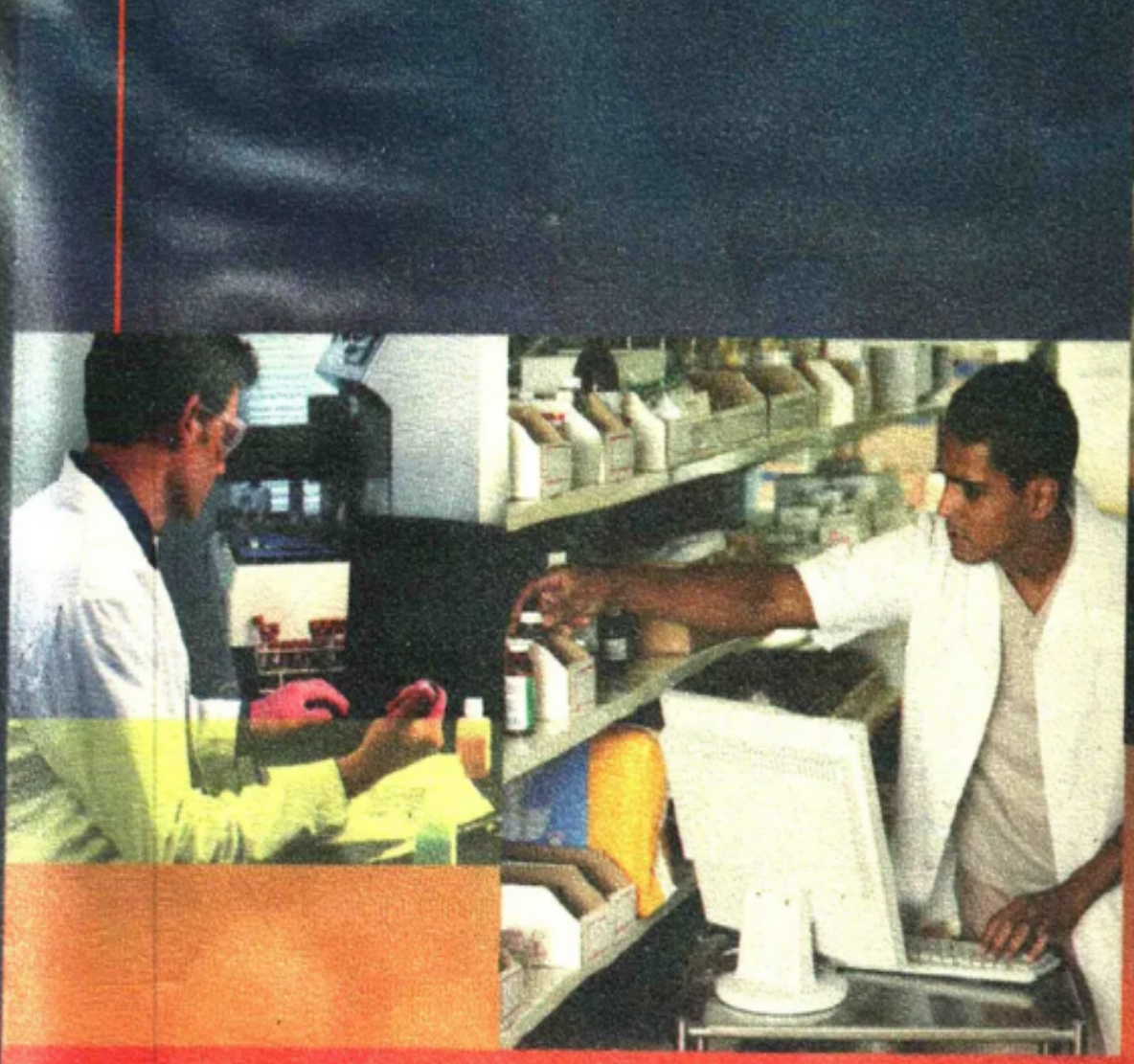
COMPREHENSIVE PHARMACY REVIEW

SEVENTH EDITION



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1

Drug Product Development in the Pharmaceutical Industry

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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

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.

(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 senistization 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.

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

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**

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.

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 Answer***1. 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 Answer***2. 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 Answer***3. 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 Answer***4. 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 Answer***5. 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 Answer***6. 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.

