13 REGULATORY CONSIDERATIONS IN CONTROLLED DRUG DELIVERY

I. FOOD & DRUG ADMINISTRATION AND THE DRUG-DEVELOPMENT PROCESS

A. SCOPE OF THE FOOD AND DRUG ADMINISTRATION

The Food and Drug Administration (FDA) regulates all phases of drug discovery, development, manufacture, and marketing of a new drug by enforcing the current Good Manufacturing Practices (cGMPs), which basically require a company to document every phase of drug research and development. Examples are:

1. Who weighed the drug?
2. What are the qualifications and training of that person?
3. Who trained the person?
4. Was the 10^{th}, 100^{th}, or 1000^{th} tablet tested and did it contain the right quantity of the drug?

Documentation of a procedure must be in writing and available when the company facilities are inspected by the FDA and data of results of all testing must be submitted to the FDA for approval before a drug is sold on the market. Without regulation, the public would be victim to fraudulent drugs that were frequently on the market before the FDA came into the picture in 1906.

B. DRUG DEVELOPMENT PROCESS

1. Drug Development

Drug can be defined as a substance used in the diagnosis, cure, treatment, prevention, etc., of a disease or that may affect the structure or function of a body organ. Foods are not drugs. Are vitamins drugs? Devices, such as syringes, catheters, pace makers, etc., are not drugs but are regulated by another division of the FDA. If a substance is recognized by the U.S. Pharmacopeia or is a component of a drug preparation, then it is considered to be a drug. Drugs used in animals are also covered by the FDA. Whether a substance is to be classified as a drug, cosmetic, food, device, or biological can be controversial and each is covered by a different statute of the FDA. Over-the-counter products are not covered by the FDA under the laws regulating "new drugs."

A series of compounds may be synthesized by chemists at research institutes or drug companies to treat specific diseases. These compounds are screened for their pharmacological activity in small animals. Then, their physical properties (solubility, stability, potential for large scale production, etc.) are investigated (*i.e.*, preformulation study). If any of the compounds looks promising they are administered to small animals to determine the minimum, therapeutic, or toxic dose.

