

Drug Product Development in the Pharmaceutical Industry

Gurvinder Singh Rekhi

Leon Shargel

I. INTRODUCTION

A. Active pharmaceutical ingredient (API)

1. A **drug substance** is the API or component that produces pharmacological activity.
2. The API may be **produced by** chemical synthesis, recovery from a natural product, enzymatic reaction, recombinant DNA technology, fermentation, or a combination of these processes. Further purification of the API may be needed before it can be used in a drug product.
3. A **new chemical entity (NCE)** is a drug substance with unknown clinical, toxicologic, physical, and chemical properties. In addition, the U.S. Food and Drug Administration (FDA) considers an NCE as an API that has not been approved for marketing in the United States.
4. The **identity, strength, quality, and purity** of a drug substance depend on proper control of the manufacturing and synthetic process.

B. Drug product

1. A drug product is the **finished dosage form** (e.g., capsule, tablet, injectable) that contains the API, generally in association with other excipients, or inert ingredients.
2. The excipients in the drug product may affect the functionality and performance of the drug product, including modification of the rate of drug substance release, improving drug stability, and masking the drug taste.
3. Different **approaches** are generally used to produce drug products that contain NCEs, product line extensions, generic drug products, and specialty drug products.

C. New drug product development

Drug products containing NCE are developed sequentially in the following phases.

1. **Preclinical.** Animal pharmacology and toxicology data are obtained to determine the safety and efficacy of the drug. Because little is known about the human and the therapeutic/toxicologic potential, many drug products will not reach the marketplace. No attempt is made to develop a final formulation during the preclinical stage.

Nonclinical studies are nonhuman studies that may continue at any stage of research to obtain additional information concerning the pharmacology and toxicology of the drug.

2. Phase I

- a. An **Investigational New Drug (IND)** application for human testing is submitted to the FDA. Clinical testing takes place after the IND application is submitted.

- b. Healthy volunteers are used in phase I clinical studies to determine drug tolerance and toxicity.
- c. For oral drug administration, a simple hard gelatin capsule formulation containing the API is usually used for IND studies.
- d. Toxicologic studies—including acute, chronic, subchronic, and mutagenicity—and other such studies in various animal species are planned during this phase.

3. Phase II

- a. A limited number of patients with the disease or condition for which the drug was developed are treated under close supervision.
- b. Dose-response studies, bioavailability, and pharmacokinetics are performed to determine the optimum dosage regimen for treating the disease.
- c. Safety is measured by attempting to determine the **therapeutic index** (ratio of toxic dose to effective dose).
- d. A drug formulation having good physico-chemical stability is developed.
- e. Chronic toxicity studies are started in two species; such studies normally last more than 2 years' duration.

4. Phase III

- a. Large-scale, **multicenter clinical studies** are performed with the final dosage form developed in phase II. These studies are done to determine the safety and efficacy of the drug product in a large patient population who have the disease or condition for which the drug was developed.
- b. Side effects are monitored. In a large population, new toxic effects may occur that were not evident in previous clinical trials.
- 5. Submission of a **New Drug Application (NDA)**. An NDA is submitted to the FDA for review and approval after the completion of clinical trials that show to the satisfaction of the medical community that the drug product is effective by all parameters and is reasonably safe as demonstrated by animal and human studies.

6. Phase IV

- a. After the NDA is submitted, and before approval to market the product is obtained from the FDA, manufacturing **scale-up** activities occur. Scale-up is the increase in the batch size from the clinical batch, submission batch, or both to the full-scale production batch size, using the finished, marketed product.
- b. The drug product may be improved as a result of equipment, regulatory, supply, or market demands.
- c. Additional clinical studies may be performed in special populations, such as the elderly, pediatric, and renal-impaired, to obtain information on the efficacy of the drug in these subjects.
- d. Additional clinical studies may be performed to determine if the drug can be used for a new or additional labeling indications.

7. Phase V

- a. After the FDA grants market approval of the drug, product development may continue.
- b. The **drug formulation** may be modified slightly as a result of data obtained during the manufacturing scale-up and validation processes.

c. **Changes in drug formulation** should always be within the scale-up and post-approval change (**SUPAC**) guidelines.

D. Product line extensions are dosage forms in which the physical form or strength, but not the use or indication, of the product changes. Product line extension is usually performed during phase III, IV, or V.

1. Developing a transdermal patch when only tablets have been available, for example:

- Progesterone
- Nicotine
- Estradiol
- Nitroglycerin

2. **Additional strengths**—as long as these strengths are within the total daily dose, for example:

- Ibuprofen

P.3

3. Controlled-release or modified-release dosage forms when only an immediate-release dosage form is available. This is an ongoing project for all brand companies; almost every NCE has or will eventually have a modified-release dosage form of the immediate-release product.