4. The answer is A *[see* V*].*
Quality control and quality assurance follow GMP regulations to ensure that the finished product meets all applicable specifications for quality. The FDA may inspect a manufacturing site (PAI) before the drug application is approved. In addition, the FDA must be notified about any proposed changes to an approved drug product.
5. The answer is E *[see* V.B*].*
The QC unit performs the appropriate tests on the dosage form. PAI is performed by FDA compliance inspectors, who examine the pharmaceutical manufacturer and review the procedures and records for manufacturing the finished dosage form before the administration grants market approval. The analytical development unit develops the analytical methods used in testing the drug product.
6. The answer is A *[see* IV.C.1*].*
All changes in the formulation must be reported to the FDA. 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 product's safety or effectiveness. Changes that are unlikely to have any detectable effect on formulation quality and performance can be instituted without approval by the FDA and need only to be reported in the annual report.

Pharmaceutical Calculations and Statistics

Riccardo L. Boni

I. FUNDAMENTALS OF MEASUREMENT AND CALCULATION.

The pharmacist is often required to perform or evaluate a variety of calculations in his or her practice. Many of these calculations involve the use of direct or inverse proportions. **Dimensional** (or **unit**) **analysis** and **approximation** can be useful in solving these problems. In dimensional analysis, dimensions (or units) are included with each number used in the calculation. Units common to the numerator and denominator may be canceled and the remaining units provide the units for the final answer. In approximation, each number used in the calculation is rounded to a single significant digit. Factors common to the numerator and denominator may be canceled and the answer to this approximation should be reasonably close to the final exact answer.

A. Ratio and proportion

1. Ratio. The relative magnitude of two like quantities is a ratio, which is expressed as a fraction. Certain basic principles apply to the ratio, as they do to all fractions.
a. When the two terms of a ratio are multiplied or divided by the same number, the value of the ratio is unchanged.

$$\frac{1}{3} \times \frac{2}{2} = \frac{2}{6} = \frac{1}{3}$$

b. Two ratios with the same value are equivalent. Equivalent ratios have equal cross products and equal reciprocals. For example:

$$\frac{1}{3} = \frac{2}{6}$$

and

$1 \times 6 = 3 \times 2 = 6$

If two ratios are equal, then their reciprocals are equal:

$$\text{if } \frac{1}{3} = \frac{2}{6}, \text{ then } \frac{3}{1} = \frac{6}{2}$$

2. Proportion. The expression of the equality of two ratios is a proportion. The product of the extremes is equal to the product of the means for any proportion. Furthermore, the numerator of the one fraction equals the product of its denominator and the other fraction (i.e., one missing term can always be found given the other three terms). Most pharmaceutical calculations can be performed by use of proportion.

a. Proper ratios. Some pharmacists use proper ratios (in which similar units are used in the numerator and denominator of each ratio) in their proportion calculations. Several examples follow.

(1) If 240 mL of a cough syrup contains 480 mg of dextromethorphan hydrobromide, then what mass of drug is contained in a child's dose, 1 teaspoonful (5 mL) of syrup?

$$\frac{240 \text{ mL}}{5 \text{ mL}} = \frac{480 \text{ mg}}{x \text{ mg}}$$

$$x = \frac{480 \times 5}{240} = 10 \text{ mg}$$

(2) If a child's dose (5 mL) of a cough syrup contains 10 mg of dextromethorphan hydrobromide, what mass of drug is contained in 240 mL?

$$\frac{240 \text{ mL}}{5 \text{ mL}} = \frac{x \text{ mg}}{10 \text{ mg}}$$

$$x = \frac{240 \times 10}{5} = 480 \text{ mg}$$

(3) If the amount of dextromethorphan hydrobromide in 240 mL of cough syrup is 480 mg, what would be the volume required for a child's dose of 10 mg?

$$\frac{x \text{ mL}}{240 \text{ mL}} = \frac{10 \text{ mg}}{480 \text{ mg}}$$

$$x = \frac{10 \times 240}{480} = 5 \text{ mL}$$

(4) How many milligrams of dextromethorphan base (molecular weight = 271.4) are equivalent to 10 mg of dextromethorphan hydrobromide (molecular weight = 352.3)?

$$\frac{x \text{ mg}}{10 \text{ mg}} = \frac{271.4}{352.3}$$

$$x = 10 \times \frac{271.4}{352.3} = 7.7 \text{ mg}$$

b. Mixed ratios. Some pharmacists use mixed ratios (in which dissimilar units are used in the numerator and denominator of each ratio) in their proportion calculations. Such computations generally give correct answers, providing the conditions in which mixed ratios cannot be used are known. A later example shows mixed ratios leading to failure in the case of dilution, when inverse proportions are required. For **inverse proportions,** similar units must be used in the numerator and denominator of each ratio. Following is an example of a mixed ratio calculation using the previous problem.

$$\frac{480 \text{ mg}}{10 \text{ mL}} = \frac{240 \text{ mg}}{x \text{ mL}}$$

$$x = 240 \times \frac{10}{480} = 5 \text{ mL}$$

The **same answer** is obtained in this example whether we use proper ratios, with similar units in numerator and denominator, or mixed ratios. This is not the case when dealing with inverse proportions.

