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Product Lifecycle in Pharmaceutical Industry:

Journey of Drug from Ideation to Commercialization

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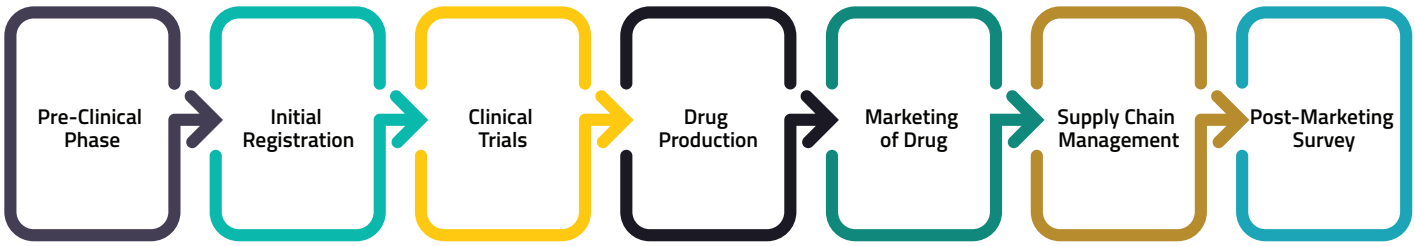
INTRODUCTION

Pharmaceutical is one of the highly regulated industries, where organizations must follow regulations and remain compliant with a local governing body such as FDA (Food & Drug Association), EMA (European Medical Agency), PMDA (Pharmaceuticals and Medical Devices Agency, Japan), CDSCO (Central Drugs Standard Control Organization, India), SFDA (Saudi Food and Drug Authority), and more, at every stage of the product lifecycle including regulations for the research, pre-clinical phase, registration phase, clinical trials, processing, manufacturing equipment, instrument validation, quality maintenance, packaging, labelling, and more. Following the lifecycle within the defined regulation is an integral part of pharmaceutical industries based on which the FDA approvals are provided to the companies. The objective of the regulation is to promote and maintain the guaranty of drug usage. These regulations coherently define the lifecycle of the drug at all phases.