E. Biologic products

1. A biologic product is any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries.

2. Biologic products are a **subset** of drug products, distinguished by their manufacturing processes (biologic vs. chemical). In general, the term *drugs* includes biologic products.

3. **Biologic license application (BLA)**. Biologic products are approved for marketing under the provisions of the Public Health Service (PHS) Act.

F. Generic drug products

1. After **patent expiration** of the API and /or brand drug product, a generic drug product may be marketed. A generic drug product is therapeutically equivalent to the brand name drug product and contains the same amount of the drug in the same type of dosage form (e.g., tablet, liquid, injectable).

2. A generic drug product must be **bioequivalent** (i.e., have the same rate and extent of drug absorption) to the brand drug product. Therefore, a generic drug product is expected to give the same clinical response (Chapter 7). These studies are normally performed with healthy human volunteers.

3. Some generic products are not absorbed; for some others bioequivalence is not a good marker. Under those conditions, **comparative clinical trials** or studies with

pharmacodynamic end points are considered to measure the equivalence of two products. Inhalation products and nonabsorbed drug products fall into this category.

4. The generic drug product may differ from the brand product in physical appearance (i.e., size, color, shape) or in the amount and type of excipients used in the formulation.

5. A generic drug product may not differ in both the qualitative and the quantitative compositions for liquids, injectables, semisolids, transdermal patches, inhalation products, and ophthalmic products, unless adequate safety studies have been performed.

6. Before a generic drug product is marketed, the manufacturer must submit an Abbreviated New Drug Application (ANDA) to the FDA for approval. Because preclinical safety and efficacy studies have already been performed for the NDA-approved brand product, human bioequivalence studies, instead of clinical trials, are generally required for the ANDA. The chemistry, manufacturing, and controls requirements for the generic drug product are similar to those for the brand name drug product.

G. Specialty drug products are existing products developed as a new delivery system or for a new therapeutic indication. The safety and efficacy of the drug product were established in the initial NDA-approved dosage form. For example, the nitroglycerin transdermal delivery system (patch) was developed after experience with nitroglycerin sublingual tablets.

II. PRODUCT DEVELOPMENT.

For each drug, various studies are required to develop a safe, effective, and stable dosage form.

A. New chemical entities

1. Preformulation is the characterization of the physical and chemical properties of the active drug substance and dosage form. The therapeutic indication of the drug and the route of administration dictate the type of drug product or drug delivery system (e.g., immediate release, controlled release, suppository, parenteral, transdermal) that needs to be developed.

a. Preformulation activities are usually performed during the preclinical stage. However, these activities may continue into phases I and II.

b. The following information is obtained during preformulation.

P.4

(1) Physical, including particle size and shape, crystallinity, polymorphism, density, surface area, hygroscopicity (ability to take up and retain moisture), and powder flow

(2) Solubility, including intrinsic dissolution, pH solubility profile, and general solubility characteristics in various solvents

(3) Chemical, including surface energy, pH stability profile, pKa, temperature stability (dry or under various humidity conditions), and excipient interactions

(4) Analytical methods development, including development of a stability indicating method (measures both the API and the related substances), and cleaning methods

2. Formulation development is a continuing process. Initial drug formulations are developed for early clinical studies. When the submission of an NDA is considered, the manufacturer attempts to develop the final (marketed) dosage form. The dose of the drug and the route of administration are important in determining the modifications needed.

a. Injectable

- (1)** A final injectable drug product is usually developed in the preclinical phase.
- (2)** Major concerns include the stability of the drug in solution and the sterility of the product.
- (3)** Because few excipients are allowed in injectable products, the formulator must choose a final product early in the development process.
- (4)** If the formulation is changed, bioavailability studies are not required for intravenous solution injections because the product is injected directly into the body.
- (5)** Formulation changes may require acute toxicity studies.

b. Topical (for local application). Includes antibacterials, antifungals, corticosteroids, and local anesthetics.

- (1)** The final dosage form for a topical drug product is usually developed during phase I studies because any major formulation changes may require further clinical trials.
- (2)** The release of the drug from the matrix is measured in vitro with various diffusion cell models.
- (3)** Significant problems encountered with locally acting topical drug products include local irritation, skin sensitization and systemic drug absorption.

c. Topical (for systemic drug absorption). Includes drug delivery through the skin (transdermal), mucous membranes (intranasal), and rectal mucosa.