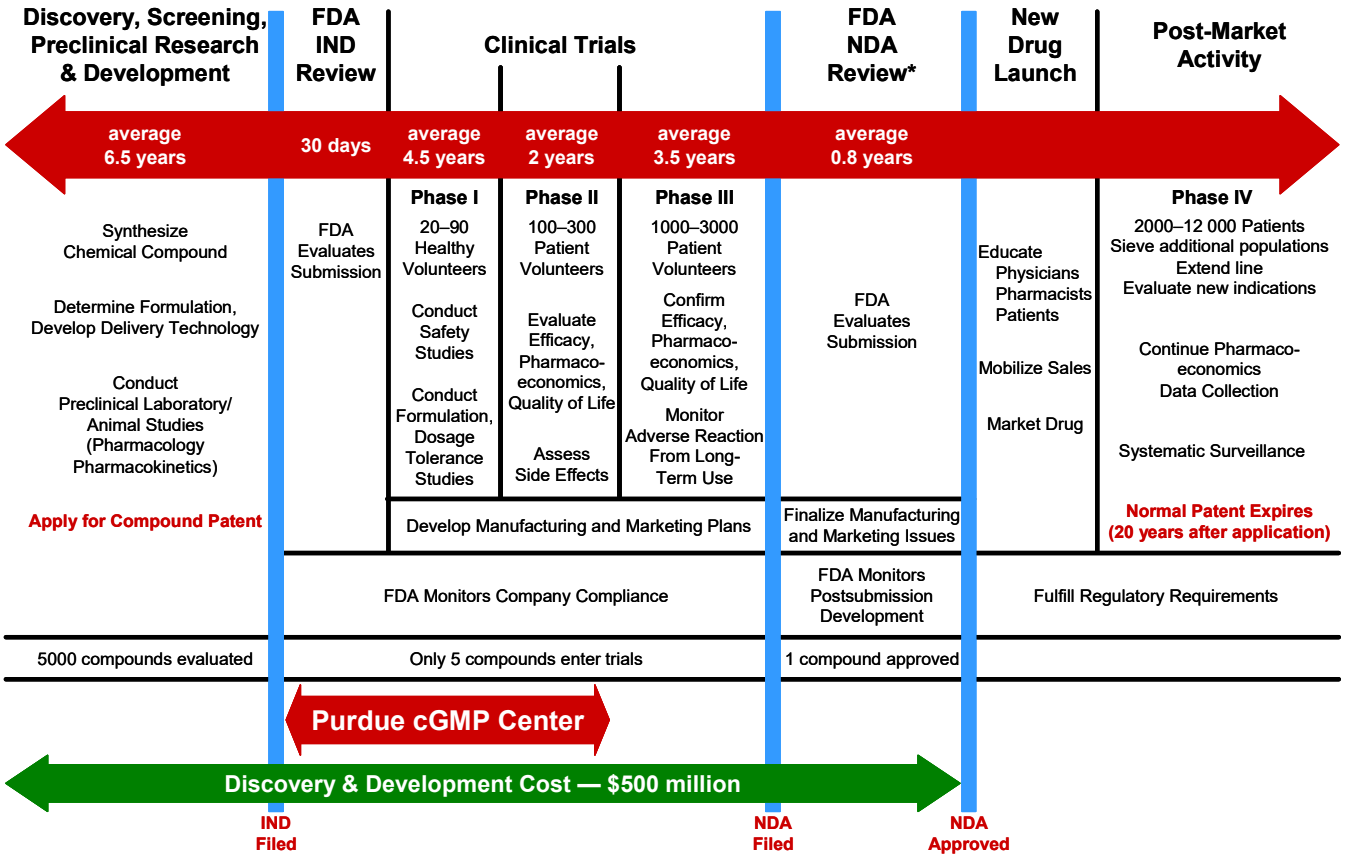
a. Orphans Drug Act of 1983

For economic reasons, companies do not develop drugs for rare diseases that occur in a limited number of people (*e.g.*, African sleeping sickness). A disease that affects less than 200,000 persons falls in this category. Under the Orphans Drug Act of 1983, a company can develop a drug and receive seven years of exclusive rights, tax credits to cover the clinical research, and some research funds to finance drug development. Input in deciding which disease is selected is given by the Veterans' Administration, Department of Defense, HEW (Health, Education and Welfare), and other groups.

2. Investigational New Drug Application (INDA)

At some point during drug development (see Figure 13.1), the decision is made to initiate an INDA for a drug with desirable bioactivity. An INDA is the first step leading to the marketing of the drug. The animal studies must have met the requirements of the Good Laboratory Practice (GLP) regulations of the FDA. In the Phase I study, the drug is administered to 20–90 healthy human volunteers to determine pharmacokinetic, pharmacodynamic properties, and tolerance to various doses. The company must submit an INDA to the FDA before Phase I studies can begin. If the application is not denied in 30 days, the company may begin the studies. Data included in an INDA are the number of humans selected, where the study is to take place, results of previous animal studies, how the drug is manufactured, how the drug is labeled, and all information known about the drug. An institutional review board (IRB) within the company must approve all steps of the study. This board is made up of professionals and lay people to protect the rights of humans participating in the study. If no serious problems are encountered in Phase I then Phase II may proceed.

The Phase II study is more extensive than the Phase I study. Between 100 and 300 volunteer patients with the disease are treated with the drug. The idea is to determine the effectiveness of the drug. Patients are randomized and the results are compared with those obtained with controls (patients who receive a placebo dosage form with no drug). In a double-blind study, neither patients nor clinicians know whether they are receiving a drug or a placebo. The data are analyzed and if the drug looks safe and effective in the patients and an exact dosage regimen is determined, and then the drug is ready for Phase III study.



* As mandated by the FDA Modernization Act of 1997, the FDA Performance Goals include reviewing Standard NDAs within 10 months by fiscal year 2002.

Figure 13.1 New-drug development timeline.

In the Phase III study, 1000–3000 human volunteers are administered the drug. This phase may require several years to complete. The dose regimen is fine tuned to give evidence of effectiveness. At the same time, animals are administered the drug to determine chronic toxicity, carcinogenicity and other properties (*e.g.*, teratogenicity).

3. New Drug Application (NDA)

An NDA is submitted to the FDA when the company is convinced that the drug is safe. The NDA includes all of the clinical, animal, chemical, manufacturing, stability, quality-control, and other data. It may also include pharmacokinetic, bioavailability, and other data. The data must also include all negative results such as the number of patients who died during the investigation and how many patients experienced adverse drug reactions. Each section of the NDA is reviewed by experts in different fields to pass on its validity. Members of the NDA review panel cannot have a conflict of interest such as owning stocks in the company who submitted the FDA. It may take 10 y and $300 million for a company to reach the point where a NDA is submitted. If the drug is to be used for a life threatening disease (AIDS), then the review process is shortened for compassionate reasons. It should be noted that after a drug is approved, a company may make changes in dosage, labeling, formulation only by consulting

with the FDA which may require submitting a supplemental NDA. But some changes can be made without prior FDA approval.

