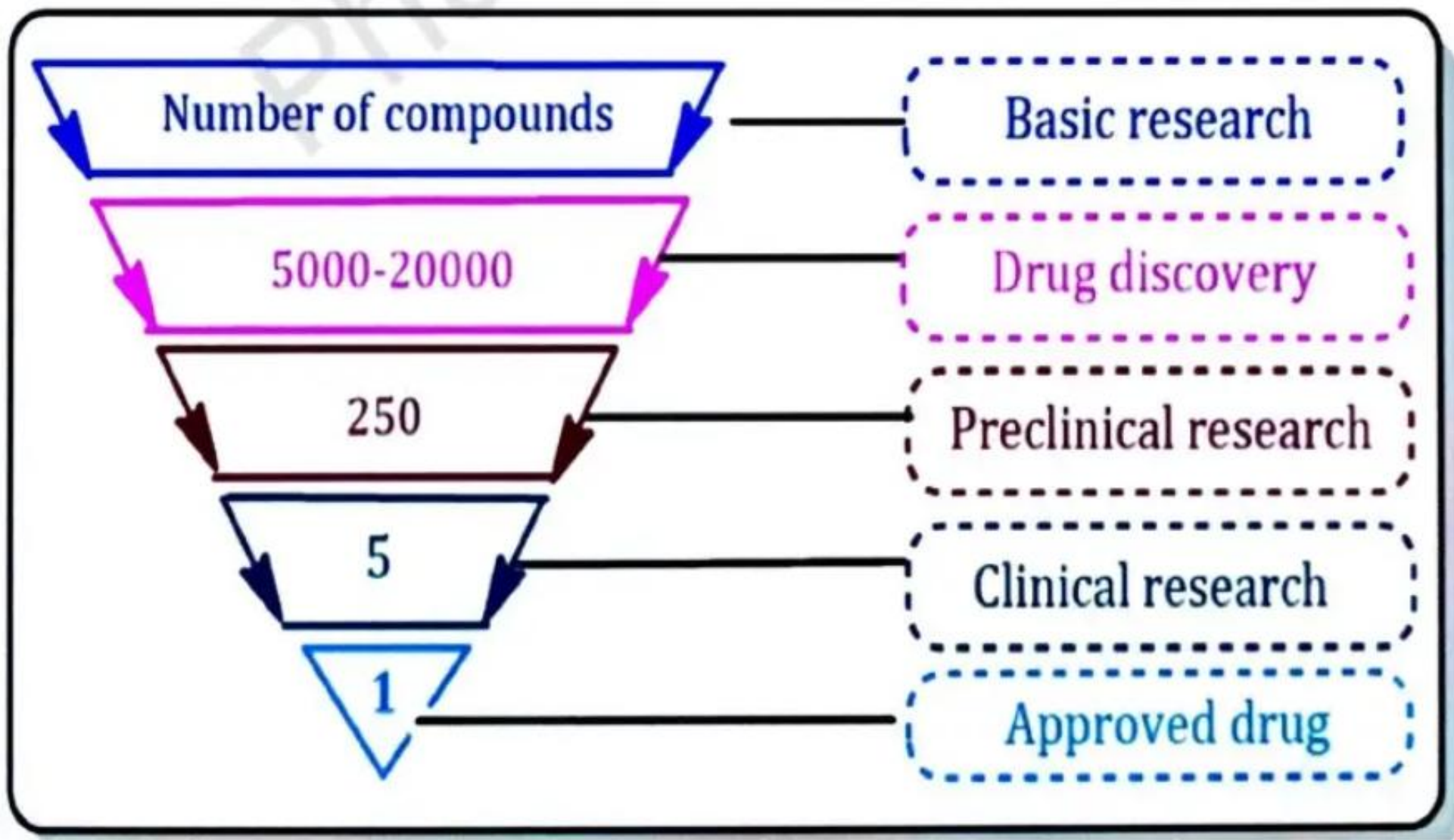


# **Drug Discovery & Development**

- Drug discovery is a process which aims at **identifying a compound therapeutically useful** in curing and treating disease.
- This process involves the identification of **candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy**.
- Once a compound has **shown its significance** in these investigations, it will initiate the process of drug development earlier to clinical trials.
- New drug development process must continue through several stages in order to make a medicine that is **safe, effective**, and has approved all regulatory requirements.
- This process is sufficiently long, complex, and expensive so that **many biological targets** must be considered for every new medicine.
- It takes about **12 - 15 years** from discovery to the approved medicine.
- On an average, a million molecules screened but only a single is explored in late stage clinical trials and is finally made obtainable for patients.

