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Review Article

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Oncology Drugs: Evolution, Comparative study of Global Drug Regulatory approval process and various measures to improve availability and accessibility

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Abstract

Cancer is the leading cause of death worldwide and is a well-known fact that it can be cured if detected and treated early. Cancer treatment has evolved from conventional therapies like vinca alkaloids, photodynamic and radiation therapy, chemotherapy to immunotherapy. Recent advances in tumour agnostic therapies based on cancer genetics and molecular features has led to a single drug treating different types of cancers. Next Generation sequencing (NGS) represents an effective way to gather large amount of genomic information about a cancer. The concept of precision medicine goes along with an understanding of the cancer genome as determined by NGS. Thus with an array of cancer diagnosis and treatment options the marketing approval process globally is challenging. This is mainly due to lack of harmonization of guidelines. This review evaluates the approval process of oncology drugs in US, EU and India. Recent USFDA initiatives like Project Orbis involving multi country collaboration and real time oncology review while EU PRIME and WHO proposed reliance pathway are several global initiatives which accelerates assessment process.

New NDCT rules introduced in India in 2019 is one of the key step towards faster availability and accessibility of Cancer drugs in the country.

Countries with high resource settings like USA and EU have recognized this and have made several initiatives to provide early access to patients. USA has several pathways for speeding up the regulatory approval process for oncology drugs. India has recently came up with New Drugs and Clinical Trial rules, 2019 (NDCT rules 2019) which laid down the provisions of Provisions of Accelerated approval, Expedited review and Clinical trial waivers ensures faster availability and accessibility of cancer drugs in the country.

Although a lot of initiatives have already been taken in this direction still there is a strong need to harmonize the requirements globally for faster availability and accessibility of drug in the country for the much-needed patients.

Keywords: Regulatory approval, FDA, NDCT rules 2019, Oncology Drugs, Next-generation sequencing (NGS), Oncology Center of Excellence (OCE), Real-Time Oncology Review (RTOR), USFDA, CDSCO

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1. Introduction

Cancer is a disease, which is characterized by the uncontrolled growth of cells and their spread to other parts of the body. Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs. The latter process is called metastasizing. A neoplasm and malignant tumor are other common names for cancer. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018. (1)

Human body is made up of trillions of cells and cancer can start anywhere. Human cells have the tendency to grow and multiply (through cell division) to form new cells for the proper functioning of the human body. When cells grow old, they die and new cells take their place. Sometimes, old and damaged cells keep on growing and dividing instead of dying which lead to the formation of lumps of tissue (tumors). These lumps can be cancerous (malignant) or not cancerous (benign).

Cancerous cells can spread to the nearby or distant places in the body to form new tumors. This process is called metastasis. Hormones are the chemical substance synthesized by the specialized glands of the human body to regulate the activity of certain organs. Some cancer cells depend upon hormones for their growth and development which make them hormone sensitive. For Example: Breast Cancer cells may depend upon Estrogen or Progesterone for their growth.

Hormonal therapy prevents the growth of cancerous cells by blocking or reducing the level of hormones in the body. For example: Tamoxifen is a hormonal therapy which blocks the Estrogen receptor and inhibits the growth of Breast cancer cells. Such therapies cannot be used for treating all types of cancers. Only hormone dependent or hormone sensitive cancers can be treated by this approach.

1.1 Statistics of cancer

Cancer represents a high and increasing burden worldwide, in part reflecting an ageing population and to some degree, the success of countries' health care systems. In some countries the lifetime risk of developing some form of cancer exceeds 50% (2) and the costs of care, especially of pharmacotherapies, are burgeoning. (3-4) Within the European Union (EU) the cancer burden was estimated to be 3.1 million new cancer cases and 1.4 million cancer deaths in 2018, with direct health costs of cancer of EUR 103 billion, of which cancer medications accounted for 31%. (5) In the United States, the Agency for Healthcare Research and Quality estimated the direct medical costs of cancer care in 2015 at over USD 80 billion. (6)

As per the latest cancer statistics of US for the year 2022, there will be likely 1.9 million new cancer cases diagnosed and 609,360 cancer deaths guesstimated due to cancer. (7)

As per the factsheet dated February 03, 2022 by World Health Organization, Cancer statistics is as follows:

- Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths.
- The most common cancers are breast, lung, colon and rectum and prostate cancers.
- Around one-third of deaths from cancer are due to tobacco use, high body mass index, alcohol consumption, low fruit and vegetable intake, and lack of physical activity.
- Cancer-causing infections, such as human papillomavirus (HPV) and hepatitis, are responsible for approximately 30% of cancer cases in low and lower-middle-income countries.
- Many cancers can be cured if detected early and treated effectively.