3. Inverse proportion. The most common example of the need for inverse proportion for the pharmacist is the case of **dilution.** Whereas in the previous examples of proportion the relationships involved direct proportion, the case of dilution calls for an inverse proportion (i.e., as volume increases, concentration decreases). The necessity of using inverse proportions for dilution problems is shown in this example.

If 120 mL **of a 10% stock solution is diluted to 240** mL, **what is the final concentration?** Using inverse proportion,

$$\frac{120 \text{ mL}}{240 \text{ mL}} = \frac{x\%}{10\%}$$

$$120 \times \frac{10}{240} = 5\%$$

As expected, the final concentration is one half the original concentration because the volume is doubled. However, if the pharmacist attempts to use direct proportion and neglects to estimate an appropriate answer, the

resulting calculation would provide an answer of 20%, which is twice the actual concentration.

$$\frac{120\ \text{mL}}{240\ \text{mL}} = \frac{10\%}{x\%}$$

$$240 \times \frac{10}{120} = 20\%\ \text{(incorrect answer)}$$

Likewise, the pharmacist using mixed ratios fails in this case.

$$\frac{120\ \text{mL}}{10\%} = \frac{240\ \text{mL}}{x\%}$$

and

$$10 \times \frac{240}{120} = 20\%\ \text{(again, incorrect answer)}$$

B. Aliquot. A pharmacist requires the aliquot method of measurement when the **sensitivity** (the smallest quantity that can be measured with the required accuracy and precision) of the measuring device is not great enough for the required measurement. Aliquot calculations can be used for measurement of solids or liquids, allowing the pharmacist to realize the required precision through a process of measuring a multiple of the desired amount followed by dilution and finally selection and measurement of an aliquot part that contains the desired amount of material. This example problem involves weighing by the aliquot method, using a prescription balance.

A prescription balance has a sensitivity requirement of 6 mg. How would you weigh 10 mg of drug with an accuracy of ± 5%, using a suitable diluent?

1. First, calculate the least weighable quantity for the balance with a sensitivity requirement of 6 mg, assuming ± 5% accuracy is required.

$$\frac{6\ \text{mg}}{x\ \text{mg}} = \frac{5}{100};\ x = 120\ \text{mg (least weighable quantity for our}$$

2. Now it is obvious that an aliquot calculation is required because 10 mg of drug is required, whereas the least weighable quantity is 120 mg to achieve the required percentage of error. Using the least weighable quantity method of aliquot measurement, use the smallest quantity weighable on the balance at each step to preserve materials.

a. Weigh 12 × 10 mg = 120 mg of drug.

b. Dilute the 120 mg of drug (from step **a**) with a suitable diluent by geometrical dilution to achieve a mixture that will provide 10 mg of drug in each 120-mg aliquot. The amount of diluent to be used can be determined through **proportion.**

$$\frac{120 \text{ mg drug}}{10 \text{ mg drug}} = \frac{x \text{ mg total mixture}}{120 \text{ mg aliquot mixture}}$$

$$x = 1440 \text{ mg total mixture}$$

$$1440 \text{ mg total} - 120 \text{ mg drug} = 1320 \text{ mg diluent}$$

c. Weigh 120 mg (1/12) of the total mixture, which will contain the required 10 mg of drug.

II. SYSTEMS OF MEASURE.

The pharmacist must be familiar with **three systems** of measure: the **metric system** and two common systems of measure (the **avoirdupois** and **apothecaries'** systems). The primary system of measure in pharmacy and medicine is the metric system. Most students find it easiest to convert measurements in the common systems to metric units. A table of conversion equivalents is provided and should be memorized by the pharmacist (see Appendix A). The metric system, because of its universal acceptance and broad use, will not be reviewed here.

A. Apothecaries' system of fluid measure. The apothecaries' system of fluid measure is summarized in Appendix A.

B. Apothecaries' system for measuring weight. The apothecaries' system for measuring weight includes units of grains, scruples, drams, ounces, and pounds (see Appendix A).

C. Avoirdupois system of measuring weight. The avoirdupois (AV) system of measuring weight includes the grain, ounce, and pound. The grain is a unit common with the apothecaries' system and allows for easy conversion between the systems. The avoirdupois pound, however,

is 16 AV ounces in contrast to the apothecaries' pound, which is 12 apothecaries' ounces (see Appendix A).

D. Conversion equivalents. See Appendix A.

III. REDUCING AND ENLARGING FORMULAS.

The pharmacist is often required to reduce or enlarge a recipe. Problems of this type are solved through proportion, or by multiplication or division by the appropriate factor to obtain the required amount of each ingredient that will give the desired total mass or volume of the formula. Formulas can be provided in amounts or in parts.