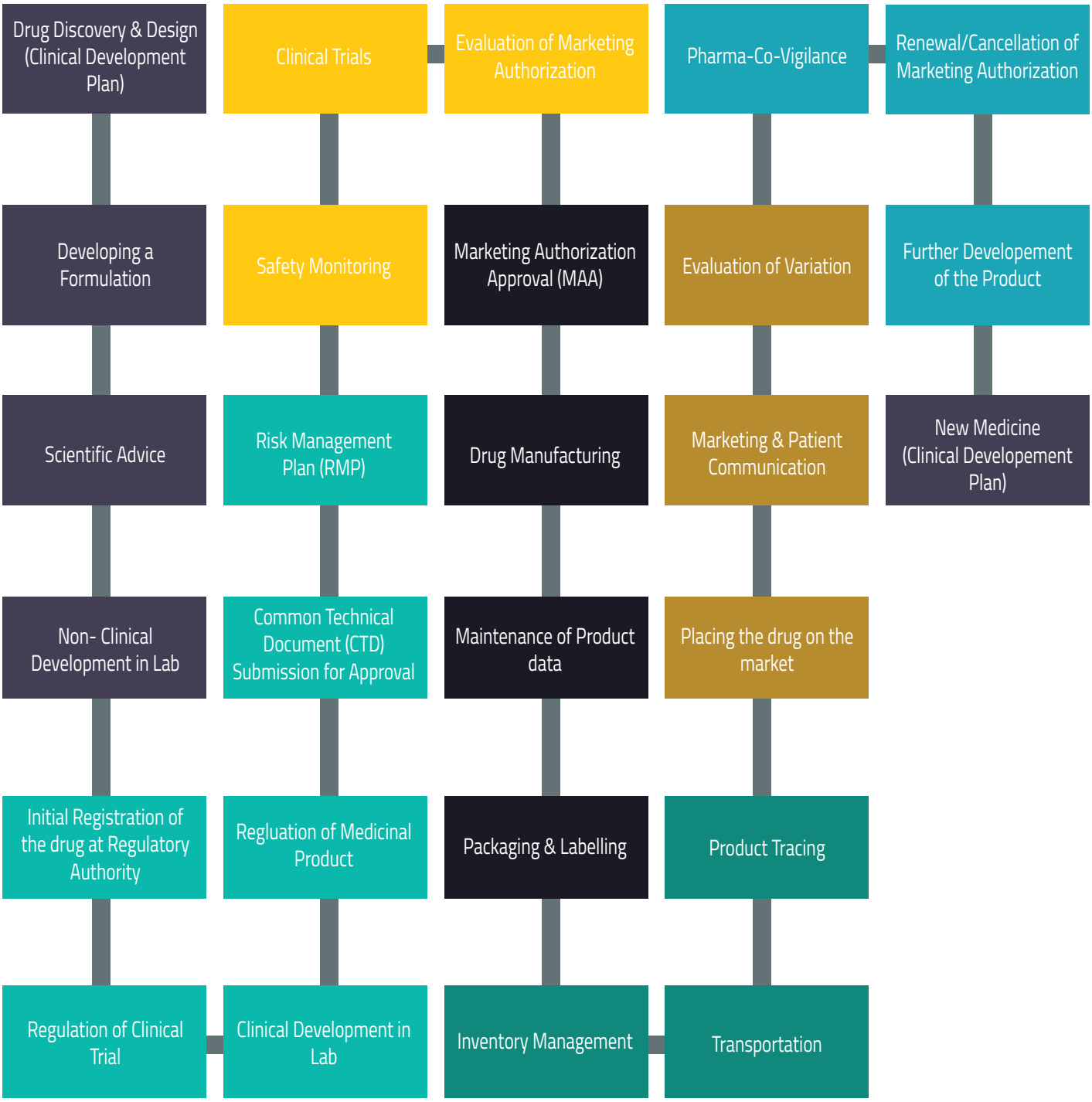
By defining a Workflow and complying to its lifecycle phases in each set of guidelines, companies can standardize their processes throughout and track each and every activity at every stage of the lifecycle. Using applications and tools eases the process and makes it less prone to errors. This whitepaper discusses various stages involved in pharmaceutical drug lifecycle and use of the software at every stage.

DRUG LIFECYCLE

In general, the Pharmaceutical industry product passes through the following lifecycle phases. On a broad level, the lifecycle has the following stages.



Which further can be fragmented in following detailed processes



PHASES OF DRUG LIFECYCLE

In the pharmaceutical domain, drug consumes a considerable amount of time, efforts, trials, risks documentations, and approvals to reach the market. At every lifecycle phase, application of different technologies and software helps in strictly adhering to the guidelines as specified by local regulatory authorities.

PRE-CLINICAL PHASE

In the Pre-clinical phase, all processes in the entire lifecycle of drug discovery till its registration in local regulatory authorities (FDA, EMA, and more) are covered.