2. Evolution of Cancer Treatment

As science and technology advances, so the treatment of cancer. The medical history of cancer has begun millions of years ago and the treatment goes evolving along with the time.

The various treatment options and evolution of oncology drugs are mentioned below (8):

i. Conventional Therapies – Naturally occurring compounds from plants known as phytochemicals, serve as vital resources for novel drugs and are also sources for cancer therapy. Some typical examples include taxol analogs, vinca alkaloids such as vincristine, vinblastine, a podophyllotoxin analogs. These phytochemicals often act *via* regulating molecular pathways which are implicated in growth and progression of cancer. Vinblastine and vincristine are the two naturally isolated alkaloids that have been used in clinical oncology for almost 50 years. These agents have been generally included in combination chemotherapy for the treatment of a variety of cancers, including leukemia, Hodgkin and non-Hodgkin lymphomas, advanced testicular carcinoma, breast and lung cancers, and Kaposi's sarcoma.

ii. Chemotherapy- Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in your body. Chemotherapy is most often used to treat cancer, since cancer cells grow and multiply much more quickly than most cells in the body. Though chemotherapy is an effective way to treat many types of cancer, chemotherapy treatment also carries a risk of side effects. Some chemotherapy side effects are mild and treatable, while others can cause serious complications. Chemotherapy is used in 5 different ways as mentioned below:

- Adjuvant therapy - Chemotherapy given after surgery, either alone or with radiation (or another type of therapy), and that is designed to kill cells that have metastasized.
- Neoadjuvant therapy - used prior to surgery to shrink a tumor, with or without concurrent radiation therapy.
- Primary therapy - used alone when leukemia or lymphoma is present. The therapy is also used alone in the management of other cancers when no hope for cure is present and chemotherapy is given to control symptoms.
- Induction chemotherapy - used as the first of many therapies. For instance, in the management of some lung cancers, chemotherapy may be given first (induction) followed by either surgery or radiation therapy. In stomach cancer (either before or after surgery), chemotherapy may be given first followed by radiation therapy.
- Combination chemotherapy - involves the use of 2 or more chemotherapeutic agents, allowing for each medication to enhance the action of the other or for the 2 to work synergistically.

iii. Hormone Therapy- Hormone therapy is a cancer treatment that slows or stops the growth of cancer that uses hormones to grow. Hormone therapy is also called hormonal therapy, hormone treatment, or endocrine

therapy. It is usually added to other cancer treatments, and can also be used to ease cancer symptoms. Hormone therapy stops your body from making certain hormones or keeps them from working the way they usually do. It can also stop them from attaching to cancer cells. The most common ways to get it are:

- A pill, capsule, or liquid you swallow
- A shot in your arm, leg, hip, or belly
- In an implant
- Surgery to take out organs that make hormones, like your ovaries or testicles.

iv. Hyperthermia- Hyperthermia is a type of treatment in which body tissue is heated to as high as 113 °F to help damage and kill cancer cells with little or no harm to normal tissue. Hyperthermia is almost always used with other forms of cancer treatment. Many clinical trials have shown that hyperthermia, when used with treatments such as radiation therapy and chemotherapy, helps shrink tumors and may make it easier for them to kill cancer cells. During treatment, the doctor numbs the treatment area and inserts small probes with tiny thermometers into the tumor. Thermometers help the doctor closely watch the temperature of the tumor and nearby tissue during treatment. Imaging techniques, such as CT scans, may be used to make sure the probes are in the proper place. Hyperthermia to treat cancer is not widely available. But at some centers it is use along with other treatments such as radiation therapy and chemotherapy, for advanced cancers. It has been used to treat these types of advanced cancers: appendix cancer, bladder, brain cancer, breast, cervical cancer, esophageal cancer head and neck cancer. Liver, lung cancer, melanoma, mesothelioma, sarcoma, rectal cancer.

v. Immunotherapy- Immunotherapy is a type of cancer treatment that helps immune system to fight against cancer. The immune system helps your body fight infections and other diseases. It is made up of white blood cells and organs and tissues of the lymph system. Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer.