A. Formulas that indicate parts. When dealing with formulas that specify parts, parts by weight will require the determination of weights of ingredients, whereas parts by volume warrant the calculation of volumes of ingredients. Always find the total number of parts indicated in the formula, and equate that total with the total mass or volume of the desired formula in order to set up a proportion. Such a proportion will allow calculation of the

mass or volume of each ingredient in units common to the total mass or volume.

What quantities should be used to prepare 100 g of camphorated parachlorophenol?

R_x	parachlorophenol	7 parts
	camphor	13 parts
	7 parts + 13 parts = 20 parts total	

$$\frac{7 \text{ parts}}{20 \text{ parts}} = \frac{x \text{ g}}{100 \text{ g}}; \; x = 35 \text{ g of parachlorophenol}$$

$$\frac{13 \text{ parts}}{20 \text{ parts}} = \frac{x \text{ g}}{100 \text{ g}}; \; x = 65 \text{ g of camphor}$$

B. Formulas that indicate quantities. The previous prescription for cold cream provides a 100 g quantity.

What mass of each ingredient is required to provide 1 pound (AV) of cream?

R_x	white wax	12.5 g
	mineral oil	60.0 g
	lanolin	2.5 g
	sodium borate	1.0 g
	rose water	24.0 g

1 lb = 454 g

$$1\ \text{lb} = 454\ \text{g}$$

$$\frac{454}{100} = 4.54\ \text{(factor to use in calculating the quantities of eac}$$

12.5 g × 4.54	=	56.8 g of white wax
60.0 g × 4.54	=	272 g of mineral oil
2.5 g × 4.54	=	11.4 g of lanolin
1.0 g × 4.54	=	4.54 of sodium borate
24.0 g × 4.54	=	109 g of rose water

IV. CALCULATING DOSES.

Calculation of doses generally can be performed with dimensional analysis. **Problems** encountered in the pharmacy include calculation of the number of doses, quantities in a dose or total mass/volume, amount of active or inactive ingredients, and size of dose. Calculation of **children's doses** is commonly performed by the pharmacist. Dosage is optimally calculated by using the child's body weight or mass and the appropriate dose in milligrams per kilogram (mg/kg). Without these data, the following formulas based on an adult dose can be used.

A. Fried's rule for infants

$$\frac{\text{age (in months)} \times \text{adult dose}}{150} = \text{dose for infant}$$

B. Clark's rule

$$\frac{\text{weight (lb)} \times \text{adult dose}}{150\ \text{lb (avg wt of adult)}} = \text{dose for child}$$

C. Child's dosage based on body surface area (BSA**)**

$$\frac{\text{BSA of child } (\text{m}^2) \times \text{adult dose}}{1.73\ \text{m}^2\ \text{(avg adult BSA)}} = \text{approximate dose for chil}$$

D. Young's rule for children ≥ 2 years old

$$\frac{\text{age (in years)}}{\text{age (in years)} + 12} \times \text{adult dose} = \text{dose for child}$$

E. Constant rate intravenous infusions. Some drugs are administered intravenously at a constant (zero-order) rate by using a continuous-drip infusion set or a constant-rate infusion pump. The flow rate (volume per unit time) required can be calculated from the volume to be administered and the duration of the infusion. The rate of drug administration can be calculated from the concentration of drug in the infused solution and the flow rate of the infusion set or pump. Conversion factors may be required to obtain the final answer in the correct units (drops per minute or milliliters per hour).

A vancomycin solution containing 1000 mg of vancomycin hydrochloride diluted to 250 mL with D5W is to be infused at a constant rate with a continuous-drip intravenous infusion set that delivers 25 drops/mL. **What flow rate (drops/min) should be used to infuse all 250** mL **of the vancomycin hydrochloride solution in 2 hr?**

$$\frac{250 \text{ mL}}{2 \text{ hr}} \times \frac{1 \text{ hr}}{60 \text{ min}} \times \frac{25 \text{ drops}}{1 \text{ mL}} = 52 \text{ drops/min}$$

V. PERCENTAGE, RATIO STRENGTH, AND OTHER CONCENTRATION EXPRESSIONS

A. Percentage weight in volume (w/v)

1. Definition. Percentage, indicating parts per hundred, is an important means of expressing concentration in pharmacy practice. Percentage w/v indicates the number of grams of a constituent per 100 mL of solution or liquid formulation. The pharmacist may be required to perform **three types** of calculations: determine the **weight** of active ingredient in a certain volume when given the percentage strength, determine the **percentage w/v** when the weight of substance and volume of liquid formulation are known, and determine the **volume** of liquid mixture when the percentage strength and amount of substance are known.

