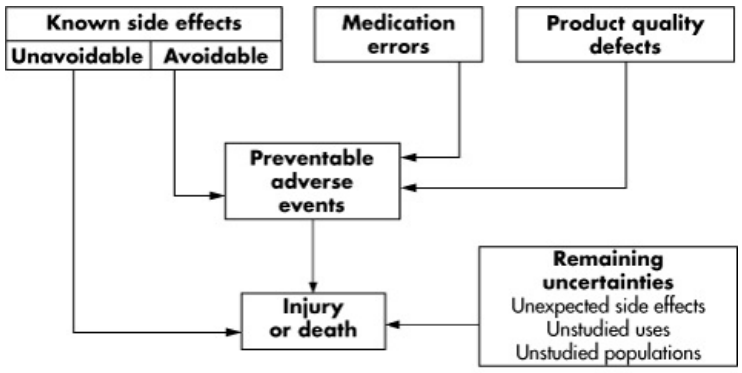
Note: Large images and tables on this page may necessitate printing in landscape mode.

RISKS FROM MEDICINES

The U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) has summarized various types of safety and efficacy risks from medicines (). Known side effects are observed adverse events that are identified in the drug's labeling. Side effects from the use of drugs are the major cause of drug related injuries, adverse events, and deaths. Some side effects are avoidable, and others are unavoidable. Avoidable side effects may include known drug–drug or drug–food interactions, contraindications, improper compliance, etc. In many cases, drug therapy requires an individualized drug treatment plan and careful patient monitoring. Some known side effects occur with the best medical practice and even when the drug is used appropriately. Examples include nausea from antibiotics or bone marrow suppression from chemotherapy. Medication errors include wrong drug, wrong dose, or incorrect administration. Some side effects are unavoidable. These uncertainties include unexpected adverse events, side effects due to long-term therapy, and unstudied uses and unstudied populations. For example, a rare adverse event occurring in fewer than 1 in 10,000 persons would not be identified in normal premarket testing.

Figure 16-1.



Sources of risk from drug products.

(Source: .)

Product quality defects are an important source of risk that may affect safety and efficacy. Product quality includes strength and purity of the drug substance and drug product and is also controlled through Good Manufacturing Practices and monitoring of the manufacturing operations. This chapter will focus on drug product quality and risks of product quality defects. Individualization of drug therapy and drug–drug interactions are discussed in later chapters.

Drug Product Quality

Drug product quality relates to the biopharmaceutic and physicochemical properties of the drug substance and the drug product, as discussed in previous chapters. The performance of each drug product must be consistent and predictable to assure both clinical efficacy and safety. Product attributes and performance are critical factors that influence product quality (). Each component of the drug product and the method of manufacture contribute to quality. Quality must be built into the product during research, development, and production. Quality is maintained by implementing systems and procedures that are followed during the development and manufacture of the drug product.

Table 16.1 Product Quality and Performance Attributes

Product quality	Chemistry, manufacturing and controls (CMC)
	Microbiology
	Information that pertains to the identity, strength, quality, purity and potency of the drug product
Product performance	Bioavailability and bioequivalence information
	Drug release/dissolution

An independent *quality assurance* (QA) unit is a vital part of drug development and manufacture. QA is responsible for ensuring that all the appropriate procedures have been followed and documented. QA provides a high probability that each dose or package of a drug product will have predictable characteristics and perform according to its labeled use. The *quality control* (QC) unit is responsible for the in-process tests beginning from receipt of raw materials, throughout production, finished product, packaging, and distribution.

Principles of quality assurance include: (1) quality, safety, and effectiveness must be designed and built into the product; (2) quality cannot be inspected or tested into the finished product; and (3) each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.

QA/QC has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. QA/QC is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

Good Manufacturing Practices

Good Manufacturing Practices (GMPs) are FDA regulations that describe the methods, equipment, facilities, and controls required for producing human and veterinary products. GMPs define a quality system that manufacturers use to build quality into their products. For example, approved drug products developed and produced according to GMPs are considered safe, properly identified, of the correct strength, pure, and of high quality. The U.S. regulations are called *current* Good Manufacturing Practices (cGMPs), to emphasize that the expectations are dynamic. These regulations are minimum requirements that may be exceeded by the manufacturer. GMPs help prevent inadvertent use or release of unacceptable drug products into manufacturing and distribution. GMP requirements include well-trained personnel and management, buildings and facilities, and written and approved Standard Operating Procedures (SOPs), as listed in .

