug product		
P.2.1.1 DRUG SUBSTANCE		
1.literature survey	required	required
2. characterization of	Solubility,	Solubility,

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API	water content crystal properties permeability particle size photo stability bulk density compressibility	water content crystal properties permeability particle size photo stability BET sterility
3.Drug-excipient compatibility study	(i)list of excipients with their function (ii)analytical test procedure (iii)drug excipient compatibility study	(i)list of excipients with their function ii)analytical test procedure (iii)drug excipient compatibility study (iv)drug constituents compatibility study
P.2.1.2 **1) choice of exciepients, concentration and function**	Diluent Binder Disintegrant Lubricant Glidant Film-former Plasticizer Purified water	Solvent Buffers Antioxidants Bulking agents Chelating agents Surfactant emulsifier
(ii)optimization of excipient concentration	Effect of binder Effect of disintegraEffectof lubricant	Buffers Antioxidants Tonicity adjusting agents
P.2.2. DRUG PRODUCT		
P.2.2.1 FORMULATION DEVELOPMENT		
1.Development	Required	required
2. characterization of innovator products	Required	required
2.1 product description and details	Required	required
2.2 chemical characterization	Selection of dissolution media Comparative dissolution profile of Test product with Reference productin3 medias Impurity profile comparison Assay	Impurity profile comparison assay
3. bioequivalence study	i) If any biowaivers with support ofbioequivalencestudy: Comparative dissolution study of all strengths with Bio batch	----------

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	ii) Batch analysis of Test and Reference product	
P.2.2.2 AVERAGES	If required	If required
P.2.2.3 PHYSICO CHEMICAL AND BIOLOGICAL PROPERTIES	Selectionofdissolution medium	Selectionofdissolution medium
P.2.3 MANUFACTURING PROCESS DEVELOPMENT	Selection ofgranulationand compressionmethodProcessOptimization: A) Process Optimizationat Laboratory scale B) B) Process Optimization at ProcessScale	Method of sterilization (Timebase/F0 basecycle) ProcessOptimisation: A) Process Optimization at Laboratoryscale B) Process Optimization at Process Scale
P.2.4 CONTAINER CLOSURE SYSTEM		
P.2.5 MICROBIAL ATTRIBUTES	Microbial tests	Microbial tests(Sterility,BET) Description about Integrity of Container closure system to prevent microbial contamination (CCIT)
P.2.6 COMPATIBILITY	If required	Compatibility with reconstitution diluents
3.2.P.3 MANUFACTURE		
P.3.1 MANUFACTURER	details	details
P.3.2 BATCH FORMULA	required	required
P.3.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROL		
1.Flow diagram of manufacturing process	Solid dosage forms	Parenteral dosage form
2.Description of manufacturing process	Sifting, Mixing, Granulation, Drying, sizing, Blending and Lubrication, Compression, Coating, Packaging.	Cleaning, Sifting, Sterilization of tank and filters, Preparation of Bulk product, Filtration, Filling with volume setup, Sealing, with IPQC checks, Sterilisation of container (If required)and Packaging.
P.3.4 CONTROL OF CRITICAL STEPS AND INTERMEDIATES	BlendingandLubrication, Compression,Coating, Packaging.	(Dry powders)Filling-leak test, wt variation purge with inert gas Solutions-Water release, Filtration (Bio burden),Fill volume, Oxygen content , leak test, sealing, sterilization and packaging.
P.3.5PROCESS	Drying ,sizing and lubrication	Sterile validation

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VALIDATION **process validation data** MODULE NO.		
3.2.P.4 CONTROL OF EXCIPIENTS		
P.4.1 SPECIFICATIONS	required	required
P.4.2 ANALYTICAL PROCEDURE	required	required
P.4.3VALIDATION OF ANALYTICAL PROCEDURE	required	required
P.4.4 JUSTIFICATION OF SPECIFICATION	List of all specifications with tests, acceptance limits and results for all excipients	List of all specifications with tests, acceptance limits and results for all excipients
P.4.5EXCIEPIENT OF HUMAN OR ANIMAL ORIGIN	required	required
P.4.6 NOVEL EXCIPIENTS	required	required
3.2.P.5 CONTROL OF DRUG PRODUCT		
P.5.1 SPECIFICATION	Description Identification test Averge weight Water content Dissolution,disintegration Hardness Uniformity of dosageunit Impurities Assay Microbial limit tests	Description Identification test Water content Uniformity of dosage units Impurities Assay Sterility Endotoxins Antimicrobial preservative Antioxidant preservative Particle size distribution Redispersibility Reconstitution time
P.5.2 ANALYTICAL PROCEDURE	For all above parameters	For all above parameters
P.5.3 VALIDATION OF ANALYTICAL PROCEDURE	1. Method validation of Identification 2. Method validation of dissolution 3. Method Validation of Impurities 4. Method validation of Assay 5. Method validation of Microbiallimittests	1. Method validation of Identification 2. Method Validation of Impurities 3. Method validation of Assay 4. Method validation ofMicrobiallimittests BET(bacterial Endotoxintest)