- (1)** A prototype formulation is developed for phase I.
- (2)** A final topical drug product is developed during phase III after the available technology and desired systemic levels are considered.

d. Oral

- (1)** Prototype dosage forms are often developed during the **preclinical phase** to ensure that the drug is optimally available and that the product dissolves in the gastrointestinal tract.
- (2)** In the early stages of product development, **hard gelatin capsule** dosage forms are often developed for **phase I** clinical trials. If the drug shows efficacy, the same drug formulation may be used in phase II studies.
- (3)** Final product development begins when the drug proceeds during phase II and before initiating phase III clinical studies.

3. Marketed Product. Considerations in the development of a final dosage form include the following:

- a.** Color, shape, size, taste, viscosity, sensitivity, skin feel, and physical appearance of the dosage form
- b.** Size and shape of the package or container

- c. Production equipment
- d. Production site
- e. Country of origin in which the drug is to be manufactured
- f. Country in which the drug will be marketed

B. Product line extensions are generally defined as drug products containing an NDA-approved drug in a different dosage strength or in a different dosage form (e.g., modified release, oral liquid).

1. Oral product line extensions

- a. The simplest dosage form to develop is a different dosage strength of a drug in a tablet or capsule. Only bioequivalence studies are needed.

P.5

- b. A **modified-release** dosage form is more difficult to develop when only an immediate-release dosage form exists. Clinical trials are normally required.
- c. Considerations in developing these dosage forms are similar to those for the final drug product (see II.A.3).

d. Marketing has a role in the choice of the dosage form.

e. Because the original brand drug product information contributes to the body of knowledge about the drug, no preformulation is needed. All other factors considered for the original product are similar. If the relation between **in vitro** dissolution and **in vivo** bioavailability is known, the innovator can progress to a finished dosage form relatively quickly.

f. Regulatory approval is based on the following:

- (1) Analytical and manufacturing controls
- (2) Stability information
- (3) Bioavailability and bioequivalence studies
- (4) Clinical trials (in the case of modified-release dosage forms)

g. A new therapeutic indication for a drug requires new **efficacy studies** and a new **NDA**.

2. Liquid product line extensions

- a. If the current marketed product is a liquid preparation, then the same factors as for the solid oral dosage forms are considered (see II.B.1.a, b, c, d, e, f and g).
- b. If the marketed product is a solid oral dosage form and the product line extension is a liquid, product development must proceed with caution because the rate and extent of absorption for liquid and solid dosage forms may not be the same.

c. Regulatory approval requires

- (1) Analytical and manufacturing controls
- (2) Stability information
- (3) Bioavailability and bioequivalence studies
- (4) Safety studies (e.g., depending on the drug substance, local irritation)
- (5) Clinical trials, if the rate and extent of drug absorption are drastically altered from the original dosage form

C. Combination products are made up of two or more regulated components (e.g., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are

physically, chemically, or otherwise combined or mixed and produced as a single entity.

1. These may be two or more separate products packaged together in a single package or as a unit and may be composed of drug and device products, device and biologic products, or biologic and drug products.

2. An **example** is an inhalation steroid (e.g., beclomethasone inhalation aerosol) in which the device component is important for delivery of the steroid.

III. PREAPPROVAL INSPECTIONS (PAIs)

A. The manufacturing facility is inspected by the FDA after an NDA, abbreviated antibiotic drug application (AADA), or ANDA is submitted and before the application is approved.

B. A PAI may also be initiated if a major change is reported in a supplemental application to an NDA, AADA, or ANDA.

C. During the PAI, the FDA investigator:

1. **Performs** a general current good manufacturing practice (cGMP) inspection relating specifically to the drug product intended for the market

2. **Reviews** the development report to verify that the drug product has enough supporting documentation to ensure a validated product and a rationale for the manufacturing directions

3. **Consults** the chemistry, manufacturing, and control (CMC) section of the NDA, AADA, or ANDA and determines the capability of the manufacturer to produce the drug product as described

P.6

4. **Verifies** the traceability of the information submitted in the CMC section to the original laboratory notebooks, electronic information, and batch records

5. **Verifies and ensures** that all the quality systems are in place to manufacture the product so it retains the identity, strength, quality, and purity of the drug product that were approved by the center.

6. **Recommends** approval for the manufacture of the drug product based on the status of the inspection

IV. SCALE-UP AND POSTAPPROVAL CHANGES (SUPACs)

A. Purpose. These guidelines are intended to reduce the number of manufacturing changes that require pre-approval by the FDA. The guidelines are published by the FDA on the Internet (<http://www.fda.gov/cder/guidance/index.htm>).