Several types of immunotherapy are used to treat cancer. These include:

- Immune checkpoint inhibitors, which are drugs that block immune checkpoints. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more strongly to cancer.
- T-cell transfer therapy, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein. T-cell transfer therapy may also be called adoptive cell therapy, adoptive immunotherapy, or immune cell therapy.
- Monoclonal antibodies, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy. Monoclonal antibodies may also be called therapeutic antibodies.
- Treatment vaccines, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.
- Immune system modulators, which enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, whereas others affect the immune system in a more general way.

vi. Photodynamic Therapy- Photodynamic therapy uses a drug activated by light to kill cancer and other abnormal cells. Photodynamic therapy (PDT) is a treatment that uses special drugs, sometimes called photosensitizing agents, along with light to kill cancer cells. The drugs only work after they have been activated or "turned on" by certain kinds of light. PDT may also be called photo radiation therapy, phototherapy, or photo chemotherapy. Depending on the part of the body being treated, the photosensitizing agent is either put into the bloodstream through a vein or put on the skin. Over a certain amount of time the drug is absorbed by the cancer cells. Then light is applied to the area to be treated. The light causes the drug to react and form a special kind of oxygen molecule that kills the cells. PDT might also help by destroying the blood vessels that feed the cancer cells and by alerting the immune system to attack the cancer. The FDA has approved photodynamic therapy to treat: actinic keratosis, advanced cutaneous T-cell lymphoma, Barrett esophagus, basal cell skin cancer. Photodynamic therapy is also used to relieve symptoms of some cancers, including: esophageal cancer when it blocks the throat and non-small cell lung cancer when it blocks the airway.

vii. Radiation Therapy- Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. At low doses, radiation is used in x-rays to see inside your body, as with x-rays of your teeth or broken bones. At high doses, radiation therapy kills cancer cells or slows their growth by damaging their DNA. Cancer cells whose DNA is damaged beyond repair stop dividing or die. When the damaged cells die, they are broken down and removed by the body. Radiation therapy does not kill cancer cells right away. It takes days or weeks of treatment before DNA is damaged enough for cancer cells to die. Then, cancer cells keep dying for weeks or months after radiation therapy end.

viii. Stem Cell Transplant- Stem cell transplants are procedures that restore blood-forming stem cells in people who have had theirs destroyed by the high doses

of chemotherapy or radiation therapy that are used to treat certain cancers. Stem cell transplants do not usually work against cancer directly. Instead, they help you recover your body's ability to produce stem cells after treatment with very high doses of radiation therapy, chemotherapy, or both. However, in multiple myeloma and some types of leukemia, the stem cell transplant may work against cancer directly. This happens because of an effect called graft-versus-tumor that can occur after allogeneic transplants. Graft-versus-tumor occurs when white blood cells from your donor (the graft) attack any cancer cells that remain in your body (the tumor) after high-dose treatments. This effect improves the success of the treatments. Stem cell transplants are most often used to help people with leukemia and lymphoma. They may also be used for neuroblastoma and multiple myeloma

ix. Surgery- Surgery, when used to treat cancer, is a procedure in which a surgeon removes cancer from your body. Surgeons are medical doctors with special training in surgery. There are other ways of performing surgery that do not involve cuts with scalpels. Some of these include:

- Cryosurgery: Cryosurgery is a type of treatment in which extreme cold produced by liquid nitrogen or argon gas is used to destroy abnormal tissue.
- Laser: This is a type of treatment in which powerful beams of light are used to cut through tissue. Lasers can focus very accurately on tiny areas, so they can be used for precise surgeries.
- Hyperthermia: Hyperthermia is a type of treatment in which small areas of body tissue are exposed to high temperatures.
- Photodynamic Therapy: Photodynamic therapy is a type of treatment that uses drugs which react to a certain type of light.

x. Targeted Therapy- Targeted therapy is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread.

a) Tumor Agnostic Therapies

A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy, also called tissue-agnostic therapy.