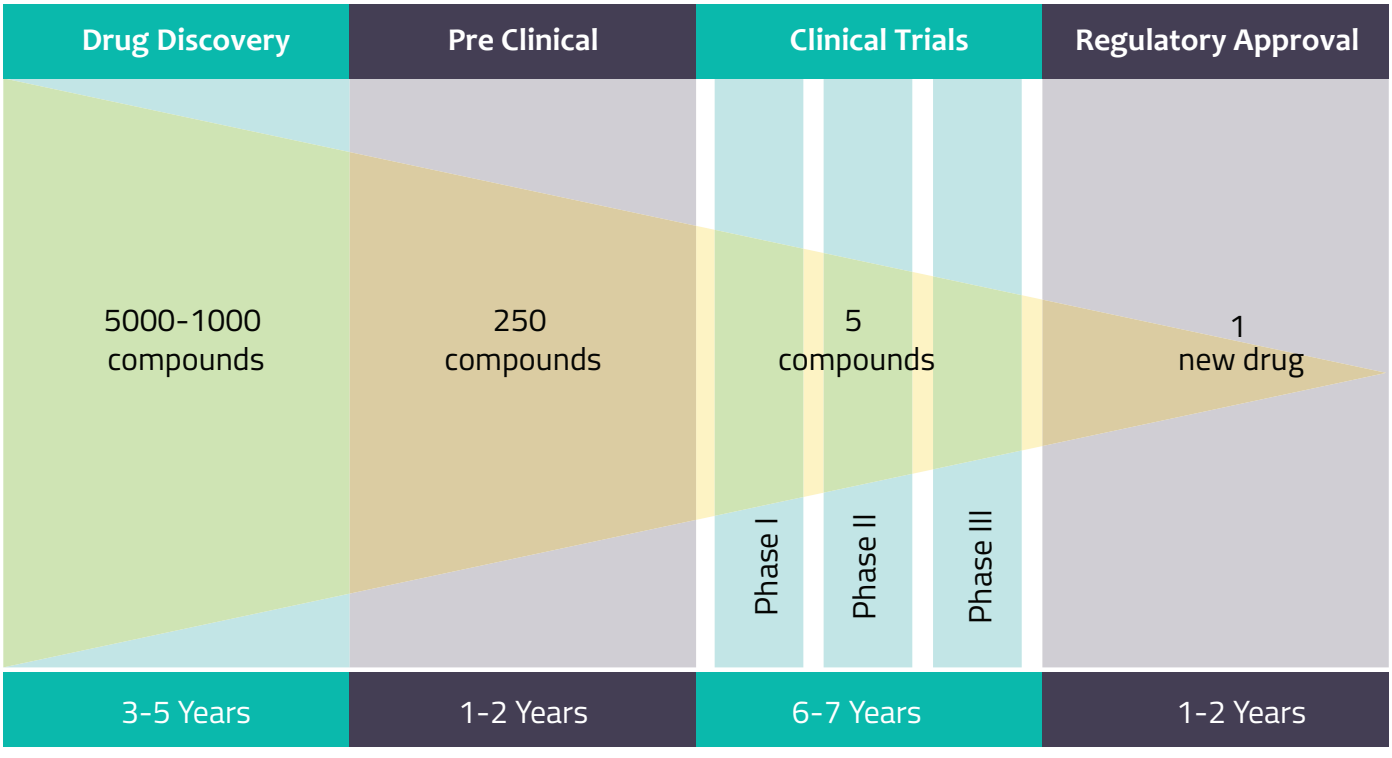
The Pre-clinical phase includes the following sub-stages:

DRUG DISCOVERY & DESIGN (CLINICAL DEVELOPMENT PLAN)

It begins with the requirement of the drug in the market; thousands of compounds and formulae are tested in a highly regulated environment by experts in that field to meet the requirement. The drugs at the early stage are scientifically tested, and the raw sample of the product is developed at the state-of-the-art lab.

DEVELOPING A FORMULATION

Medicine is a successful result of thousands of permutation and combination of Active Pharmaceutical Ingredients (API) along with compatible excipients that will cure the disease. Hence the formulation of the ingredient is an iterative and complex effort of selection, proportionating and processing of APIs and excipients to come up with a successful formula.



SCIENTIFIC ADVICE

EMA gives scientific advice[1] by responding to developer's specific questions and advice the plan on the developer's proposals to the medicine developer on the development of a particular medicine.

1. Reference : scientific advice - https://www. ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

NON-CLINICAL DEVELOPMENT

There are mainly two types of preclinical researches based on environments where they are being tested named as "In Vitro (work that's performed outside of a living organism)" and "In Vivo (research or work is done with or within an entire living organism)". Preclinical safety studies must be performed in compliance with GLP (Good Laboratory Practice)[2] in a GLP-certified laboratory.

Pharmacokinetic (PK) and LADME (Liberation/Absorption/Distribution/Metabolism/Excretion) studies provide useful feedback for formulation scientists. The non-clinical (or pre-clinical) development phase primarily aims to identify which candidate therapy has the greatest probability of success, assess its safety, and build solid scientific foundations before the transition to the clinical development phase. Any preparation of pharmaceutical product for human use go through the process of reviewing and assessing the dossier of a pharmaceutical product which contains details information about administrative, quality, non-clinical and clinical data. This process is governed and permitted by the Drug Regulatory Authority. The documentations and regulations, as defined by the local authority, are strictly maintained.