4. Abbreviated New Drug Application.

The INDA and NDA are related to new drugs only. Suppose a company wishes to market a generic version of a drug that was previously approved by the FDA. Then they will submit an ANDA. Safety and effectiveness of the drug need not be proven. The formulation, ingredients, chemical properties, manufacturing controls, and bioequivalence data are submitted as part of the ANDA. Depending on the drug clinical bioequivalency or only results of in vitro studies need to be submitted. In short, the data must show that the generic and the original patented drug are absorbed and function in the same way within statistical parameters. The FDA publishes an Orange Book that lists all the drugs that are covered in FDA bioequivalence guidance documents that describe the kind of data to be submitted to prove bioequivalency. Clinical bioequivalency is the most important factor to be considered for approval. It is noted that a controlled-release form of a drug is considered as a new drug and governed by the regulations for a new drug

5. Phase IV studies

After an NDA has been approved and the drug is marketed, the FDA may require information regarding experience of the drug after millions of patients are administered the drug. The frequency of adverse drug reactions, dosage regimens, defects, deaths, etc., may be required. The FDA may ask for safety and effectiveness data and effects in different populations (not done in previous studies). Phase IV studies may be a condition upon which the NDA was approved. The FDA may inspect the company if there was a problem with the manufacture of the product.

6. Registration and Listing

All companies that manufacture, process, repackage or design the package or label must register with the FDA. All drugs must be listed with the FDA who assigns the drug or drug product a number. This number is part of the National Drug Code and appears on the label of all prescriptions drugs sold in the USA.

7. Inspections

FDA inspects every drug company every 2 y to assure the company is manufacturing drugs according to the specifications of the cGMPs.

8. Packaging

Packing must be tamper resistant for OTC products. Packing for prescription only drugs should be child resistant. The consumer should be able to see if a package has been tampered with before opening. In 1982, a number of innocent consumers died after taking Tylenol® capsules whose contents were replaced with cyanide by an individual intent on kill his spouse.

II. FOOD, DRUG, & COSMETIC ACT AND SUBSEQUENT REGULATIONS

A. FOOD & DRUG ACT OF 1906

At the turn of the century, numerous materials were traded and used for treating diseases even though they were not of appropriate quality or standards. Most compounds used for therapy at that time were derived from natural sources. They were imported from all over the world to the United States, and thus it was difficult to control the quality of those materials. The original purpose of the Food & Drug Act of 1906 was to prevent the distribution of adulterated materials to the consuming public.

B. FOOD, DRUG, & COSMETIC ACT OF 1938

In 1938, a major revision occurred as a result of the serious tragedy that took place concerning the formulation of sulfanilamide elixir. This solubilized, potent drug substance and the product caused numerous deaths upon introduction into the marketplace. The revisions to the act became known as the Food, Drug, & Cosmetic Act of 1938. The act had major new provision which included:

1. Extended coverage to cosmetics and devices
2. Required pre-distribution clearance for safety of new drugs
3. Provided for tolerances for unavailable poisonous substances
4. Authorized standards of identity, quality, and fill for foods
5. Authorized factory inspections
6. Add the remedy of court injunctions to previous remedies of seizure and prosecution

These additions to the act became highly significant. They introduced various concepts which would begin to become concerned with the formulation and manufacturing of pharmaceutical drug products as well as foods, cosmetics and devices. There are regulations within the act that have indirect impact on the formulation of pharmaceutical products that would include an addition to the act in 1960 of the Color Additive Amendments. This allowed the Food & Drug Administration to have full control over these particular colorants to ensure safety of whatever was added for that purpose.

C. KEFAUVER-HARRIS DRUG AMENDMENTS IN 1962

In 1962 another major amendment took place known as the Kefauver-Harris Drug Amendments. These amendments were also brought about by a tragedy involving thalidomide that had been marketed in various countries of the world but was still under clinical test in the United States. The amendments required a greater degree of safety assurance and strength of any new drug substance before it could be cleared for the marketplace. It increased the amount of testing, for example, to ensure that no substance would harm or have the potential of causing any detrimental effects to the patient or to those who might be affected by the ingestion of the drug which potentially could cause harmful effects over and above the thera-

peutic effect. At this time increased interest was placed upon new drug testing and the methods by which the material would be evaluated in clinical studies.

Thalidomide, with its known tragic side effects, has been reintroduced on the market for wasting in AIDS patients and chemotherapy because of its effectiveness to reduce the nausea caused by the medication used to treat these conditions. The use of thalidomide is highly regulated and is not used where women of child-bearing age can inadvertently come in contact with it.

D. Good Manufacturing Practices and Regulations

In addition to the regulations that impact upon the development of new products came in 1963 when the Good Manufacturing Practices (GMP) and Regulations were established. These were later changed in 1978 to increase the impact of these regulations upon the drug products that were to be distributed by various manufacturers. About that time another set of regulations were generated that became guidelines. These regulations involved current Good Laboratory Practices (cGLP). With these two sets of documents, the Food & Drug Administration was able to implement control over the operations of most pharmaceutical firms as well as numerous research centers involved in new drug development and new product development. The overall purpose is to protect the consuming public and to ensure a quality product for all those taking drug substances either for therapy, immediate treatment, or long term therapy.