Tumor agnostic therapy refers to cancer treatments that work across various cancer types. In other words, instead of working for only one type of cancer, such as breast cancer, these treatments may work for a number of different cancers, for example, melanoma, breast cancer, and sarcomas. In addition, they may work for both adults and children.

Instead of treatments based on where a tumor originated, this therapy treats a cancer that originates anywhere based on the particular molecular characteristics that drive the growth of the tumor. Despite arising in different tissues, it's not uncommon for very different types of cancer to use the same pathway to grow

An increased understanding of cancer biology, the ability to do genomic testing to determine what is driving the growth of a particular cancer, and the availability of medications that target these pathways has given researchers the ability to treat a wide range of cancers at a molecular level. There are currently only a few drugs approved specifically for tumor agnostic treatment but this is expected to expand rapidly in the very near future.

Criteria for Tumor Agnostic Treatments

In order for a treatment to be effective across cancer types, there are few criteria that need to be met.

- The particular mutation (or other alteration) must be found. In other words, testing has to be available to detect the alteration and be performed fairly often.
- Tumors that have the particular mutation must respond to treatments that target the treatment.
- The mutation must be found across many different types of cancer.(9)

Regulations on Tumor Agnostic Therapies (International and India)

As of now, no regulations with respect to Tumor Agnostic Therapies are in place internationally or in India. However, USFDA has a brief document on *"Tissue Agnostic Therapies in Oncology Regulatory Considerations for Orphan Drug Designation"*.

Apart from this there are no significant guidelines/ regulations across the world to provide specific guidance to industry in this area.

b) Personalized Cancer Medicines

Personalized cancer medicine comes from studies of human genes and the genes in different cancers. These studies have helped researchers design more effective treatments. They have also used genetic information to develop tests for cancer and ways to prevent it.

Personalized healthcare is the process of taking into account a patient's unique characteristics such as clinical history and risk factors to provide them personalized care and treatments. The term, personalized care or personalized medicine has increased in popularity recently thanks to the following two factors:

- Deeper understanding of disease and human characteristics, thanks to advances in genome sequencing.
- New diagnostic approaches, thanks to advances in machine learning including deep learning.(9,10)

Regulations on PHC (International and India)

USFDA has a guidance document on *"Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) - Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases"*

Apart from this, there are no significant guidelines/ regulations for any other country (including India) to provide specific guidance to industry in this area.

c) Next Gene Sequencing

A newer strategy called next generation sequencing (NGS) allows clinicians to test many genes of a cancer simultaneously. Next generation sequencing can be performed on material from a patient's tumour that has been biopsied or surgically removed.

Next-generation sequencing (NGS) is a massively parallel sequencing technology that offers ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA. NGS has revolutionized the biological sciences, allowing labs to perform a wide variety of applications and study biological systems at a level never before possible.

The understanding of genetics and the genome has been transformed in the last decade by the revolution in sequencing technology. Next-generation sequencing (NGS) has been widely implemented for whole-genome sequencing, whole-exome sequencing, transcriptome sequencing, targeted region sequencing, epigenetic sequencing, and other sequencing. NGS holds a lot of importance for the oncology space.

Advantages of NGS

NGS can be used to analyze DNA and RNA samples and is a popular tool in functional genomics. In contrast to microarray methods, NGS-based approaches have several advantages including:

- a prior knowledge of the genome or genomic features is not required
- it offers single-nucleotide resolution, making it possible to detect related genes (or features), alternatively spliced transcripts, allelic gene variants and single nucleotide polymorphisms
- higher dynamic range of signal
- requires less DNA/RNA as input (nanograms of materials are sufficient)
- higher reproducibility

NGS technologies

- Sequencing by Synthesis: Pioneered by Illumina, inc. It works by simultaneously identifying DNA bases, as each base emits a unique fluorescent signal, and adding them to a nucleic acid chain
- Pyro-sequencing: This method was developed by Roche, a technique which detects pyrophosphate release, again using fluorescence, after nucleotides are incorporated by polymerase to a new strand of DNA.
- Ion Torrent sequencing: Ion Torrent sequencing measures the direct release of H+ (protons) from the incorporation of individual bases by DNA polymerase and therefore differs from the previous two methods as it does not measure light. (8,11-12)