INITIAL REGISTRATION

Following sub-stages are followed in this phase.

INITIAL REGISTRATION OF THE DRUG AT REGULATORY AUTHORITY

After the drug discovery, initial registration of the new drug/new API (Active Pharmaceutical Ingredients)/changes of medical product at local authority is mandatory to get approval from them as well as it helps to preserve the intellectual property rights of the drugs. Medicine is needed to be registered following the Standardized Initial Registration Process[3] as suggested by the FDA.

REGULATION OF CLINICAL TRIAL

Well-maintained documents and regulations in the pre-clinical phase are utilized to register the drug. The regulations as defined by local regulatory authorities of the medicinal product are followed while developing the drug in lab.

CLINICAL DEVELOPMENT IN LAB

Clinical development procedure must be strictly followed as per Good Clinical Practices (GCP) standards set by the FDA and make sure the drugs are developed under the lab atmosphere itself.

REGULATION OF MEDICINAL PRODUCT

Once the registration of the drug is done, it is further processed for clinical trials whose regulations or Good Clinical Practices (GCP)[4] are set and followed; accordingly the drug are clinically developed in the lab.

COMMON TECHNICAL DOCUMENT (CTD) SUBMISSION FOR APPROVAL

All the data and information obtained at each stage of drug development lifecycle are recorded under Common Technical Document (CTD) to demonstrate drug's quality, safety, and efficiency.
The technical documentation included in an application for the registration of a human pharmaceutical product are compiled and designed in a standardized format common across Europe, USA & Japan. This design is achieved through the Common Technical Document and is submitted for approval to a local regulatory authority. The CTD dossier is divided into five main modules:

- Module 1: Administrative information and prescribing information
- Module 2: Overviews and summaries of Modules 3–5
- Module 3: Quality (pharmaceutical documentation)
- Module 4: Non-clinical reports (pharmacology/toxicology)
- Module 5: Clinical study reports (clinical trials)

2. Reference: GLP (Good Laboratory Practice) - https://www. accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1
3. Reference: Standardized Initial Registration Process- https://www. fda.gov/medical-devices/device-registration-and-listing/how-register-and-list#6
4. Reference: Good Clinical Practices (GCP) - https://www. fda.gov/files/medical%20devices/published/Presentation--Good-Clinical-Practice-1 01--An-Introduction-%28PDF-Version%29.pdf

RISK MANAGEMENT PLAN (RMP)

Risk Management Program starts with risk identification associated with the product/process used while developing, manufacturing or distribution. Hence an effective quality risk management ensures delivering a high-quality product to the patients.

CLINICAL TRIAL

A clinical trial is the most vital and time-consuming process throughout the lifecycle of the medicine. This can be broadly divided into below sub-stages.

SAFETY MONITORING OF CLINICAL TRIALS

As clinical trials are experiments on humans, they must be conducted following established standards to protect the rights, safety, and well-being of the participants. These standards include the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines, etc. GCP is the "standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that rights, integrity and confidentiality of trial subjects are protected". Permission for clinical trials must be obtained from the Ethical Committee. Clinical trials are carefully designed, reviewed, and completed, and need to be approved before they can start.

CLINICAL TRIALS

Clinical trials are conducted to study and evaluate the effect of news test and treatments made on human health. People voluntarily take part in clinical trials to test medical interventions, including drugs, cells, biological products, surgical procedures, radiological procedures, behavioral treatments, devices, and preventive care.

There are 4 phases of biomedical clinical trials:

Phase 0, also known as "Human pharmacology trial" to estimate the dosage form, dosage size and its safety and tolerability. Phase 0 is experimented to study and test new drugs for the first time. This Phase 0 trial is experimented on a small group of people to evaluate a safe dosage range and identify side effects.