III. CONTROLLED-RELEASE DOSAGE FORMS: REGULATORY REQUIREMENTS

A. New Drugs

According to the Code of Federal Regulations, a new drug is one that is not presently recognized by experts in the field of clinical pharmacology to be safe and effective based upon currently available clinical evidence. A new drug substance is defined as any substance that, when used in the manufacturing process or packaging of a drug, causes the drug to be a new drug.

The newness of a drug may arise by a variety of reasons. One of them is as follows. Normally an approved drug is used in a certain dosage form for treatment of a certain disease under specified administration conditions. If the dosage form, administration method, duration of administration, or other condition is changed, then it constitutes the newness. Thus, the controlling of the release of the drug substance over time is an example of newness.

Whether a new substance has to be filed as an IND or not requires preclinical studies including acute toxicity test, pre-formulation studies, and pharmacological evaluation. In many instances when a controlled release system is being designed, there may be adequate data already available for the drug that satisfies the above requirements. In many instances the development of a controlled release system is considered to be an additional

way by which the product may be utilized in the treatment of either individuals or animals with a suitable system that will perform over an extended period of time that is different from the product that may have been prepared as an immediate release system. However, it is hoped that there will be a place for the evolution of new polymer systems that will produce different release profiles or profiles that may be more easily reproduced.

B. Approval of New Controlled Release Systems

There is no current separate method or category by which a controlled release system would be approved. It is a modification generally of a currently available drug, and it thus contains new substances and new claims that would place the system into the new drug area. Once it is decided to delay the release of the material, change the site of release, control the release of the system that would include prolonging the release by current definition, this becomes a new drug and would require a new drug application.

Generally, this type of system is developed for a specific reason. Some of these reasons may include the following: avoid patient compliance problems, employ less total drug, and improve efficiency in treatment that may include improved bioavailability of some drugs. This may also include the ability of controlling symptoms while the patient is asleep. Finally, there may be some economic gain by developing such a dosage form. These reasons have been indicated to be important as far as generating a system that would control the release of the drug substance. All of these possible potential advantages of the system in part could place the material in the new drug area.

The mechanism by which a controlled release system would need governmental approval is thus obviously a situation that would follow the development of any new drug product. However, data would be available to support any pre-clinical information as from the aspect of what the drug may do and its safety. However, it may be necessary to establish a safety level should the dosage form contain more than was previously administered by a conventional dosage form. This higher level would obviously not have had a safety determination done and thus may require such studies. The studies at a higher dose level, however, may or may not be a complicating factor. The establishment of an appropriate release profile as far as toxicity is concerned would be of concern. There are numerous examples in the literature covering the drug theophylline. This was due to the narrow therapeutic window of the particular drug substance and thus a requirement for appropriate studies to establish that controlled release administration of this particular substance was justified. This remains in the area of clinical pharmacology of an active moiety.

As with most drug substances, an adequate demonstration of the release profile *in vitro* should be established within the appropriate limits being chosen for the controlled-release system. For claims that are being made, this profile must be adequate to demonstrate sufficient release of the material *in vitro*. A reasonable release profile must match with the claims of the particular product. Once established, adequate *in-vivo* studies should

be conducted to demonstrate the capability of the system used for controlling the release. There are a number of ways to interpret the *in-vivo* data to establish the claims that will be made under a new drug application. This portion of the studies may become complicated and detailed if there is an unusual mechanism by which the profile needs to be judged.

Once sufficient data have been gathered to demonstrate that the product is both safe and effective, a new drug application for this particular system would be filed. The new delivery system is definitely in the new drug area and would need to be appropriately reviewed by the agency before approval could be obtained. However, the length of time for approval may be shorter than the original approval of the new drug substance.

IV. NEW CONTROLLED-RELEASE DOSAGE FORMS: MANUFACTURE & CONTROL

Since controlled-release systems or extended-release products have unique properties and characteristics, it may be necessary to add additional manufacturing parameters and control requirements to ensure that the products will perform as outlined in any study of the system. In particular, if currently available polymers are used, there are some requirements that need to be observed as far as the material is concerned.