- In past drug have been discovered by identifying active ingredients from traditional medicine or by serendipitous.
- Innovator company synthesises **NCE** or **NBE** which can be probably be a cure for a disease.
- Research can be performed by 2 ways
  - **Basic research**
    1. Development of lead molecule
    2. Starts from cellular level
    3. Screening of newly synthesized molecule
    4. Time consuming , very complex, highly expensive.
  - **Applied research** work by chemistry on known molecule for its alteration
    1. Identification of new drug target
    2. Drug design
    3. Chemical alteration
    4. Screening
    5. Biotechnology



- **Stages of Drug Discovery and Development Process**

**1.Target identification**

**2.Target validation**

**3.lead identification**

**4.lead optimization**

**5.Product characterization**

**6.Formulation and development**

**7.Pre- clinical research**

**8.Investigational New Drug**

**9.Clinical trials**

**10.New Drug Application & Approval**

# Target identification

- The first step in the discovery of a drug is **identification of the biological origin of a disease**, and the potential targets for intervention.
- Target identification starts with isolating the function of a possible therapeutic target (**gene/nucleic acid /protein**) and its role in the disease.
- Identification of the target is followed by **characterization of the molecular mechanisms** addressed by the target.
- An ideal target should be efficacious, safe, meet clinical and commercial requirements and be druggable.

- The techniques used for target identification may be based principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.

<b>APPROACHES FOR TARGET IDENTIFICATION</b>	
<b>Data mining using bioinformatics</b>	Identifying, selecting and prioritizing potential disease targets
<b>Genetic association</b>	Genetic polymorphism and connection with the disease
<b>Expression profile</b>	Changes in mRNA/protein levels
<b>Pathway and phenotypic analysis</b>	In vitro cell-based mechanistic studies
<b>Functional screening</b>	Knockdown, knockout or using target specific tools

# Target Validation

- Target validation is the process by which the expected molecular target, example gene, protein or nucleic acid of a small molecule is actually involved in a disease process, and that binding of a drug to the target is likely to have a curative effect.
- Target validation is the **process of demonstrating the functional role of the identified target** in the disease phenotype.
- The validation of a drug's efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable, the ultimate test is whether the drug works in a clinical setting.

- It involves **critical analysis and comparison of various targets** and their association with specific disease
- It discuss **ability of target to regulate biological and chemical compound present in the body**

#### **TARGET VALIDATION INCLUDES:-**

- ✓ Determining the structure activity relationship (SAR) of analogs of the small molecule
- ✓ Generating a drug-resistant mutant of the presumed target
- ✓ Knockdown or over expression of the presumed target
- ✓ Monitoring the known signaling systems downstream of the presumed target.

## Lead Identification

- Is a substance which have potential to treat or modify the disease or disorder
- A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity for the target receptor
- Characteristics of a chemical lead are:
  - SAR defined
  - Drug ability (preliminary toxicity)
  - Synthetic feasibility
  - Select mechanistic assays
  - In vitro assessment of drug resistance and efflux potential
  - Evidence of in vivo efficacy of chemical class
  - PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

- In order to decrease the number of compounds that fail in the drug development process, a drug ability assessment is often conducted.
- This assessment is important in transforming a compound from a lead molecule into a drug.
- For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound's pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion.
- Other assays will evaluate the potential toxicity of the compound in screens.

## Lead Optimization

- Lead optimization is the process by which a **drug candidate is designed** after an initial lead compound is identified.
- The process involves iterative series of synthesis and characterization of a potential drug to build up a representation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism.
- In initial drug discovery, the resulting leads from **hit-to-lead** high throughput screening tests undergo lead optimization, to identify promising compounds.
- Potential leads are evaluated for a range of properties, including **selectivity and binding mechanisms during lead optimization**, as the final step in early stage drug discovery.