2. Tolu balsam syrup. Tolu balsam tincture contains 20% w/v tolu balsam. **What is the percentage concentration of tolu balsam in the syrup?**

tolu balsam tincture	50 mL
magnesium carbonate	10 g
sucrose	820 g
purified water, qs ad	1000 mL

a. First, determine what the amount of tolu balsam is in the 50 mL quantity of tincture used for the syrup. Then, by proportion, calculate the concentration of tolu balsam in the syrup.

$$\text{tolu balsam tincture} = 50 \text{ mL} \times \frac{20 \text{ g}}{100 \text{ mL}} = 10 \text{ g tolu bals}$$

$$\frac{10 \text{ g}}{1000 \text{ mL}} = \frac{x \text{ g}}{100 \text{ mL}}; \; x = \frac{1 \text{ g}}{100 \text{ mL}} = 1\% \text{ tolu balsam in the}$$

In answering this one question, the first two types of problems listed above have been solved, while exhibiting two methods of solving percentage problems—namely, by **dimensional analysis** and **proportion.**

b. For an example of the **third type** of percentage w/v problem, determine what volume of syrup could be prepared if we had only 8 g of magnesium carbonate. Use proportion to find the total volume of syrup that can be made using only 8 g of magnesium

carbonate. If we have 8 g of magnesium carbonate in 1000 mL of solution, then, according to the recipe, 800 mL of solution can be prepared using all 8 g of the drug.

$$\frac{10 \text{ g}}{1000 \text{ mL}} = \frac{8 \text{ g}}{x \text{ mL}}; \; x = 800 \text{ mL}$$

B. Percentage volume in volume (v/v). Percentage v/v indicates the number of milliliters of a constituent in 100 mL of liquid formulation. The percentage strength of mixtures of liquids in liquids is indicated by percent v/v, which indicates the parts by volume of a substance in 100 parts of the liquid preparation. The **three types** of problems that are encountered involve calculating **percentage strength,** calculating **volume of ingredient,**

and calculating **volume of the liquid preparation.** Using the same tolu balsam syrup formula from earlier, we'll now work a percent v/v problem. **What is the percentage strength v/v of the tolu balsam tincture in the syrup preparation?** By proportion, we can solve the problem in one step.

$$\frac{50 \text{ mL tolu balsam tincture}}{x \text{ mL tolu balsam tincture}} = \frac{1000 \text{ mL syrup}}{100 \text{ mL syrup}}; \; x = 5\%$$

C. Percentage weight in weight (w/w). Percentage w/w indicates the number of grams of a constituent per 100 g of formulation (solid or liquid). Solution of problems involving percentage w/w is straightforward when the total mass of the mixture is available or when the total mass can be determined from the available data. In calculations similar to those for percentage w/v and v/v, the pharmacist might need to solve several types of problems, including determination of the weight of a constituent, the total weight of a mixture, or the percentage w/w.

1. How many grams of drug substance should be used to prepare 240 g **of a 5% w/w solution in water?**

a. The first step in any percentage w/w problem is to attempt identification of the total mass of the mixture. In this problem, the total mass is, obviously, provided (240 g).

b. The problem can be easily solved through **dimensional analysis.**

$$240 \text{ g mixture} \times \frac{5.0 \text{ g drug}}{100 \text{ g drug}} = 12 \text{ g}$$

2. When the total mass of the mixture is unavailable or cannot be determined, an **extra step** is required in the calculations. Because it is usually impossible to know how much volume is displaced by a solid material, the pharmacist is unable to prepare a specified volume of a solution given the percentage w/w.

How much drug should be added to 30 mL **of water to make a 10% w/w solution?** The volume of water that is displaced by the drug is unknown, so the final volume is unknown. Likewise, even though the mass of solvent is known (30 mL × 1 g/mL = 30 g), it is not known how much drug is needed, so the total mass is unknown. The water represents 100% - 10% = 90% of the total mixture. Then, by proportion, the mass of drug to be used can be identified.

$$\frac{30 \text{ g of mixture (water)}}{x \text{ g of mixture (drug)}} = \frac{90\%}{10\%}; \; x = 3.33 \text{ g of drug required to r}$$

The **common error** that many students make in solving problems of this type is to assume that 30 g is the total mass of the mixture. Solving the problem with that assumption gives the following incorrect answer.

$$\frac{x \text{ g drug}}{10 \text{ g drug}} = \frac{30 \text{ g mixture}}{100 \text{ g mixture}}; \; x = 3 \text{ g of drug (incorrect answ}$$

D. Ratio strength. Solid or liquid formulations that contain low concentrations of active ingredients will often have concentration expressed in **ratio strength.** Ratio strength, as the name implies, is the expression of concentration by means of a ratio. The numerator and denominator of the ratio indicate grams (g) or milliliters (mL) of a solid or liquid constituent in the total mass (g) or volume (mL) of a solid or liquid preparation. Because **percentage strength** is

essentially a ratio of parts per hundred, conversion between ratio strength and percentage strength is easily accomplished by proportion.