An example of a material that might be used in the controlled-delivery area would be ethylcellulose. It currently has Generally Recognized As Safe (GRAS) status that indicates that it may be used as a food additive in a number of different products. Thus, it would allow easy use in a pharmaceutical system for whatever purpose that is being considered. This material has a number of specific specifications that include the degree of substitution of various groups on the cellulosic backbone. Other standard specifications are used to judge this material from the standpoint of use in a controlled-release system. Sufficient data are available, for example, in the solubility area for judgment of its utility. There are a number of references in the literature as to specific applications of this substance that would support its use in a controlled release system. But what is important is that the manufacture of the material is clearly defined as well as having appropriate specifications of the basic polymer substance. Once this material is selected for a system then how it is used to prepare the controlled release device would have to be outlined with appropriate processing parameters given. This becomes important from the regulatory standpoint to ensure reproducibility of the system that is meant to delay the release of a medicinal agent. This may become an important point with the regulatory agency to ensure that performance will be sufficiently equivalent from batch to batch and to also have the appropriate release profile over time. Thus, adequate long-term dissolution stability data must be determined. In most cases, a method will be used taken from the USP/NF that may be appropriately modified for the system under consideration. However, pHs that are normally experienced in the gastrointestinal tract would be used in any *in vitro* test procedure. The degree of reproducibility of these tests is an important part of the control package that would be presented for the agency. It has been observed over time that there may be a long term dissolution problem with a polymer, depending

on the material into which it is incorporated. Data must be sufficient to support whatever stability claims that are made for the finished dosage form. Concerns thus may be present about the stability of the plasticizer that is normally used with most polymeric systems in the controlled release product design.

As with all dosage forms that are being marketed, the establishment of adequate controls of the manufacturer of the finished dosage form as well as its control and stability evaluation are of extreme importance. From time to time products have failed, in particular, based upon their changes in the dissolution profiles. It is important to establish some feeling for the stability of the system early in product formulation so that no surprises happen at a later date. It also allows the formulator to attempt to modify the system so that appropriate product specifications are in place to reflect long term expiration dating of a product.

A. Current Good Laboratory Practices (cGLPs) and Current Good Manufacturing Practices (cGMPs).

Although the researcher within an organization has motives to produce products that could be of life saving capabilities, it is necessary to recognize the fact that, throughout the time span of the development process, it is possible for the Food and Drug Administration to request certain information that involves the basic and product-development information that may be in the laboratory notebooks or files. Knowing this, it becomes common place for researchers so involved in pharmaceutical and medical device products to accurately record information and document the activities within the different types of laboratory environments. To this end, there needs to be a sensitivity about certain issues and to understand how some of these practices may be implemented by FDA.

B. Current Good Laboratory Practices (cGLPs)

It was noted in the mid-1970s that there were deficiencies in the record keeping of information pertaining to animal studies, chemical and physical testing within laboratories, and the ability to certify such things as instruments were in calibration and were able to be certified as to their accuracy and precision. The reasons behind these concerns were the simple facts to support the idea that the data generated would confirm the safety and efficacy of the product with the data being generated to support the research concerning new drug substances as well as to support the evaluation of medical devices. Numerous examples were cited at that time involving the deficiencies of animal studies. These included poor record keeping of short- and long-term dosing of animals for efficacy studies. Some deficiencies were also noted as far as the record keeping for human studies. In the case of chemical assays, it was noted that many reagents were not dated as to the length of preparation of the reagents and the application of possible expiration dating to these particular materials. It was also noted that stability testing on finished dosage forms and products were not supported by adequate information as to the validity of the test methods.

C. Current Good Manufacturing Practices (cGMPs).

What is paramount in these regulations is the ability to reproduce a product on a continuing basis and thus the introduction of the concept of validation of process and process design. There are a number of elements covered in these regulations that include organization scheme, buildings and facilities, equipment, laboratory facilities, components, packaging and distribution of pharmaceuticals. There are other elements of these regulations that could be reviewed by appropriate individuals who specialize in regulatory affairs.

What is important is the control of the components used in the preparation of dosage forms. Components require specifications that would ensure that when used in a product, the performance of that product would be as claimed. In many of the dosage forms involving controlled drug delivery, various polymeric substances are utilized. These substances must have adequate specifications to ensure reproducibility. It has also been noted over the years that some systems have contained trace contaminants that must be eliminated before approval of these particular materials or if there is a possibility of a contaminant that there are methods for testing for their presence. This is a new concept as far as raw materials are concerned coming from the harmonization efforts of various agencies that began in 1991. There will be further concern about the amount of trace toxic substances in the near future. It is important that there is a sensitivity to this particular issue. The methacrylates were suspect as far as trace monomers were concerned for a number of years. They are now used extensively in the preparation of controlled release products.