Regulations on NGS (US, EU and India)

- US: Two guidance documents are available for NGS of which one was finalized in April 2018 *"Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) - Based In-Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases"*. Another document related to infectious diseases is still in draft stage *Infectious Disease Next Generation 2 Sequencing Based Diagnostic Devices: 3 Microbial Identification and Detection 4 of Antimicrobial Resistance and 5 Virulence Markers*. Classification regulations outlining special controls.
- Europe: There are no regulations or Draft guidance in place for NGS in Europe. However, Pharma Biotech industry groups are actively working and has put out a discussion paper in 2018.
- India: No regulations exist

3. Regulatory considerations in approval of Oncology Drugs in US, EU and India

3.1 Drug Regulatory approval process of Oncology drugs in US

In US the drugs get approved by various regulatory pathways like Investigational New Drugs (INDs), New Drug Applications (NDAs), and Biological Licensing Applications (BLAs). For the approval of oncology drugs or drugs for life threatening diseases Treatment IND's are also one of the regulatory frameworks for approval.

Speeding the availability of drugs that treat serious diseases is in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. The Food and Drug Administration has developed four distinct and successful approaches to making such drugs available as rapidly as possible (13):

- **Priority Review**: A Priority Review designation means FDA's goal is to take action on an application within 6 months.
- **Fast track Process:** Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
- **Breakthrough Therapy:** A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy**.**
- **Accelerated Approval:** These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.

Authorized by the 21st Century Cures Act, the Oncology Centre of Excellence (OCE) was established on January 19, 2017 to conduct expedited review of drugs, biologics and devices. OCE work with FDA in the below mentioned way (14):

Applicants submit applications to the product center they normally would, and those centers decide whether the product will be under an expedited program. For products selected, the OCE forms a Medical Oncology Review and Evaluation (MORE) team that includes a medical oncology specialist and specialists from the relevant product center.

The MORE team:

- Provides a unified clinical review to promote development of safe and effective oncology products.
- Builds on cross-center collaboration by providing input to selected INDs that are under expedited program.
- Implements common decision-making standards for Breakthrough Therapy and Fast Track designation for all oncology therapeutic products.

The completed clinical review is sent to the product center, which makes the final application approval determination, taking into account both clinical and non-clinical information.

Project Orbis

The FDA Oncology Center of Excellence (OCE) initiated Project Orbis in May 2019 to provide a framework for concurrent submission and review of oncology products among international partners. Australian Therapeutic Goods Administration (TGA) and Health Canada (HC) took part in the first Project Orbis collaborative review. Since then, other countries viz. Brazil's National Health Surveillance Agency (ANVISA), Israel Ministry of Health (MOH), Singapore Health Science Authority (HSA), Switzerland Swiss Medic and UK MHRA have joined and become Project Orbis Partners. The Partner regulatory agencies collaboratively review an application allowing for simultaneous decisions in all countries while retaining their own timelines. This also helps to identify any regulatory divergence across review teams. In the first year 60 oncology marketing applications were received, representing 16 unique projects and resulting in 38 approvals. (15)

Real -Time Oncology Review (RTOR)

The Oncology Center of Excellence Real-Time Oncology Review (RTOR) aims to provide a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible, while improving review quality and engaging in early iterative communication with the applicant. Under this process, FDA can do a preliminary review of data from pivotal trials before applicant formally submits the application. It includes key raw and derived datasets, safety, efficacy tables, study protocols, amendments and draft prescribing information. The FDA also prefers to Assessment Aid (AAid) to be used along with RTOR. The main objective of AAid is to focus on critical thinking, increase review efficiency and decrease time spent on administrative tasks such as formatting. The applicants are advised only to include critical information with total document length between 75-100 pages. (16)

3.2 Drug Regulatory approval process of Oncological drugs in EU

The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA. This network is what makes the EU regulatory system unique.

To protect public health and ensure the availability of high quality, safe and effective medicines for European citizens, all medicines must be authorized before they can be placed on the market in the EU. The European system offers different routes for such an authorization.