Phase 1, also called as "Exploratory trial" are conducted to explore the effectiveness and short-term side effects of the drug on a larger group of people. After a successful trial in phase 0, the test is conducted on a larger group of humans to monitor adverse effects. The primary purpose of the phase 1 trial is to find the best dose of a new drug with the fewest side effects.

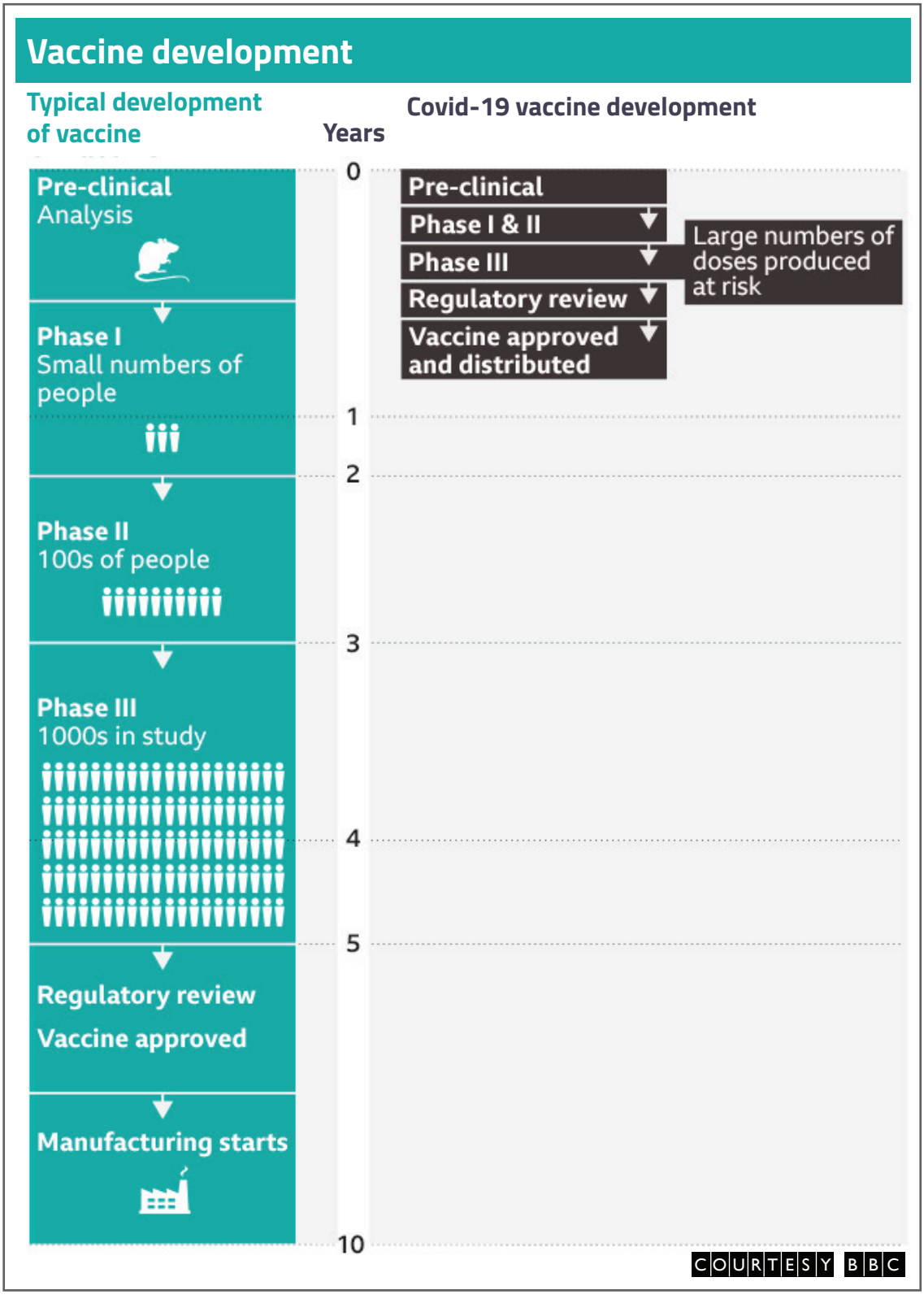
Phase 2 also called as "Confirmatory trial". As the name suggests, this phase is carried out to confirm the therapeutic benefits of the drug. Studies are conducted on even larger populations and in different regions and countries. This phase ensures the approval of the drug or treatment.