1. Express 0.1% w/v as a ratio strength.

a. Ratio strengths are by convention expressed in reduced form, so in setting up our proportion to solve for ratio strength, use the numeral 1 in the numerator of the righthand ratio as shown:

$$\frac{0.1 \text{ g}}{100 \text{ mL}} = \frac{1 \text{ part}}{x \text{ parts}}; \; x = 1000 \text{ parts, for a ratio strength of 1:1}$$

b. Likewise, conversion from ratio strength to percentage strength by proportion is easy, as seen in the following example. Keep in mind the definition of percentage strength (parts per hundred) when setting up the proportion.

2. Express 1:2500 as a percentage strength.

$$\frac{1 \text{ part}}{2500 \text{ parts}} = \frac{x \text{ parts}}{100 \text{ parts}}; \; x = 0.04, \text{ indicating } 0.04\%$$

E. Other concentration expressions

1. Molarity (M) is the expression of the number of moles of solute dissolved per liter of solution. It is calculated by dividing the moles of solute by the volume of solution in liters.

$$M_A = \frac{n_A}{\text{solution (L)}}$$

2. Normality. A convenient way of dealing with acids, bases, and electrolytes involves the use of equivalents. One equivalent of an acid is the quantity of that acid that supplies or donates 1 mole of H^+ ions. One equivalent of a base is the quantity that furnishes 1 mole of OH^- ions. One equivalent of acid reacts with 1 equivalent of base. Equivalent weight can be calculated for atoms or molecules.

$$\text{Equivalent weight} = \frac{\text{atomic weight or molecular weight}}{\text{valence}}$$

The **normality** (N) of a solution is the number of gram-equivalent weights (equivalents) of solute per liter of solution. Normality is analogous to molarity; however, it is defined in terms of equivalents rather than moles.

$$\text{Normality} = \frac{\text{\# equivalents of solute}}{\text{\# liters of solution}}$$

3. Molality (m) is the moles of solute dissolved per kilogram of solvent. Molality is calculated by dividing the number of moles of solute by the number of kilograms of solvent. Molality offers an advantage over molarity because it is based on solvent weight and avoids problems associated with volume expansion or contraction owing to the addition of solutes.

$$m_A = \frac{n_A}{\text{mass}_{\text{solvent (kg)}}}$$

4. Mole fraction (X) is the ratio of the number of moles of one component to the total moles of a mixture or solution.

$$X_A = \frac{n_A}{n_A, n_B, n_C \ldots}, \text{ where } X_A + X_B + X_C + \ldots = 1$$

VI. DILUTION AND CONCENTRATION.

If the amount of drug remains constant in a dilution or concentration, then any change in the mass or volume of a mixture is inversely proportional to the concentration.

A. Dilution and concentration problems can be solved by:

1. Inverse proportion (as mentioned earlier)

2. The equation $\text{quantity}_1 \times \text{concentration}_1 = \text{quantity}_2 \times \text{concentration}_2$

3. Determining the amount of active ingredient present in the initial mixture and, with the assumption that the initial quantity does not change, calculating of the final concentration of the new total mass or volume

4. Alligation medial. A method for calculating the average concentration of a mixture of two or more substances

5. Alligation alternate. A method for calculating the number of parts of two or more components of known concentration to be mixed when the final desired concentration is known

B. Dilution of alcohols and acids

1. Dilution of alcohols. When alcohol and water are mixed, a contraction of volume occurs. As a result, the final volume of solution cannot be determined accurately. Nor can the volume of water needed to dilute to a certain percentage v/v be identified. Accordingly, percentage w/w is often used for solutions of alcohol.

2. The **percentage strength** of concentrated acids is expressed as percentage w/w. The concentration of diluted acids is expressed as percentage w/v. Determining the volume of concentrated acid to be used in preparing a diluted acid requires the specific gravity of the concentrated acid.

C. Dilution and concentration of liquids and solids. Dilution and concentration problems are often easily solved by identifying the amount of drug involved followed by use of an appropriate proportion.

1. How many milliliters of a 1:50 stock solution of ephedrine sulfate should be used in compounding the following prescription?