B. Function. These guidelines provide recommendations to sponsors of NDAs, AADAs, and ANDAs during the postapproval period when

1. Making slight changes in the amount of the **excipient** to aid in the processing of the product during scale-up

2. Changing the **site** of manufacture

3. Scaling up (increasing) or **scaling down** (decreasing) the batch size of the formulation

4. Changing the manufacturing process or equipment

C. The FDA must be notified about a proposed change to a drug product through different regulatory documentation, depending on the type of change proposed.

1. Annual report. Changes that are unlikely to have any detectable effect on formulation quality and performance can be instituted without approval by the FDA and reported annually. Examples of these changes include:

a. Compliance with an official compendium

b. Label description of the drug product or how it is supplied (not involving dosage strength or dosage form)

c. Deletion of an ingredient that affects only the color of the product

d. Extension of the expiration date based on full shelf-life data obtained from a protocol approved in the application

e. Container and closure system for the drug product (except a change in container size for nonsolid dosage forms) based on equivalency to the approved system under a protocol approved in the application or published in an official compendium

f. Addition or deletion of an alternate analytical method

2. Changes being effected (CBE) supplement. Changes that probably would not have any detectable effect but require some validation efforts require specific documentation, depending on the change. A supplement is submitted, and the change can be implemented without previous approval (**CBE-0**) by the FDA or, in some cases, the FDA has 30 days to review the change (**CBE-30**). FDA may reject this supplement. Examples of reasons for submitting a supplement include

a. Addition of a new specification or test method or changes in methods, facilities, or controls

b. Label change to add or strengthen a contraindication, warning, precaution, or adverse reaction

c. Use of a different facility to manufacture the drug substance and drug product (the manufacturing process in the new facility does not differ materially from that in the former facility, and the new facility has received a satisfactory cGMP inspection within the previous 2 years covering that manufacturing process)

3. Pre-approval supplement. Changes that could have a significant effect on formulation quality and performance require specific documentation. This supplement must be approved before the proposed change is initiated. Appropriate examples for pre-approval supplement are:

a. Addition or deletion of an ingredient

b. Relaxation of the limits for a specification

P.7

c. Establishment of a new regulatory analytical method

d. Deletion of a specification or regulatory analytical method

e. Change in the method of **manufacture** of the drug product, including changing or relaxing an in-process control

f. Extension of the **expiration date** of the drug product based on data obtained under a new or revised stability testing protocol that was been approved in the application

D. When any change to a drug product is proposed, the manufacturer must show that the resultant drug product is **bioequivalent** and **therapeutically equivalent** to the original approved drug product (see Chapter 7).

1. A **minor change** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. If the proposed change is considered minor by the FDA, bioequivalence may be demonstrated by comparative dissolution profiles for the original and new formulations.

2. A **major change** is one that has substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. If the proposed change is considered major by the FDA, bioequivalence must be demonstrated by an in vivo bioequivalence study comparing the original and new formulations.

V. GOOD MANUFACTURING PRACTICES (GMPs)

are regulations developed by the FDA. GMPs are minimum requirements that the industry must meet when manufacturing, processing, packing, or holding human and veterinary drugs. These regulations, also known as **cGMPs**, establish criteria for personnel, facilities, and manufacturing processes to ensure that the finished drug product has the correct identity, strength, quality, and purity characteristics.

A. Good Manufacturing Practices are described in the Code of Federal Regulations (CFR), title 21, sections 210 and 211.

B. **Quality control (QC)** is the group within the manufacturer that is responsible for establishing process and product specifications.

1. **Specifications** are the criteria to which a drug product should conform to be considered having acceptable quality for its intended use.

2. The QC unit **tests** the product and verifies that the specifications are met. QC testing includes the **acceptance or rejection** of the incoming raw materials, packaging components, drug products, water system, and environmental conditions (e.g., heating, ventilation, air-conditioning, air quality, microbial load) that exist during the manufacturing process.

C. **Quality assurance (QA)** is the group within the manufacturer that determines that the systems and facilities are adequate and that the written procedures are followed to ensure that the finished drug product meets the applicable specifications for quality.