Through the cGMP regulations, the FDA can ensure to a great degree that adequate manufacturing processes are in place for the preparation and distribution of pharmaceutical dosage forms. It is worth noting that the regulations that are used for products sold in commerce are also applied to those products used in clinical research. Thus, there must be in place an identical system with supporting groups to ensure compliance to these regulations. As far as the pharmaceutical scientist is concerned, the important elements from early on to later considerations have to do with the specifications of the raw materials and the finished dosage forms. The understanding and the implementation of good processing methodology and the assurance of adequate stability for the protection of the consumer is essential. Since cGMPs are very important, they are in more depth in the following section.

V. CURRENT GOOD MANUFACTURING PRACTICES (cGMPs)

A. Legal Aspect

1. Authority

The FDA enforces the Food, Drug, & Cosmetic Act. The drug is considered adulterated if the methods, facilities, controls, processing, packaging and holding of the drug does not conform to cGMPs. The drug product

must meet the requirements related to safety, identity, strength, and purity that are claimed by the manufacturer.

2. Penalties

Failure to comply to cGMPs can render a product "adulterated," and FDA then recall the product. The CEO of the company may be liable depending on the seriousness of the damage caused by the adulteration. The FDA does not need to prove actual harm resulting from a product to declare it adulterated. A nail or a piece of plastic from a container entering a product can be enough to cause to declare it "adulterated." cGMPs are minimum requirements of the law.

3. Current

Companies must adhere to published regulations and employ current methods and controls that are accepted by the pharmaceutical industry. The FDA has electronic bulletin boards and various publications to inform the industry of current regulations.

B. SUBPARTS OF GMPS

1. GMP Subpart B. Organization and Personnel

a. Responsibilities of quality control unit

This is about responsibility and authority to approve or reject all components, containers, materials, packaging, labeling, etc., related to the drug product. The FDA will review the production record and make sure no errors have occurred. Responsibility holds even if product is prepared by a contract company. All the responsibilities of this unit must be expressed in writing. FDA prefers that quality control (QC) exists as a separate unit not associated with production personnel. The technical director of quality assurance and his group have the final word regarding any decision.

Many companies have a Regulatory Affairs Department with people who study and interpret GMPs that can be very complicated. Some companies hire consultants to help them make decisions regarding GMPs.

b. Personnel qualifications

Personnel must be qualified by training or experience to carry out specific responsibilities related to the manufacture of a drug product. Their qualifications must be documented as well as those of personnel who train them. Other considerations are education, level of skill, responsibilities, protective clothing worn to avoid contamination of product, etc. Persons who are ill, especially with open lesions, shall not have direct contact with the drug product.

2. Subpart C. Buildings and Facilities

a. Design and construction features

Adequacy of heating, cooling, lighting, plumbing units, etc., must be thoroughly described, including their state of repair. For parenteral products, the requirements are very specific. The type of finish and construction of the walls, ceilings, floors are specified depending on the intended use of the facility. Separate areas must be made available for each operation (packaging, storage, etc.). Should materials be stored at 25°C, 30°C or between 25°C and 30°C? This is controversial. Penicillin production must be in a separate area since the antibiotic may enter other products being processed nearby.

3. Subpart D. Equipment

Equipment design, size and location must be specified. Metallic surfaces of the equipment must not react with any components of the drug product. Any other surface must not leach or adsorb ingredients from the product. Cleaning of equipment and its parts can be very complicated. Residues of the previous product prepared using the equipment must not be detected in the rinse water. For some products $1/1000^{th}$ of the minimum therapeutic dose can be carried over. Detergent levels remaining in the equipment cannot exceed 10 ppm. Hardware, wiring, software, codes, etc. must be validated. Can the computer be used to perform checking functions? This is a controversial subject at this time. Sterilizing filters shall not release fibers in the product.

4. Subpart E. Control of Components and Drug Product Containers and Closures

a. Written procedures for receiving, identifying, storing, handling, sampling, testing and approval of components and containers, closures

This also includes steps to prevent use of rejected materials. Batch lots must be identified (lot number) and the status of different materials must be known and separated from each other. Computers have made it possible to eliminate labels that identified the status of a lot of materials making it unnecessary to separate batches of materials. The computer does not eliminate controls and checking. Containers and cartons must be opened in a separate room free of contamination and on surfaces that can be easily be cleaned.

b. Receipt of untested containers and closures

Look for errors in labeling, damage, broken seals and contamination. Quarantine all products until examined. (What about sabotage of a product or container by an angry employee?) Parenteral glass, plastic, and rubber containers must pass certain biological and chemical tests. (Are there carcinogens in the rubber stoppers?)

c. Testing of drug products containers and closures

Most chemicals are analyzed for identity and purity before using. Do not trust the label. From a 250-kg drum of chemical, a sample is removed from the top, middle, and bottom for analysis. Written specifications for each product are required.

d. Use of approved components, drug product containers and closures

Use oldest stock first. Chemicals decompose. Moisture enters into container when opened frequently.

e. Rejected components and closures

To prevent their use they should be labeled and quarantined. Too many of these rejects will mean that the vendor is not reliable and the FDA inspector will let the company know about it.

f. Quality of containers

Specific tests must be performed (chemical and biological).