Table 16.2 Current Good Manufacturing Practice for Finished Pharmaceuticals

Subpart A—General Provisions
Scope, Definitions
Subpart B—Organization and Personnel
Responsibilities of quality control unit, Personnel qualifications, Personnel responsibilities, Consultants
Subpart C—Buildings and Facilities
Design and construction features, Lighting, Ventilation, air filtration, air heating and cooling, Plumbing, Sewage and refuse, Washing and toilet facilities, Sanitation, Maintenance
Subpart D—Equipment
Equipment design, size, and location, Equipment construction, Equipment cleaning and maintenance, Automatic, mechanical, and electronic equipment, Filters
Subpart E—Control of Components and Drug Product Containers and Closures
General requirements, Receipt and storage of untested components, drug product containers, and closures, Testing and approval or rejection of components, drug product, containers, and closures, Use of approved components, drug product containers, and closures, Retesting of approved components, drug product containers, and closures, Rejected components, drug product containers, and closures, Drug product containers and closures
Subpart F—Production and Process Controls
Written procedures; deviations, Charge in of components, Calculation of yield, Equipment identification, Sampling and testing of in-process materials and drug products, Time limitations on production, Control of microbiological contamination, Reproccessing
Subpart G—Packaging and Labeling Controls
Materials examination and usage criteria, Labeling issuance, Packaging and labeling operations, Tamper-resistant packaging requirements for over-the-counter human drug products, Drug product inspection, Expiration dating
Subpart H—Holding and Distribution
Warehousing procedures, Distribution procedures
Subpart I—Laboratory Controls
General requirements, Testing and release for distribution, Stability testing, Special testing requirements, Reserve samples, Laboratory animals, Penicillin contamination
Subpart J—Records and Reports
General requirements, Equipment cleaning and use log, Component, drug product, container, closure, and labeling records, Master production and control records, Batch production and control records, Production record review, Laboratory records.
Distribution, Complaint files
Subpart K—Returned and Salvaged Drug Products
Returned drug products, Drug product salvaging

Source: U.S. Code of Federal Regulations (CFR), 21 CFR Part 211.

Guidances for Industry

The FDA publishes guidances for the industry to provide recommendations to pharmaceutical manufacturers for the development and manufacture of drug substances and drug products (www.fda.gov/cder/guidance/index.htm). The International Conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use (ICH) is composed of the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry. The ICH is interested in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health (www.ifpma.org/ich1.html).

Quality Standards

Public standards are necessary to assure that drug substances and drug products have consistent and reproducible quality. The *United States Pharmacopeia* National Formulary, USP-NF (www.usp.org), is legally recognized by the U.S. Food, Drug and Cosmetic Act and sets public standards for drug products and drug substances. The USP-NF contains monographs for drug substances and drug products that include standards for strength, quality, and purity. In addition, the USP-NF contains general chapters that describe specific procedures that support the monographs. The tests in the monographs may provide *acceptance criteria*, i.e., numerical limits, ranges, or other criteria for the test for the drug substance or drug product. An *impurity* is defined as any component of the drug substance that is not the entity defined as the drug substance. Drugs with a USP or NF designation that do not conform to the USP monograph may be considered adulterated. *Specifications* are the standards a drug product must meet to ensure conformance to predetermined criteria for consistent and reproducible quality and performance.

RISK MANAGEMENT

Regulatory and Scientific Considerations

The FDA develops rational, science-based regulatory requirements for drug substances and finished drug products. The FDA establishes quality standards and acceptance criteria for each component used in the manufacture of a drug product. Each component must meet an appropriate quality and performance objective.

Drug Manufacturing Requirements

Assurance of product quality is derived from careful attention to a number of factors, including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end-product testing. Because of the complexity of today's medical products, routine end-product testing alone often is not sufficient to assure product quality. The *Chemistry, Manufacturing Controls* (CMC) section of a Drug Application describes the composition, manufacture, and specifications of the drug substance and drug product ().