- The purpose of lead optimization is to **maintain favorable properties in lead compounds**, while improving on deficiencies in lead structure.
- In order to produce a pre-clinical drug candidate, the chemical structures of lead compounds (small molecules or biologics) **need to be altered** to improve target specificity and selectivity.
- **Pharmacodynamic** and **pharmacokinetic** parameters and toxicological properties are also evaluated. Labs must acquire data on the toxicity, efficacy, stability and bio-availability of leads, in order to accurately characterize the compound and establish the route of optimization.

## **Product Characterization**

- When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity.
- Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

## Formulation and Development

- Pharmaceutical formulation is a stage of drug development during which the **physicochemical properties of active pharmaceutical ingredients (APIs) are characterized** to produce a bio-available, stable and optimal dosage form for a specific administration route.
- During pre-formulation studies the following parameters are evaluated:
  - Solubility** in different media and solvents
  - Dissolution** of the active pharmaceutical ingredient (API)
  - Accelerated **Stability** under various conditions
  - Solid state properties** (polymorphs, particle size, particle shape etc.)
  - Formulation and capabilities
  - Formulation development of new chemical entities (NCE)
  - Optimization** of existing formulations
  - Process development** for selected dosage forms
  - Novel formulations** for improved delivery of existing dosage forms
  - Controlled release and sustained release formulations
  - Colloidal drug delivery systems
  - Sub-micron and nano-emulsions

## Pre- clinical Testing

- Pre-clinical research in drug development process involves **evaluation of drug's safety and efficacy in animal species** that conclude to prospective human outcome.
- The pre- clinical trials also **have to acquire approval** by corresponding regulatory authorities.
- The regulatory authorities must **ensure** that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective.
- ICH has established a basic guideline for technical necessities of acceptable preclinical drug development.
- The pre-clinical trials can be conducted in two ways: **General pharmacology and Toxicology**. Pharmacology deals with the pharmacokinetic and pharmacodynamic parameters of drug. It is essential to explore unwanted pharmacological effects in suitable animal models and monitoring them in toxicological studies
- Toxicological studies of the drug can be performed by **in- vitro and in-vivo test** which evaluate the toxicological effects of the drug.
- In-vivo studies to evaluate pharmacological and toxicological actions, including mode of action, are often used to support the basis of the proposed use of the product in clinical studies.

## **The Investigational New Drug Process (IND)**

- Drug developers must file an Investigational New Drug application to FDA before commencement clinical research. In the IND application, developers must include:

Preclinical and toxicity study data

Drug manufacturing information

Clinical research protocols for studies to be conducted

Previous clinical research data (if any)

Information about the investigator/developer

## Clinical Research

- Clinical trials are conducted in people (**volunteer**) and intended to answer specific questions about the safety and efficacy
- Clinical trials follow a specific study **protocol** that is designed by the researcher or investigator or manufacturer.
- As the developers design the clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND)
- Before a clinical trial begins, researchers **review prior information** about the drug to develop research questions and objectives. Then, they decide:
  - Selection criteria for participants
  - Number of people take part of the study
  - Duration of study
  - Dose and route of administration of dosage form
  - Assessment of parameters
  - Data collection and analysis

# PHASES OF A CLINICAL TRIAL

0

## PRE-CLINICAL

Lab – based research to tell if a treatment is useful and safe



1

## SAFETY

10 – 80 participants to assess effect of treatment in humans



2

## SAFETY & DOSING

100 - 300 participants to evaluate safety & effective dose of treatment



3

## SAFETY & EFFICACY

300 - 3000 participants to confirm benefit and safety of the treatment



4

## POST-APPROVAL

Post-approval surveillance to evaluate long - term effects of treatment



## Phase 0- clinical trial

1. Implicates investigative, **first-in-human (FIH) trials** that are conducted according to FDA guidelines.
2. Phase 0 trials besides termed as **human micro dose studies**, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data
3. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans.

- **Phase 1- Safety and dosage**

1. Phase I trials are the first tests of a drug with a lesser number of healthy human volunteers.
2. In most cases, 20 to 80 healthy volunteers with the disease/condition participate in this
3. Patients are generally only used if the mechanism of action of a drug indicates that it will not be tolerated in healthy people.
4. However, if a new drug is proposed for use in diabetes patients, researchers conduct Phase 1 trials in patients with that type of diabetes. Phase 1 studies are closely monitored and **collect information about Pharmacodynamics in the human body**.
5. Researchers adjust **dosage regimen** based on animal study data to find out **what dose of a drug can tolerate the body and what are its acute side effects**.
6. As a Phase 1 trial continues, researchers find out research **mechanism of action, the side effects accompanying with increase in dosage, and information about effectiveness**. This is imperative to the design of Phase 2 studies. Almost 70% of drugs travel to the next phase.