Phase 3 also known as "Post marketing trial". In this phase, the drug is tested after drug approval or when it is launched in the market. Trials are carried out after country approves the drug for commercial purpose and is studied to evaluate the need for further testing in a wide population over a longer timeframe.

EVALUATION OF MARKETING AUTHORIZATION

Marketing Authorization Approval (MAA)/New Drug Application (NDA) is essentially a license to place a medicinal product in the market to be used by patients. The drugs are first evaluated for marketing authorization before promotion. The evaluations are of different type. A full marketing authorization is the standard type, which requires a comprehensive amount of information on clinical benefit and safety for the drug in question. If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files an MAA/NDA, the actual request to manufacture and sell the drug in the United States.

**Due to unprecedented pandemic events COVID-19, FDA, EMA & other regulatory authorities have relieved their evaluation and authorizations procedures ("Fast track" procedure) for clinical test trials for speedy development of the vaccine.*



DRUG PRODUCTION

After successful clinical trials and approvals, drug production can be started. Below stages are observed during this phase.

MARKETING AUTHORIZATION APPROVAL (MAA) / NEW DRUG APPLICATION (NDA)

A Marketing Authorization Approval (MAA)/New Drug Application (NDA) can be filed only when the drug successfully passes all the phases of clinical trials and includes all animal and human data, data analysis, clinical trial results, the pharmacokinetics of the drug and its manufacturing and proposed labeling. MAA grants generally take two months to several years (on an average it takes two years).

DRUG MANUFACTURING

Drug Manufacturing is a sensitive and important process. Production of a drug can be started once the drug is authorized for marketing. Drug Manufacturing is the process of industrial-scale amalgamation of pharmaceutical drugs by pharmaceutical companies. This phase can be considered from procuring the quality raw material/substance with defined ingredients and quality equipment meeting regulatory requirements required to manufacture the drug, processing the drug in physical condition compliant to the Good Manufacturing Practices[5], till delivering it in the market. GLP should be followed throughout the drug manufacturing phase.

MAINTENANCE OF PRODUCT DATA

Maintaining the product drug data and protecting intellectual property rights till the end of the patent once the product is manufactured. Product data also needs to be revised if required. Maintenance of the product data is important as the whole efforts and cost of the drug discovery is dependent on the product data maintenance.

SUPPLY CHAIN MANAGEMENT

Providing the product to the market without losing its quality is still one of the challenging tasks in the whole lifecycle. Below are the typical four phases of Supply Chain Management.

PACKAGING & LABELLING

Packaging & labelling on the drug plays a vital role in maintaining the product quality as well as its directions to use. The artworks used to label the medicine should adhere to the standard FDA's Prescription Drug Labelling Resources website which provides over 150 labelling resources for the Prescribing Information, FDA-approved patient labelling, and/or carton and container labelling for human prescription drugs, including biological products (including over 50 guidelines[6] with labelling content). Packaging of the drugs should be complied with as per the guidelines[7] for Good Manufacturing Practices as provided by FDA.

INVENTORY MANAGEMENT & TRANSPORTATION

Shipment and inventory management should be done in containers for bulk drug substances with a proper qualification of the container closure system may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as per appropriate suitability as mentioned by FDA guidelines "Container Closure Systems for Packaging Human Drugs and Biologics" with the storage conditions indicated on the packaging information and on the label of the product.

5. Reference: Good Manufacturing Practices - https://www. accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1

6. Reference: Good Labelling - https://www. fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

7. Reference: Good Packaging guidelines - https://www. fda.gov/media/70788/download

DISTRIBUTION

The distribution of the drugs is based on the sensitivity of the product. Narcotics Control Boards highly monitors controlled substances. The distribution of the drugs should adhere to local guidelines on "Good Distribution Practices for Pharmaceutical Products".