5. Subpart F. Production and Process Controls

a. Written procedures for production and process control.

Other departments may have input and approve the procedures but final approval is made by the quality control unit (QC). QC is responsible for making sure that procedures are followed. Changes in the original NDA (such as a change of solvents, excipients, equipment, etc.) should be checked with the FDA but this may take months.

b. Verification of compliance to approved procedures

Use internal or external audit. Use some kind of rating for each procedure. Batch records should be reviewed to make sure they conform to FDA requirements. Audit reports may be requested by the FDA.

cGMPs are legal guidelines. They do not tell you how to do something. Most companies know the acceptable procedures for any process. Before l978 (before validation) the final product was tested analytically, for sterility, etc. But product testing is not reliable enough to tell you the true quality of your product since only a statistical sample of your product was tested. You cannot test every tablet or every ampoule. Thus failures occurred (thalidomide and large volume solutions in 1971 sold by Abbott were recalled). Validation is process control or control of outcome. Results are predictable. It means you have documented evidence and assurance that a specific process (such as sterilization) consistently produces a product that meets predetermined specifications and quality attributes. Validation requires demonstration of repeatability. You repeat a process at least three times to see if you get the same product with the same degree of quality.

6. Subpart G. Packaging and Labeling Control

a. Label contents

The content of a label has legal, marketing, medical, and regulatory implications and thus should be checked before printing. Look-alike labels (same design but different strengths) have caused errors in pharmacies. Keep records that describe receipt, identification, storage, handling, etc. of all labels.

b. Issuing labels

The identity of the label should match the product being labeled. Supervisor must confirm that the labels used for a previous product were removed. The number of labels used, destroyed, spoiled, should match the total number issued. Discrepancies mean that an error has occurred. Electronic scanning using a bar code is now used to make sure that each container has the correct label.

c. Product inspection

A certain number of containers are collected and inspected to make sure that the label is correct. Suppose a label is off center. Acceptance levels are specified and recorded.

d. Expiration dating

The date is determined after a stability test is performed for that product. Sterile products will bear an expiration date after it has been reconstituted (antibiotics).

7. Subpart H. Holding and Distribution (Warehousing)

Temperature, humidity, and other conditions must be known for storing drugs. If a computer is used to control the conditions then the computer must be validated for accuracy.

8. Subpart I. Laboratory controls

a. Calibration of instruments used in analytical control

The methods must be able to evaluate the product (such as stability studies). Reagents must be known to function over a period of time. The data derived from the analysis using a piece of equipment must be able to support the safety and reliability claimed for your product. You may use your own analytical method to replace that of the USP but you must show that the two methods are comparable.

b. Control charts

Let's use tablet weight as an example. The chart sets the weight, warning limits and action limit. Remove the tablets every 15 min. The variation from the ideal (target weight) is calculated. Adjust machine or determine the cause of the variation.

c. Testing before releasing for distribution

Each batch shall conform to the final specs of strength. No objectionable microorganisms should exist. Topical products must be free of *P. aeruginosa* and *S. aureus*.

d. Analytical validation

The method must be dependable, accurate and reproducible and compared to reference standards (purchased from the USP). Know the reason for a failure to reach the expected data. Personnel must be trained in conducting the method being used to validate the product.

e. Stability testing

The stability testing is said to determine the storage conditions and the expiration date. Changes in the glass of the container during storage must be known. Light transmitted must be known. Migration of chemicals in plastic containers to your solution must be known. Moisture may leave your plastic container and migrate outwards (usually 1 mL per month for a 1-L bag). Metal and rubber components are tested using very specific methods. Animals used in certain tests must be housed in a government certified facility.

VI. PHARMACOKINETIC/PHARMACODYNAMIC CONSIDERATIONS

For many years, pharmacokinetic input into controlled drug delivery products involved a fairly straightforward thought process. The emphasis was placed on clearance and absorption rate constant with much less thought given to the concentration of a drug necessary for activity. While disposition and absorption pharmacokinetic parameters are still of great importance, today, a more complete understanding of the concentration-response relationship is needed to most appropriately design a controlled drug-delivery product. Research efforts to quantify the pharmacodynamics of a drug will enhance the development of a controlled drug-delivery system and, importantly, should lead to faster regulatory approval for a novel dosage form.