- **Phase 2- Efficacy and side effects**

1. Phase II trials are conducted on **larger groups of patients** (few hundreds) and are aimed to evaluate the **efficacy of the drug** and to endure the Phase I safety assessments.
2. These trials aren't sufficient to confirm whether the drug will be therapeutic.
3. Phase 2 studies provide with additional safety data to the researchers.
4. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.
5. Around 33% of drugs travel to the next phase.

- **Phase 3- Efficacy and adverse drug reactions monitoring**

1. Phase III of a clinical trial usually involves up to **3,000** participants who have the condition that the new medication is meant to treat. Trials in this phase can last for several years.
2. The purpose of phase III is to evaluate how the new medication works in comparison to **existing medications for the same condition**.
3. To move forward with the trial, investigators need to demonstrate that the **medication is at least as safe and effective** as existing treatment options. To do this, investigators use a process called randomization.
4. This involves randomly choosing some participants to receive the new medication and others to receive an existing medication.
5. The FDA usually requires a phase III clinical trial before approving a new medication. Due to the larger number of participants and longer duration of phase III, rare and long-term side effects are more likely to show up during this phase.
6. If investigators demonstrate that the medication is at least as safe and effective as others already on the market, the FDA will usually approve the medication.

- Phase 4- Post-Market Drug Safety Monitoring

1. Phase 4 trials are conducted when the drug or device has been approved by FDA.
2. These trials are also recognized as post-marketing surveillance involving pharmacovigilance and continuing technical support after approval.
3. There are numerous observational strategies and assessment patterns used in Phase 4 trials to evaluate the efficacy, cost- effectiveness, and safety of an involvement in real-world settings.
4. Phase IV studies may be required by regulatory authorities (e.g. change in labelling, risk management/minimization action plan) or may be undertaken by the sponsoring company for competitive purposes or other reasons.
5. FDA reviews reports of complications with prescription and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions.

## **New Drug Application**

- A New Drug Application (NDA) expresses the full story of a drug molecule.
- Its purpose is to verify that a drug is safe and effective for its proposed use in the people studied.
- A drug developer must include all about a drug starting from preclinical data to Phase 3 trial data in the NDA.

# INNOVATOR & GENERICS

## 1. Innovator

- An innovator drug is the **first drugs created** containing its specific active ingredient to receive approval for use.
- It is usually the product for which **efficacy, safety and quality** have been fully established.
- When a new drug is first made, **drug patent** usually will be acquired by the founding company.
- Most drug patents are protected up to **20 years**. During the patent period, other companies cannot make or sell the same drug until the patent expires.

## GENERIC

- A generic drug is made of the **same active ingredient** as its innovator drug.
- An active ingredient is the **chemical contained inside** a drug that makes it work.
- In other words, the **pharmacological effect** of a generic drug is **exactly the same** as those of its innovator counterpart.
- Other companies can manufacture the generic drugs when **patent expires**.
- There are similarities between generic and innovator drug, such as:
  1. Active ingredient
  2. Strength (dose)
  3. Therapeutic effect
  4. Side effects
  5. How to take

## CONCEPT OF GENERICS

- On September 24, 1984, in the 98th U.S. Congress, the Act named 'The Drug Price Competition and Patent Term Restoration Act' was passed, also known as the **Hatch-Waxman Act**.
- The objective of this act was to **encourage the manufacturing of generic drugs** by the pharmaceutical industries and to establish the modern system of government generic drug regulation in the USA.
- The requirement for this was to **submit an Abbreviated New Drug Application** (ANDA) by the pharmaceutical companies to the regulatory authorities for getting the approval to market a generic drug.
- Generics are formulated, developed, and manufactured by other companies when patent and other exclusivity **rights of the innovator have expired**.
- As generic drug development does not involve large investment for drug discovery and preclinical and clinical trials, they are available at a lower cost and provide an opportunity for savings in drug expenditure of a country.