Table 16.3 Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application

I. Drug Substance
A. Description, including physical and chemical characteristics and stability
1. Name(s)
2. Structural formula
3. Physical and chemical characteristics
4. Elucidation of Structure
5. Stability
B. Manufacturer(s)
C. Method(s) of manufacturer and packaging
1. Process controls
2. Container-closure system
D. Specifications and analytical methods for the drug substance
E. Solid-state drug substance forms and their relationship to bioavailability
II. Drug Product
A. Components
B. Composition
C. Specifications and analytical methods for inactive components
D. Manufacturer(s)
E. Method(s) of manufacture and packaging
1. Process controls
2. Container closure system
III. Methods validation package
IV. Environmental assessment

Source: .

Process Validation

Process validation is the process for establishing documented evidence to provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation is a key element in assuring that these quality assurance goals are met. Proof of validation is obtained through collection and evaluation of data, preferably beginning at the process development phase and continuing through the production phase.

The product's end use should be a determining factor in the development of product (and component) characteristics and specifications. All pertinent aspects of the product that may affect safety and effectiveness should be considered. These aspects include performance, reliability, and stability. Acceptable ranges or limits should be established for each characteristic to set up allowable variations. *Specifications* are the quality standards (ie, tests, analytical procedures, and acceptance criteria) that confirm the quality of drug substances, drug products, intermediates, raw material reagents, components, in-process material, container closure systems, and other materials used in the production of the drug substance or drug product.

Through careful design and validation of both the process and process controls, a manufacturer can establish with a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence on intensive in-process and finished product testing. In most cases, end-product testing plays a major role in assuring that quality assurance goals are met; ie, validation and end-product testing are not mutually exclusive.

Drug Recalls and Withdrawals

The FDA coordinates drug recall information and prepares health hazard evaluations to determine the risk to public health by products being recalled. The FDA classifies recall actions in accordance to the level of risk. The FDA and the manufacturer develop recall strategies based on the potential health hazard and other factors, including distribution patterns and market availability. The FDA also determines the need for public warnings and assists the recalling firm with public notification. lists some of the major reasons for drug recalls.

Table 16.4 Major Reasons for Drug Recalls
Failure or inability to validate drug analysis methods
Subpotency
Stability data failing to support expiration date
Failure or inability to validate manufacturing processes
Deviations from good manufacturing practices
Failure of drug to dissolve properly Labeling mix-ups
Marketed without a new or generic approval
Lack of assurance of sterility
Cross-contamination with other products

SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)

A *postapproval change* is any change in a drug product after it has been approved for marketing by the FDA. A change to a marketed drug product can be initiated for a number of reasons, including a revised market forecast, change in an active pharmaceutical ingredient source, change in excipients, optimization of the manufacturing process, and upgrade of the packaging system. A change within a given parameter can have varied effect on different types of products. For example, a change in the container closure/system of a solid oral dosage form may have little impact for an oral tablet dosage form unless the primary packaging component is critical to the shelf life of the finished product.

If a pharmaceutical manufacturer makes any change in the drug formulation, scales up the formulation to a larger batch size, or changes the process, equipment, or manufacturing site, the manufacturer should consider whether any of these changes will affect the identity, strength, purity, quality, safety, and efficacy of the approved drug product. Moreover, any changes in the raw material (ie, active pharmaceutical ingredient), excipients (including a change in grade or supplier), or packaging (including container closure system) should also be shown not to affect the quality of the drug product. The manufacturer should assess the effect of the change on the identity, strength (eg, assay, content uniformity), quality (eg, physical, chemical, and biological properties), purity (eg, impurities and degradation products), or potency (eg, biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

The FDA has published several SUPAC guidances, including *Changes to an Approved NDA or ANDA* (www.fda.gov/cder/guidance/index.htm) for the pharmaceutical industry. These guidances address the following issues:

- Components and composition of the drug product
- Manufacturing site change
- Scale-up of drug product
- Manufacturing equipment
- Manufacturing process

- Packaging
- Active pharmaceutical ingredient

These documents describe (1) the level of change, (2) recommended chemistry, manufacturing and controls tests for each level of change, (3) *in-vitro* dissolution tests and/or bioequivalence tests for each level of change, and (4) documentation that should support the change. The level of change is classified as to the likelihood that a change in the drug product as listed above might affect the quality of the drug product. The levels of change as described by the FDA are listed in .