The centralized procedure allows the marketing of a medicine on the basis of a single EU-wide assessment and marketing authorization which is valid throughout the EU. Pharmaceutical companies submit a single authorization application to EMA. The Agency's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) then carries out a scientific assessment of the application and gives a recommendation to the European Commission on whether or not to grant a marketing authorization. Once granted by the European Commission, the centralized marketing authorization is valid in all EU Member States. The use of the centrally authorized procedure is compulsory for most innovative medicines including medicines for rare diseases and Biological Drugs. EMA enables one application, one assessment, one market authorization for the whole of the EU. The oncology drugs in EU get approved by Centralized procedure. (17)

The centralized procedure is compulsory for (18):

- human medicines containing a new active substance to treat:
- human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
- cancer;
- diabetes;
- neurodegenerative diseases;
- auto-immune and other immune dysfunctions;
- viral diseases.
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- orphan medicines (medicines for rare diseases);

- veterinary medicines for use as growth or yield enhancers.

The various regulatory mechanisms for approval of oncology drugs are mentioned below

a. Accelerated assessment in EU

Accelerated assessment reduces the timeframe for the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorization application. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation.

Evaluating a marketing-authorization application under the centralized can take up to 210 days, not counting clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment. (19)

b. Conditional marketing authorization

Conditional marketing authorization (CMA) can be granted to drugs intended for orphan, seriously debilitating or life-threatening diseases, or public health emergencies, on the basis of less than comprehensive clinical evidence. All of the following legal requirements have to be met (20):

- the benefit – risk (B/R) balance of the drug is positive,
- it is likely that comprehensive confirmatory clinical data will be provided in a reasonable timeframe,
- the unmet medical need will be fulfilled by a major therapeutic advantage if alternatives are available or a favorable B/R is established in settings without viable treatment options, and
- the potential benefit to public health of the drug's immediate availability outweighs the potential risks associated with the greater level of uncertainty about its B/R.

c. Authorisation under exceptional circumstances

The legal scope is limited to exceptional situations in serious or life-threatening indications where it is not considered feasible together comprehensive clinical evidence according to conventional regulatory standards, primarily due to the extreme rarity of the indication. It is subject to annual re-assessment of the B/R and to specific obligations and conditions throughout the life-cycle, but without necessarily envisaging conversion into regular approval. (21)

d. Priority Medicines PRIME

Many patients with serious diseases have no or only unsatisfactory therapeutic options and should be able to benefit from scientific advancement and cutting edge medicines as early as possible. The European Medicines Agency (EMA) set up PRIME in March 2016 in line with the European Commission's priorities and the common strategy to 2020 for the European medicines regulatory network. The goal is was to foster research on and development of medicines for patients whose diseases cannot be treated or who need better treatment options to help them live healthier lives. PRIME was built on the existing regulatory framework, including the provision of scientific advice and the accelerated assessment procedure used for innovative medicines that address an unmet medical need and bring a major therapeutic advantage to patients. A 5 year report released has indeed shown that it has reduced time to marketing authorization, accelerated assessment, benefitted more complex medicines and has significantly contributed to the unmet needs of patients. (22)

e. *Drug Approval Process in India*

In India the drugs gets approved by various regulatory pathways like

- ✓ Investigational New Drugs (INDs),
- ✓ New Drug Applications (NDAs), and
- ✓ Biological Licensing Applications (BLAs).

As per NDCT 2019, Second Schedule, rule 2 (a) Accelerated approval process may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment. It also considers serious or life threatening conditions or disease of special relevance to the country. Rule 2 (b) also states situations where quick or expeditious review process can be sought for approval of a new drug after clinical development e.g. orphan drugs. Subject Expert Committee (SEC) Oncology & Hematology is the major scientific committee to give scientific inputs to DCGI Office for approval of oncology drugs. (23)

Table 1. Comparison of Drug Approval process of Oncology Drugs (14-23)

S.No	Requirements	US	EU	India
1	Agency	*One Agency* United State Food and Drug Administration (USFDA)	*Multiple agencies* The European Commission is the authorizing body for all centrally authorized product, who takes a legally binding decision based on EMA's recommendation. This decision is issued within 67 days of receipt of EMA's recommendation. Once granted by the European	*One Agency* Central Drug Standard Control Organization (CDSCO)