P.8

STUDY QUESTIONS

Directions: Each statement in this section can be correctly completed by **one or more** of the suggested phrases. Choose the **correct** answer, A-E:

1. Healthy human volunteers are used in drug development for

I. phase I testing after the submission of an investigational new drug (IND) application.

II. generic drug development for an abbreviated new drug application (ANDA) submission.

III. phase III testing just before the submission of a new drug application (NDA).

A if I only is correct

B if III only is correct

C if I and II are correct

D if II and III are correct

E if I, II, and III are correct

[View Answer1.](#) *The answer is C[see].*

2. The required information contained in a new drug application (NDA) that is *not* included in the abbreviated new drug application (ANDA) consists of

I. preclinical animal toxicity studies.

II. clinical efficacy studies.

III. human safety and tolerance studies.

A if I only is correct

B if III only is correct

C if I and II are correct

D if II and III are correct

E if I, II, and III are correct

[View Answer2.](#) *The answer is E[see].*

3. A product line extension contains the new drug application (NDA) approved drug in a new

I. dosage form.

II. dosage strength.

III. therapeutic indication.

A if I only is correct

B if III only is correct

C if I and II are correct

D if II and III are correct

E if I, II, and III are correct

[View Answer3.](#) *The answer is C[see].*

Directions: Each statement in this section can be correctly completed by **one** of the suggested phrases. Choose the **best** answer.

4. The regulations developed by the U.S. Food and Drug Administration (FDA) for the pharmaceutical industry for meeting the minimum requirements in the manufacturing, processing, packing, or holding of human and veterinary drugs are known as

(A) good manufacturing practices (GMPs).

(B) quality assurance (QA).

(C) quality control (QC).

- (D) pre-approval inspection (PAI).
- (E) scale-up and post-approval changes (SUPACs).

View Answer4. The answer is A[see].5. The unit within the pharmaceutical manufacturer that ensures that the finished dosage form has met all the specifications for its intended use is the

- (A) analytical methods unit.
- (B) marketing and sales unit.
- (C) pre-approval inspection (PAI) unit.
- (D) quality assurance (QA) unit.
- (E) quality control (QC) unit.

View Answer5. The answer is E[see].6. Manufacturers may make a change in the formulation after market approval. If the change in the formulation is considered a minor change, the manufacturer needs to report the change to the FDA only in the

- (A) annual report.
- (B) pre-approval supplement.
- (C) investigational new drug (IND) submission.
- (D) changes being effected supplement, 30 days (CBE-30).
- (E) no report is required for a minor change.

View Answer6. The answer is A[see].P.9

ANSWERS AND EXPLANATIONS

1. The answer is C (I, II) [see I.C.2.b; I.F.2].

Phase I testing is the first set of human studies performed during new drug development. Phase I studies establish the tolerance and toxicity of the drug in humans. Bioequivalence studies for generic drug development are most often performed in healthy human volunteers. These studies establish the bioequivalence of the generic drug product against the brand drug product. Phase III testing entails large-scale, multicenter clinical studies performed in patients with the disease or condition to be treated. Phase III studies determine the safety and efficacy of the drug in a large patient population.

2. The answer is E (I, II, and III) [see I.C.5; I.F.6].

The development of a new drug requires extensive toxicity and efficacy testing in animals and humans. The NDA documents all studies performed on the drug. The ANDA is used for generic drug product submissions. The generic drug product is similar to the original brand drug product that has already been marketed. Because the efficacy, safety, and toxicity of this drug product have been studied and documented, further studies of this nature are unnecessary.

3. The answer is C (I, II) [see I.D].

Product line extensions are developed after further studies with the original NDA-approved drug product. From these studies, the manufacturer may develop a new dosage form (e.g., controlled-release product) or a new dosage strength. A new therapeutic indication requires an NDA.

ANSWERS AND EXPLANATIONS

1. The answer is C (I, II) [see I.C.2.b; I.F.2].

Phase I testing is the first set of human studies performed during new drug development. Phase I studies establish the tolerance and toxicity of the drug in humans. Bioequivalence studies for generic drug development are most often performed in healthy human volunteers. These studies establish the bioequivalence of the generic drug product against the brand drug product. Phase III testing entails large-scale, multicenter clinical studies performed in patients with the disease or condition to be treated. Phase III studies determine the safety and efficacy of the drug in a large patient population.

2. The answer is E (I, II, and III) [see I.C.5; I.F.6].

The development of a new drug requires extensive toxicity and efficacy testing in animals and humans. The NDA documents all studies performed on the drug. The ANDA is used for generic drug product submissions. The generic drug product is similar to the original brand drug product that has already been marketed. Because the efficacy, safety, and toxicity of this drug product have been studied and documented, further studies of this nature are unnecessary.

3. The answer is C (I, II) [see I.D].

Product line extensions are developed after further studies with the original NDA-approved drug product. From these studies, the manufacturer may develop a new dosage form (e.g., controlled-release product) or a new dosage strength. A new therapeutic indication requires an NDA.