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<table>
<tr><td></td><td colspan="5"></td><td colspan="5">5. Sterile validation Time/Fo base cycle</td></tr>
<tr><td>P.5.4BATCH ANALYSIS (tests , Acceptance limits and results)</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>P.5.5 CHARACTERISATION OF IMPURITIES</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>P.5.6 JUSTIFICATION OF SPECIFICATIONS</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>3.2.P.6 REFERENCE STANDARD MATERIAL</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>3.2.P.7 CONTAINER CLOSURE SYSTEM</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>Description of the container closure system</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>Composition and quality of packing materials</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>Container size</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>Specifications and analytical procedures and batch analysis data for the primary packaging materials</td><td colspan="5">Required</td><td colspan="5">required</td></tr>
<tr><td>Secondary packaging materials</td><td colspan="5">---------</td><td colspan="5"></td></tr>
<tr><td rowspan="3">P.8.1 STABILITY SUMMARY AND CONCLUSIONS
Formal study:
Long term
Accelerated
Intermediate
Photo stability</td><td colspan="5">General case</td><td colspan="5">General case</td></tr>
<tr><td>study</td><td>Storage condition</td><td colspan="2">Min. Time in months</td><td>Study</td><td>Storage condition</td><td colspan="2">Min . time in months</td></tr>
<tr><td>EU</td><td>US</td><td></td><td></td><td>EU</td><td>US</td></tr>
<tr><td>L</td><td>25°C±2°C/ 60% RH± 5%RHor 0°C± 2°C/65% RH± 5%RH</td><td>6</td><td>3</td><td>L</td><td>25°± 2°C/60% RH± 5%RHoor 30°C± 2°C/65% RH± 5%RH</td><td>6</td><td>3</td></tr>
</table>

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	I	30°C± 2°C/65% RH± 5%RH	6 months	3 months	I	30°C± 2°C/65%RH ± 5%RH	6 months	3 months
	A	40°C± 2°C/75% RH± 5%RH	6 months	3 months	A	40°C± 2°C/75% RH± 5%RH	6 months	3 months
P.8.2 POSY APPROVAL STABILITY AND PROTOCOL STABILITY COMMITEMENT	required				required			
P.8.3 STABILITY DATA Results of Formal stability study: **Long term** **Accelerated** **(If needed)** **Intermediate** **Results of Photo stability study**	required				required			

ONCOLOGY DRUG PRODUCT MARKET APPROVAL PROCESS

US FDA: FAST TRACK MECHANISM

- The Food and Drug Administration Modernization Act of 1997 (FDAMA, P.L.105-115) directed the Secretary to create a mechanism whereby FDA could designate –Fast Track‖ certain products that met two criteria.
- First, the product must concern a serious or life-threatening condition; second, it has to have the potential to address an unmet medical need.
- Once FDA grants a Fast Track designation, it encourages the manufacturer to meet with the agency to discuss development plans and strategies before the formal submission of an NDA/BLA. The early interaction can help clarify elements of clinical study design and presentation whose absence at NDA/BLA submission could delay approval decisions. However, FDA makes similar interactions available to any sponsor who seeks FDA consultation throughout the stages of drug development.
- A unique option within FastTrack is the opportunity to submit sections of an NDA/BLA to FDA as they are ready, rather than the standard requirement to submit a complete application at one time [9].

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EUROPEANMEDICAL AGENCY:

- There are currently two main mechanisms available in the EU that may be used to facilitate the development and the marketing authorization process of oncology drugs: Exceptional circumstances provision and the Accelerated evaluation procedure.
- **Exceptional circumstances provision:**
- The EU drug law, as currently codified in the Commission Directive 2003/63/EC, allows that a marketing authorization may be granted based on a reduced development programme (e.g. based only on phase II studies) under so-called ‗exceptional circumstances'.
- These exceptional circumstances include development for use in a rare condition (e.g. orphan condition) or where in the present state of scientific knowledge, comprehensive information cannot be provided or when it would be unethical to collect further data. For anticancer agents the CPMP **Note for Guidance on Anticancer Medicinal Products** explains how to use these provisions in order to facilitate the development of oncology drugs.
- According to the Note for *Guidance on Anticancer medicinal Products* a marketing authorization application can be based on data from uncontrolled clinical trials when there is no approved treatment available and an investigational drug shows outstanding anticancer activity.
- Additionally, this guideline endorses the use of tumor response as a surrogate endpoint, if it is justified to predict clinical benefit.
- Overall, the exceptional circumstances provision has been used frequently over the past three years to facilitate the marketing authorisation of innovative oncology drugs in the EU.
- **Accelerated approval process:**
- The EMEA first provided guidance on an accelerated evaluation of products in 1996. This guidance for saw a scientific review time of 120 days instead of the standard 210 days for drugs that meet the following three cumulative criteria:
- Indicated for treatment of a heavily disabling or life threatening disease
- Absence of an appropriate alternative therapeutic approach

Table 3: Comparison of Distinguishing Parameters and Requirements for Generic Drug Approval Process Between USFDA And EU (EMA)

	EUROPE	USA
Regulatory authority	EMA	USFDA
Governance	Various Directives/ Eudralex	21CFR
Address	7 West ferryCircus, CanaryWharf,LondonE14 4HB	5600 FishersLane Rockville, MD20852-1750, United States
Members states	30	1
Climatic zone	II	I
Type of fillings	ASMF/NDA/Abridged	DMF/NDA/ANDA

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DMF type	ASMF	Type I, II,III& IV
Application form	CP-Administrativeinformation Application form for a Scientific Opinion accordingto Article 58ofRegulation (EC) 726/2004 MRP/DCP– Depends on country	356h
Dossier format	EU CTD	US CTD
RLD	European Pharmacopeia/ innovator drug	Orange Book
Exhibit batches required	2	1
Stability studies batches API Drug Product	2Production scale or 3Primaryscale 2Pilot Scale– API known to bestable 3PrimaryScale– APIknown to be unstable.	3Primarybatches 1Primarybatch
Testing frequency Accelerated	Amin.of3points include initial and final	0,1,2,3,6.
Fees	CP– 242600Euro MRP/DCP- Depends oncountry	Right now no fees (But implementation is under process)
Approval time	CP- 289(Exclusive ofclockoff)MRP- 210to 270+ DCP– 135to300+	15months inclusive of clock stops
Language	English	English
Application	CP-ENGLISH	CP-ENGLISH
Labeling	MRP/DCP depends on country	MRP/DCP depends on country
CTD 3.2.R. regional informatiom	• Process Validation Scheme forthe Drug product • Certificate(s) ofSuitability • Medicinal products containing orusing inthe manufacturingprocess	• ExecutedBatchRecords • MethodValidation Package • ComparabilityProtocols

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Table 4: Protection Period Comparison between EU & US

Protection	EU	US
Basic Product Patent	Yes(20years)	Yes (20years)
PatentExtensions SupplementaryProtection Certificates,	Yes	Yes
Bolar Provision Right to perform generic R&D before patent expiration	Yes	Yes
ImmediateGeneric Competition Upon patent expiration	No	Yes
Pediatric Extensions	Yes	Yes
Data Exclusivity Blocks market authorization procedures for generics	8years data exclusivity(non disclosure/reliance) + 2years market exclusivity(non disclosure) + 1year market exclusivityfornew indications (non disclosure)	5years data ExclusivityforNCE (non disclosure/reliance) + 3years market exclusivityfornew indications (non disclosure)

ENTRY OF ONCOLOGY DRUGS INTO MARKET

USFDA: For marketing authorization of a generic drug product should submit Abbreviated New Drug Application (ANDA) 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, lowcost alternative to the public.

- Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and effective ness.Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug).Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984,"

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also known as the Waxman-Hatch Act. This Act expedites the availability of less costly generic drugs by permitting FDAThe Office of Generic Drug (OGD) is part of the Center for Drug Evaluation and Research (CDER) and it evaluate the safety and bioequivalence of generic drug products prior to approval for marketing Genericdrug application reviewers focus on bioequivalence data, chemistry and microbiology data,requests for plant inspection, and drug labeling information

Europe: European generics association

For the Marketing Authorization of Generic medicinal product in Europe, the applicant should submit a bridged application to the authority. Marketing authorisation for a pharmaceutical product in more than one country in the European Union must currently be applied for through one of two procedures: either the Centralised Procedure or the –Mutual Recognition Procedure(MRP).A third, the Decentralised Procedure, came into force with the newly revised EU pharmaceutical Directive in November 2005.Authorisation of medicines is done by four procedures:

- Centralised Procedure ,
- MutuallyRecognition Procedure
- Decentralised Procedure,
- National Procedure

An approval for a medicinal product intended for use in all EU countries may be obtained by applying to the EMEA (European Medicines Agency) in London. It consists of a single application which, when approved, grants marketing authorization for all markets within the European Union.