R_x	ephedrine sulfate	0.25%
	rose water, ad	30 mL

$$\frac{0.25\ \text{g}}{100\ \text{mL}} \times 30\ \text{mL} = 0.075\ \text{g drug required}$$

$$\frac{50\ \text{mL}}{1\ \text{g}} = \frac{x\ \text{mL}}{0.075\ \text{g}}$$

$$x = 3.75\ \text{mL of stock solution required for}$$

2. How many milliliters of a 15% w/v concentrate of benzalkonium chloride should be used in preparing 300 mL **of a stock solution such that 15** mL **diluted to 1** L **will yield a 1: 5000 solution?**

a. First, determine the amount of drug in 1 L of a 1:5000 solution.

$$\frac{5000\ \text{mL}}{1000\ \text{mL}} = \frac{1\ \text{g}}{x\ \text{g}}\ x = 0.2\ \text{g of benzalkonium chloride in the}$$

b. Now, because 15 mL of the stock solution is being diluted to 1 L, a stock solution is needed in which 15 mL contain 0.2 g of drug. The amount of drug required to make 300 mL of the stock solution is found by proportion.

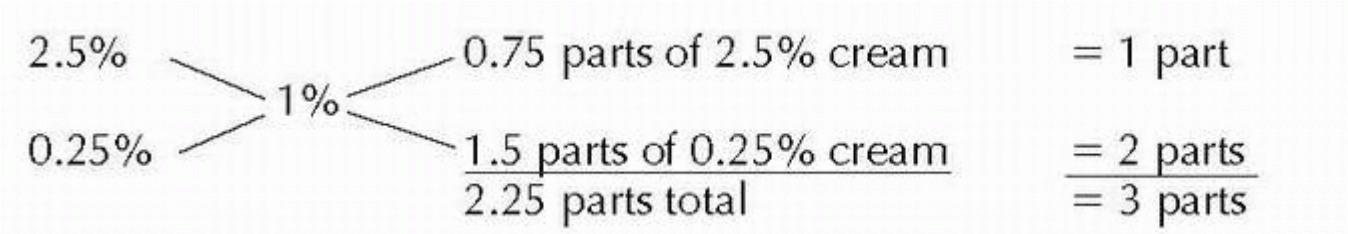
$$\frac{0.2\text{ g}}{x\text{ g}} = \frac{15\text{ mL}}{300\text{ mL}};\ x = 4\text{ g of drug required to make 300 mL}$$

c. Finally, to determine the amount of 15% concentrate required,

$$\frac{15\text{ g}}{4\text{ g}} \times \frac{100\text{ mL}}{x\text{ mL}};\ x = 26.7\text{ mL of 15\% solution required to obtain necessary drug}$$

3. When the relative amount of components must be determined for preparation of a mixture of a desired concentration, the problem is most easily solved using alligation alternate.

How many grams of 2.5% hydrocortisone cream should be mixed with 360 g of 0.25% cream to make a 1% hydrocortisone cream?



The relative amounts of the 2.5% and 1% creams are 1 to 2, respectively. By proportion, the mass of 2.5% cream to use can be determined. **If 2 parts of 0.25% cream is represented by 360 g, then the total mass (3 parts) is represented by what mass?**

$$\frac{2\text{ parts}}{3\text{ parts}} = \frac{360\text{ g}}{x\text{ g}};\ x = 540\text{ g total}$$

With the total mass known, the amount of 2.5% cream can be identified. If 3 parts represent the total mass of 540 g, then 1 part represents the mass of 2.5% cream (x g = 180 g).

$$\frac{1\text{ part}}{3\text{ parts}} = \frac{x\text{ g}}{540\text{ g}};\ x = 180\text{ g of 2.5\% cream}$$

VII. ELECTROLYTE SOLUTIONS.

Electrolyte solutions contain species (electrolytes) that dissociate into ions. The **milliequivalent** (mEq) is the unit used to express the concentration of

electrolytes in solution. Table 2-1 exhibits some physiologically important ions and their properties.

A. Milliequivalents. The milliequivalent is the amount, in milligrams, of a solute equal to 1/1000 of its gram-equivalent weight. Conversion of concentrations in the form of milliequivalent to concentrations in percentage strength, milligrams per milliliters (mg/mL) or any other terms, begins with calculation of the number of milliequivalents of drug. The following examples demonstrate the computation of milliequivalents and manipulation of data from Table 2-1 to perform the required calculations for preparing electrolyte solutions.

What is the concentration, in percent w/v, of a solution containing 2 mEq of potassium chloride per milliliter?

Calculations involving milliequivalents are easily solved if the practitioner follows a predefined procedure to determine the milliequivalent weight. This involves three steps.