TRACK & TRACE

Product Tracing is important to safeguard the authenticity of the product eventually, avoiding the counterfeit drugs in the market, which risks the patient health, the company's brand image and its revenue. To avoid this, serialization is used as a measure to track, trace & identify each product providing transparency in the supply chain.

MARKETING OF DRUG

PLACING THE DRUG ON THE MARKET

Post-Production, marketing of the drug is an essential part of the lifecycle. Proper care needs to be taken that counterfeit product is not circulated in the market, which could risk the lives of the patients and tarnish the brand image.

MARKETING & PATIENT COMMUNICATION

The labelling should clearly give instruction about storage and transportation. Also, the distribution should be made region-wise with compliance of the local governing authorities. Drugs can be marketed by medical representatives.

EVALUATION OF VARIATION

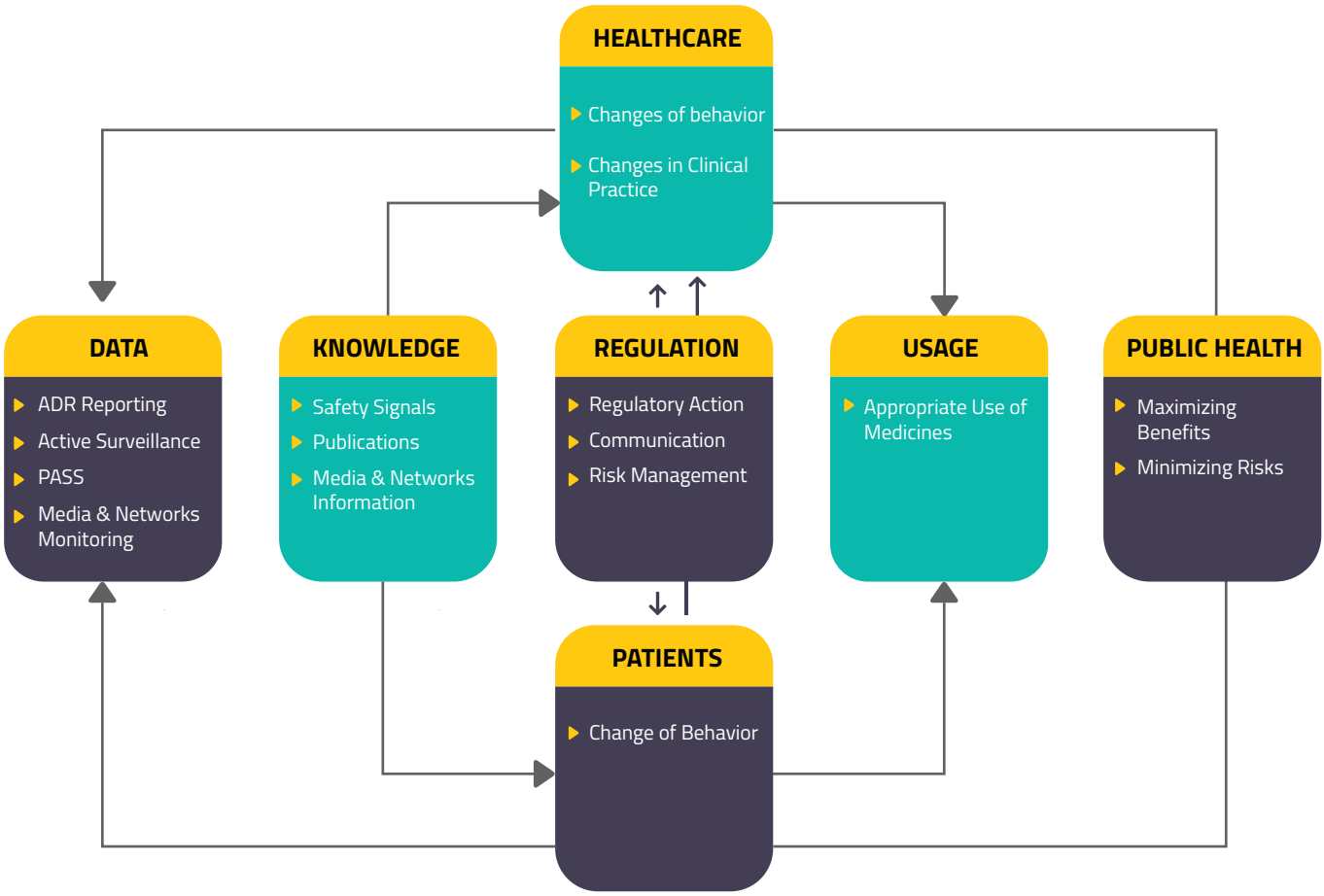
The effects of the drugs on patients should be monitored continuously throughout all regions, all age groups with different health conditions. The variation in the drug effects & it's variations should be communicated with patients & feedbacks should be evaluated.