A. PHARMACODYNAMIC/PHARMACOKINETIC PRINCIPLES

The goal of drug treatment is to elicit a desired pharmacologic response without an undesired toxicological response. But the process by which a drug entity is released from the dosage form/delivery system and provides this response is not a simple process, owing to physicochemical properties, physiologic constraints, and biochemical principles. This process has most frequently been described on a chronological basis with release and absorption of the drug molecule as the first steps. Then, the drug in a central compartment or plasma may distribute to the biophase where the receptor, enzyme, or other active site is located. But, as the importance of pharmacodynamics has become apparent, the final step may actually be the key one for understanding and designing a controlled drug-delivery system.

The most useful pharmacokinetic parameter for determining dosing strategies is total plasma clearance (*CL*). The *CL* is meaningful because of its relationship with dosing rate and plasma concentration at steady state (C_{ss}). For a zero-order input (R_o),

$$C_{ss} = R_o/CL$$

Therefore, the plasma concentration, which in turn produces a desired effect, is determined solely by the input rate for drug delivery and the plasma clearance. This equation is most routinely utilized for a constant intravenous infusion, but would also hold for other methods of drug delivery if a true zero-order release is present for the drug substance.

Thus, the product of drug clearance and the effective steady-state plasma concentration is needed to determine the input rate necessary for the controlled drug-delivery system. This straightforward calculation assumes that the drug obeys linear pharmacokinetic principles (*i.e.*, the clearance is constant and first-order elimination is observed at several doses). Also, the concentration must be chosen based on pharmacodynamic principles and steady-state, human data. For each of these measures, mean *CL* and C_{ss} are the preferred parameters, but one must realize that there is inherent intersubject variability for each parameter. A range of input rates may be calculated based on a range of expected parameters. For example, theophylline has a relatively narrow range of effective plasma concentrations 10–20 μg/mL. While a mean C_{ss} value of 15 μg/mL could be used for calculation purposes, one should appreciate the entire target range and, if serious or numerous toxicities occur frequently at the upper end of this range, the input rate calculation must be weighted toward the lower end of the therapeutic range.

The plasma elimination half-life, though a widely used pharmacokinetic parameter, is not directly needed for determining the input rate for a controlled drug-delivery system. The half-life will help provide an initial estimate of the usefulness of a controlled-delivery dosage form. A compound with a relatively long elimination half-life (greater than 12–24 h) for the active drug moiety would be a poor candidate for a controlled-release dosage form, while treatment with a drug exhibiting a shorter half-life, but not extremely short, would be improved by delivery in a controlled-release system. The half-life is primarily needed to determine a dosing interval for a regular-release dosage form; the dosing interval for a controlled-release system is more a function of the maximum quantity of drug available in and the release rate from the dosage form.

The *in vitro* release rate for a dosage form, though not strictly a pharmacokinetic parameter, is clearly quite critical to the eventual regulatory approval and the effectiveness of the controlled-release delivery system. The rate of release from the dosage form is the first step in the sequence leading to the desired response. From a pharmacokinetic perspective, this process is also important because it is the rate determining step leading to drug in the plasma and at the active site. Therefore, the release rate from the drug-delivery system is most often the only variable available in drug

development to achieve the expected pharmacologic activity. This release rate must be reproducible, be unaffected as much as possible by physiologic factors, and, as a final result, provide the therapeutic plasma concentration.

B. Development of a Controlled-Release Product for a Marketed Drug

Although immediate-release dosage forms are accompanied by a multitude of formulation difficulties, it is generally easier to develop a solution, capsule, tablet, or other dosage form with normal-release characteristics than it is to develop a controlled-release dosage form. Many immediate-release products are currently under investigation or are marketed as approved drugs. However, owing to a low therapeutic index or to improve patient compliance, a controlled-release dosage form can contribute positively to patient drug therapy.

For many drugs, a narrow therapeutic window places limits on the dosage form and resulting plasma concentrations, making it difficult to provide the needed pharmacologic activity without unnecessary toxicity. For example, theophylline is an older drug with notorious difficulty in dosing because of peak concentrations (generally, > 20 μg/mL) that led to increased heart rate, headache, dizziness, and other, more serious, toxic responses at higher concentrations. Also, though concentrations below 8–10 μg/mL might exacerbate breathing problems at the end of a dosing interval. A controlled-release dosage form is ideally suited to decrease this inherent fluctuation in plasma concentrations for theophylline or other drugs with this low therapeutic index and relatively wide swings in concentration during a dosing interval.

C. Summary

Quite simply, the pharmacodynamics of drug itself must be characterized and the pharmacokinetics of the dosage form must be optimized as a controlled release dosage form is developed. The key link for these formulation processes and pharmacokinetic parameters is the plasma drug concentration. As drug concentration is proportional to pharmacologic and toxicologic responses, determination of the pharmacodynamics is the first step involved in designing a controlled drug-delivery product and leading to improved patient therapy.