1. Find the molecular weight (mol wt).

Atomic wt K	=	39
Atomic wt Cl	=	35.5
39 + 35.5 = 74.5 g	=	mol wt of KCl

2. Calculate the equivalent weight (Eq wt) of KCl.

$$\text{Eq wt} = \frac{\text{mol wt}}{\text{valence}} = \frac{74.5}{1} = 74.5 \text{ g}$$

3. Determine the milliequivalent weight, which is of the equivalent weight.

mEq wt = 74.5 g / 1000 = 0. 745 g or 74.5 mg

Table 2-1. Valences, Atomic Weights, and Milliequivalent Weights of Selected Ions

Ion	Formula	Valence	Atomic/Formula Weight	Milliequivalent Weight (mg)
Aluminum	A^{+++}	3	27	9
Ammonium	NH_4^+	1	18	18
Calcium	Ca^{++}	2	40	20
Ferric	Fe^{+++}	3	56	18.7
Ferrous	Fe^{++}	2	56	28
Lithium	Li^+	1	7	7
Magnesium	Mg^{++}	2	24	12
Bicarbonate	HCO_3^-	1	61	61
Carbonate	CO_3^-	1	60	30
Chloride	Cl^-	1	35.5	35.5
Citrate	$C_6H_5O_7^{---}$	3	189	63
Gluconate	$C_6H_{11}O_7^-$	1	195	195
Lactate	$C_3H_5O_3^-$	1	89	89
Phosphate	$H_2PO_4^-$	1	97	97
Sulfate	SO_4^{--}	2	96	48
Potassium	K^+	1	29	39

Sodium	Na^+	1	23	23
Acetate	$C_2H_3O_2^-$	1	59	59

Now that we know the milliequivalent weight, we can calculate by dimensional analysis and proportion the concentration in percentage in a fourth step.

4. 0.0745 g/mEq × 2 mEq = 0.149 g of drug

$$\frac{0.149 \text{ g drug}}{1 \text{ mL}} = \frac{x \text{ g drug}}{100 \text{ mL}}, \; x = 14.9\text{g}/100 \text{ mL} = 14.9\%$$

How many milliequivalents of Na^+ would be contained in a 15-mL volume of the following buffer?

$Na_2HPO_4 \cdot 7H_2O$		180 g
$NaH_2PO_4 \cdot H_2O$		480 g
Purified water	ad	1000 mL

For each salt, the mass (and milliequivalents) must be found in a 15-mL dose.

mol wt $Na_2HPO_4 \cdot 7H_2O$ (disodium hydrogen phosphate)

Eq wt = 268 / 2 = 134 g

1 mEq = 0.134 g or 134 mg

$$\frac{180 \text{ g}}{x \text{ g}} = \frac{1000 \text{ mL}}{15 \text{ mL}};\ x = 2.7 \text{ g of disodium hydrogen phosphat}$$

$$2.7 \text{ g} \times \frac{1 \text{ mEq}}{0.134 \text{ g}} = 20.1 \text{ mEq of disodium hydrogen p}$$

mol wt $NaH_2PO_4 \cdot H_2O$ (sodium biphosphate) = 1

Eq wt = 138 g

1 mEq = 0.138 g

$$\frac{480 \text{ g}}{x \text{ g}} = \frac{1000 \text{ mL}}{15 \text{ mL}};\ x = 7.2 \text{ g of sodium biphosphate in e}$$

$$7.2 \text{ g} \times \frac{1 \text{ mEq}}{0.138 \text{ g}} = 52.2 \text{ mEq of sodium biphosph}$$

20.1 mEq + 52.2 mEq = 72.3 mEq of sodium in each 15 r

B. Milliosmoles (mOsmol). Osmotic pressure is directly proportional to the total number of particles in solution. The milliosmole is the unit of measure for osmotic concentration. For nonelectrolytes, 1 millimole represents 1 milliosmole. However, for electrolytes, the total number of particles in solution is determined by the number of particles produced in solution and influenced by the degree of dissociation. Assuming complete dissociation, 1 millimole of KCl represents 2 milliosmoles of total particles, 1 millimole of $CaCl_2$ represents 3 milliosmoles of total particles, etc. The ideal osmolar concentration can be calculated with the following equation.

$$\text{mOsmol/L} = \frac{\text{wt of substance in g/L}}{\text{mol wt in g}} \times \text{number of species} \times$$

The pharmacist should recognize the difference between **ideal** osmolar concentration and **actual** osmolarity. As the concentration of solute increases, interaction between dissolved particles increases, resulting in a reduction of the actual osmolar values.

C. Isotonic solutions. An **isotonic** solution is one that has the same osmotic pressure as body fluids. **Isosmotic** fluids are fluids with the same osmotic pressure. Solutions to be administered to patients should be