When EMEA has received a centralized application the responsible committee appoints a rapporteur /co-rapporteur. On the basis of the opinion from the scientific committees the Commission (or the Council) issues the formal decision to authorize a product in the centralised procedure. The Commission is assisted in the decision-making procedure by a Standing Committee with representatives from each Member State. In **centralised procedure** there are 2 categories of new drugs. They are

1. Mandatoryscope
2. Optional scope

Mandatoryscope: products which fall under this category are

1.Biotechnological medicinal products,

2. Orphan medicinal products

3.New active substances for which the therapeutic indication is the treatment of Diabetes, Cancer, Acquired immune deficiency syndrome(HIV) Neuro degenerative disorder, Auto-immune disorders, Viral diseases.

Optional scope: products which fall under this category are

1. Generic medicinal products of nationally authorized reference medicinal products
2. OTC medicinal products3. Generic medicinal products of reference medicinal products authorized by the C[11].

2. The Mutual Recognition Procedure

The majority of authorizations for generic medicines are granted through the Mutual Recognition Procedure and the Decentralised Procedure. Under MRP,the assessment and marketing

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authorization of one MemberState,(the–Reference MemberState‖) should be–mutually recognisedby other–Concerned Member States‖.

Since the introduction of the DCP, the MRP is mainly used for extending the existingmarketing authorisationto other countries in whatis known as the —repeat useprocedure.The Mutual Recognition Procedure is where a Marketing Authorisation is assessed
and granted by a National Authority (the reference member state or RMS).The applicant then applies inselected Member States,who recognize the original assessment following a 90-day procedure. If agreed, the National Authorities (the concerned Member States or CMS),grant national marketing authorisations.
Mutual recognition means that EU countries may approve the decision made about a medicinal product by another EU country.The pharmaceutical company submits their application to the country chosen to carry out the assessment work, which then approves or rejects the application. The other countries have to decide within 90days whether they approve or reject the decision made by the original country.....
Decentralized procedure:
The decentralised procedure should be used for products that have not yet received authorization in an EU country. The applicant may request one or more concerned Member State(s) to approve a draft assessment report, summary of product characteristics, labeling and package leaflet as proposed by the chosen reference Member State in 210 days. CMD (h) work for the facilitation of the decentralised procedures. DCP is divided into four steps
Pre-procedural step: Day-14to 0
Assessment step I: Day0to 120 (incl. the clock-off period)
Assessment step II: Day120– 210,
Discussion at the CMD,
if needed(60 days)
National step: 30 days
(CMD –Coordination Group for the Mutual Recognition and the Decentralised Procedure
4. The National Procedure
Until 1998, the pharmaceutical industry could apply for a national approval.The product can then only be sold in that particular EU country. A marketing authorization (MA) is valid for five years and after the first renewal, the MA is valid for an unlimited period. Inorder to obtainan approval the product must be submitted with an SPC (Summary of Products Characteristics) which is the basis for the marketing of the product. For some products, I.e. products intended for national use in one Member State only, it will be possible to use thenational procedure also after 1998[12].
Advantages of National Procedure:
Fees are affordable even for small firms (procedure supports a wide variety of the regional pharmaceutical landscape)
No need for translation of the dossier
National Marketing authorization (MA) is the basis for the MRP procedure
Application forms and requirements of thenational competent authority are well know
Disadvantages of National Procedure: Not all national competent authorities meet the time line of 210 days. Regionally limited validity of the MA.

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CONCLUSION:

In United States and European Union, the regulatory requirements for anticancer drugs have additional requirements with regard to premises, equipment, training, waste disposal when compare to the Regulatory requirements for other class of drugs. The WHO guideline requires that the cytotoxic drugs must be handled in Biosafety level IIpremise. Regulatory requirements for Bioequivalence studies and the approval procedure for anticancer drug registration are different in both EU and US. In case of Bioequivalence study, the regulations of USFDA have additional procedure of Bio-IND application an disstringent than EMA. The Bio-IND application procedure takes additional 30 days for registration. The investment required for generic anticancer drug development process is very expensive, so that before beginning of the development process the sponsor or applicant there ore must consider the following aspects: The sponsor must take into consideration, the regulatory requirements of each region where the drug is proposed to be marketed. The sponsor must keep in mind the possibility of marketing the drug in various regions and accordingly set up manufacturing facilities and conduct human trials in such a way that there is no need to create separate facilities and carry out human trials once again.

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