POST-MARKETING SURVEY

This is the last stage of the drug life cycle. It has mainly three sub-phases.

PHARMA-CO-VIGILANCE

Once the drug reaches the market and prescribed to the patients, its effects on the patient are studied from different regions and on all age groups. This study is called as Pharmacovigilance. World Health Organization (WHO) defines the Pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems". Following are the steps involved in Pharmacovigilance studies.



RENEWAL/CANCELLATION OF MARKETING AUTHORIZATION

Based on Pharmacovigilance studies, the drugs should be evaluated & can be upgraded, renewed, or cancelled.

FURTHER DEVELOPMENT OF THE PRODUCT

Furthermore, the product is improved, developed and new lifecycle for the new product begins.

BENEFITS OF IT SERVICES IN PHARMA

Pharmaceutical companies have quickly adopted rapid advancements in the technology, which resulted in a considerable increase in efficiency, transparency and security in communication and productivity in daily transactions. Digitalization has brought up more uniformity and compliant, friendly environment, which has standardized the process throughout the lifecycle. Except for the human trials, each and every phase in the lifecycle is now technology dependent in all verticals of pharmaceutical irrespective of the nature and size of the business.

With the use of Software, it has become easy to manage business more efficiently. Pharmaceutical Software solutions can be implemented quickly and help industries to fulfil requirements effectively. Also, the existing data held by the organization can be migrated as per requirement without compromising the security and data loss. The quality of the product is enhanced with better decision-making, and stakeholders have crystal-clear visibility to real-time & accurate information.

Various IT services which are proving as a boon to Pharma industry through are:

Analytics and Artificial Intelligence	Internet of Things (IoT)	The Cyber-Physical Security of Pharmaceutical Processes	Data Mining in Clinical IT
Electronic CTD Submissions	Regulatory Information Management	Marketing and Supply Chain Intelligence	Quality Management
Business Intelligence			

JOURNEY OF HAPPIEST MINDS

Happiest Minds has emerged as one of the highly competitive and quality-oriented service providers in the market. Along with multiple customers, Happiest Minds has been associated with the world's second-largest generic and specialty pharmaceuticals company for the last three years and has helped in Infrastructure support, on-premise, cloud migration, End-user computing services and Enterprise Application Support. We have smoothly executed migration and onboarding projects after the merger and acquisition of two big pharma players and we are growing continuously.

Happiest Minds bring deep technical skills and exposure to pharmaceutical industry and has successfully helped organizations in their digital transformation journey, including infrastructure, security, product and platform engineering, IOT, Big Data Analytics and Artificial Intelligence, Supply chain management, Revenue Management System, Quality Management, Regulatory and Audit services.

AUTHOR INFO

Umesh Kokane has over 5 years of experience in Product Lifecycle Management in Infrastructure Design and Architecture. He is currently part of the IMSS - DMAS team at Happiest Minds Technologies Ltd. Umesh is an IT enthusiast and very passionate about learning new & emerging technologies.

Ashish has over 17 years of experience in Design, Architecture, Application Development and Support in Open Source and Big Data technologies. He is currently working as Pre-sales Architect in IMSS – DMAS practice at Happiest Minds Technologies Ltd. He has keen interest in sharing his knowledge on different platforms and forums.