## ACCORDING TO WHO

- "Generic drug is a pharmaceutical product which is usually intended to be **interchangeable** with an innovator product, is manufactured without a license from the innovator company, and is marketed after the expiry date of the patent or other exclusive rights".
- In generic pharmaceutical products, there is no standard categorization as it does not cover the specifics of this industry.
- Thus, the new generic products can be defined as:
  - **Line extensions:** Line extensions are **small adaptations of an existing product**, which is normally already available on the market.
  - **Retargeting:** Retargeting refers to existing products registered, launched, and marketed in a new market.
  - **New product:** A new product is a completely new product for the company and for the market in the generics segment.

- A generic drug is approved by the regulatory agency if it is
  1. **Pharmaceutically equivalent** to an approved safe and effective reference product in that it:
    - a) Contains **identical amounts** of the same active drug ingredient in the same dosage form and route of administration and
    - b) Meets compendial or other applicable standards of strength, quality, purity, and identity.
  2. Bioequivalent to the reference product in that it:
    - a) Does not present a known or potential bioequivalence problem and it meets an acceptable in vitro standard (usually dissolution testing) or
    - b) If it does present such a known or potential problem, it is shown to meet an appropriate bioequivalence standard.
  3. Adequately labeled.
  4. Manufactured in compliance with CGMP regulations.

# GENERIC DRUG PRODUCT DEVELOPMENT

- Drug product development is a creative and multidisciplinary process that turns a technological innovation and a market Opportunity in products with economic profitability for the company.
- Generic drug products are proven therapeutically equivalent to the corresponding innovator's product, and hence can be substituted in clinical practice.
- The objective of generic drug product development is to develop a stable and bioequivalent generic drug product with desirable properties.

- The process of development includes three sequential stages essential for successful generic drug development.

1. First, a **predevelopment** stage involves collecting and evaluating data and information related to a drug such as its physicochemical properties and critical quality attributes, before implementing any development activities.

2. Second, **development stages** begin with a thorough characterization of the innovator's product, followed by an initial compatibility study between the drug and proposed excipients to be used in the formulation, suitable selection of method for formulation development, and suitable selection of manufacturing process.

3. Third, Once a **pilot batch** of the generic product is obtained, an in vivo bioequivalent test is conducted in accordance with the GCP to assure that the generic drug product is therapeutically equivalent to the innovator's product.

- Generic drug product development is the process that completely covers a **series of stages** required to bring a generic drug product to the market.

### 1. Drug candidate selection

This phase covers the broad **selection of potential drug candidates**. A team decides which drug candidates should be selected to proceed into the preliminary assessment phase.

### 2. Candidate drug screening

In this phase drug candidates selected in the earlier phase is carefully **screened** to roughly assess the potential drug candidates. The simple strategy followed is **to accept the best and eliminate the poor**. Development proceeds with only one or two candidates for the next phase.

### 3. Concept development

It is an exercise in which the screened candidate drug is **translated into the product concept**. The product concept is a detailed version of the product idea. The needs of the target market are identified, alternative product concepts are generated and evaluated, and a single development is selected for further development.

- **System-level design**

The final **formulation scheme** for the production system is usually defined during this phase. A preliminary **process flow diagram** for the final manufacturing.

- **Detail design**

This phase includes the **complete specification** of the materials and limits of all the components in the product and the identification of all the probable suppliers.

- **Concept testing**

This phase is the **laboratory development of a generic product**. This phase starts with experimental and accelerated stability study work, the development based on a laboratory scale, including the (pilot) bio-equivalent-study and development of the primary packaging.

- **Business analysis**

Landmarks and milestones of the **product development process and time required for the completion should be fixed**. Also, in this phase, the impacts of delays and time of product arrival in the market are analyzed carefully.

- **Development of a prototype**

This phase is also called **production ramp-up**. It also describes the period from completed initial product development to maximum capacity utilization, characterized by product and process experimentation and improvements.

- **Development of technology**

This phase includes the transfer to the industry measure and the **preparation of registration documentation**. It includes clinical studies, toxicological studies, bio-equivalent studies, and completed stability studies.

- **Registration**

Registration is a phase of filing of registration dossiers at regulatory authorities, It finishes when the product is registered and the registration documentation and marketing authorization is obtained.

- **Launch**

The launch phase includes all final pre-launch activities such as ordering of materials, production of launch stock, ordering of raw materials, packaging materials etc. including the launch of the product on the selected market.