			Commission, thecentralized marketing authorization is valid in all EU states	
2	Registration Process	*One Registration Process* • Project Orbis • Real Time Oncology Review (RTOR)	*Multiple Registration Process* Centralized Procedure Decentralized Procedure Mutual Recognition Procedure National Procedure	One Registration Process
3	Approval process for Oncology Drugs	Oncology Centre of Excellence in collaboration with FDA is responsible for approval of oncology drugs	EMA CHMP	Subject Expert Committee Oncology & Hematology along with CDSCO Office
4	Type of Applications for Oncology Drugs	IND NDA BLA	IND MAA Biological Applications	IND NDA BLA
5	Priority Review	Defined	Defined	On a case to case basis
6	Accelerated Approval	Defined	Defined	On a case to case basis
7	Breakthrough Therapies	Defined	Defined (PRIME)	Not defined
8	Fast Track Process	Defined	Defined (PRIME)	Defined (Expedited approval process)
9	Orphan Drug Approval process for Rare Cancers	Defined	Defined	Defined for the first time in NDCT rules 2019.
10	Surrogate End points	Defined	Defined	On a case to case basis
11	Concept of Treatment IND	Defined	Defined	On a case to case basis
12	Concept of Basket Trials without comparator	Defined	Defined	On a case to case basis
13	Regulations on Tumor Agnostic Therapies	No regulations in place as of now. However, USFDA has a brief document on *"Tissue Agnostic Therapies in Oncology Regulatory Considerations for Orphan Drug Designation*	Not Defined	Not defined
14	Regulations on personalized medicines	USFDA has a guidance document on *"Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) - Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases"*	Not defined	Not defined
15	Next Gene Sequencing (NGS)	Two guidance documents are available for NGS of which one was finalized in April 2018 *"Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) - Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of*	Not defined	Not defined

		Suspected Germline Diseases". Another document related to infectious diseases is still in draft stage *Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and 5 Virulence Markers.* Classification regulations outlining special controls.		

4. Regulatory Reliance Pathway for drug approval Process

In August 2020, WHO put forth a draft document "*Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations*" The draft guideline follows a meeting in September 2019 that identified the Pan American Health Organization (PAHO) and Pan American Network for Drug Regulatory Harmonization (PANDRH) concept note and recommendations "as a starting point" for the development of the current document.

Public Health emergencies as the recent Covid pandemic has necessitated the need for National regulatory authorities to consider enhanced, innovative and more effective forms of collaboration. WHO recommends to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts unique to their country. As per WHO a country can qualify as WHO listed authority (WLA) based on their performance and level of maturity. A number of approaches to reliance, including joint assessments, unilateral and mutual recognition, abridged regulatory pathways and work-sharing arrangements are possible. (24)

5. Conclusion and recommendations

Cancer being the leading cause of death globally has encouraged scientists to bring in innovative diagnostic & treatment therapies. Unless these scientific advances are acceptable to the world-wide regulatory authorities the accessibility to patients remains elusive. Countries with high resource settings like USA and EU have recognized this and have made several initiatives to provide early access to patients. USA has several pathways for speeding up the regulatory approval process for oncology drugs. Besides various accelerated assessments Project Orbis & Real Time Oncology Review offer tremendous support for faster approval of oncology drugs. EMA has provided guidelines for accelerated assessments through CHMP for products which are a major concern to public health. Conditional marketing authorization, marketing under exceptional circumstances and PRIME provides the benefit of faster drug approval process satisfying the unmet need of patients. India has recently came up with New Drugs and Clinical Trial rules, 2019 (NDCT rules 2019) which laid down the provisions of Provisions of Accelerated approval, Expedited review and Clinical trial waivers ensures faster availability and accessibility of cancer drugs in the country.

Although a lot of initiatives are in place still there is a strong need to harmonize the requirements further for faster availability and accessibility of drug in the country.

The WHO draft document on Good reliance practices in regulatory decision-making is indeed a need for oncology drug approval process for countries with low resource setting. Abridged pathways facilitated by use of reliance can be resource saving and can shorten drug approval timelines leading to faster accessibility of drugs globally to cancer patients**.**

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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