Table 16.5 FDA Definitions of Level of Changes that May Affect the Quality of an Approved Drug Product

Change Level	Definition of Level
Level 1	Changes that are unlikely to have any detectable impact on the formulation quality and performance.
Level 2	Changes that could have a significant impact on formulation quality and performance.
Level 3	Changes that are likely to have a significant impact on formulation quality and performance.

As noted in , a Level 1 change, which could be a small change in the excipient amount (eg, starch, lactose), would be unlikely to alter the quality or performance of the drug product, whereas a Level 3 change, which may be a qualitative or quantitative change in the excipients beyond an allowable range, particularly for drug products containing a narrow therapeutic window might require an *in-vivo* bioequivalence study to demonstrate that drug quality and performance were not altered by the change.

Assessment of the Effects of the Change

Assessment of the effect of a change should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications. A *specification* is a quality standard (ie, tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. *Acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. *Conformance* to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria. Additional testing may be needed to confirm that the material affected by manufacturing changes continues to meet its specification. The assessment may include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment may involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing depends on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. Examples of additional tests include:

- Evaluation of changes in the impurity or degradant profile
- Toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level
- Evaluation of the hardness or friability of a tablet
- Assessment of the effect of a change on bioequivalence (may include multipoint and/or multimedia dissolution profiles and/or an *in-vivo* bioequivalence study)
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system

Equivalence

The manufacturer usually assesses the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product by comparing test results from *pre-* and *postchange* material and then determining if the test results are equivalent. The drug product after any changes should be equivalent to the product made before the change. An exception to this general approach is that when bioequivalence should be redocumented for certain Abbreviated New Drug Application (ANDA) postapproval changes, the comparator should be the reference listed drug. Equivalence does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (eg, stability) rather than a single performance of a test.

Critical Manufacturing Variables

Critical manufacturing variables (CMVs) include changes in the formulation, process, equipment, materials and methods for the drug product that can significantly affect *in-vitro* dissolution. If possible, the manufacturer should determine whether there is a relationship between CMV, *in-vitro* dissolution and *in-vivo* bioavailability. The goal is to develop product specifications that will assure bioequivalence of future batches prepared within limits of acceptable dissolution specifications. One approach to obtaining this relationship is to compare the bioavailability of test products with slowest and fastest dissolution characteristics to the bioavailability of the marketed drug product. Dissolution specifications for the drug product are then established so that future production batches do not fall outside the bioequivalence of the marketed drug product.

Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. For example, a type of process change could cause a new degradant to be formed that requires qualification and/or quantification. The manufacturer must show that the new degradant will not affect the safety or efficacy of the product. Changes in the qualitative or quantitative formulation, including inactive ingredients, are considered major changes and are likely to have

a significant impact on formulation quality and performance. However, the deletion or reduction of an ingredient intended to affect only the color of a product is considered to be a minor change that is unlikely to affect the safety of the drug product.

Bulk Actives Postapproval Changes (BACPACs)

Manufacturing changes of the *active pharmaceutical ingredient* (API)—also known as the drug substance or bulk active—may change its quality attributes. These quality attributes include chemical purity, solid-state properties, and residual solvents. Chemical purity is dependent on the synthetic pathway and purification process. Solid-state properties include particle size, polymorphism, hydrate/solvate, and solubility. Small amounts of residual solvents such as dichloromethane may remain in the API after extraction and/or purification. Changes in the solid-state properties of the API may affect the manufacture of the dosage form or product performance. For example, a change in particle size may affect API bulk density and tablet hardness, whereas different polymorphs may affect API solubility and stability. Changes in particle size and/or polymorph may affect the drug's bioavailability *in vivo*. Moreover, the excipient(s) and vehicle functionality and possible pharmacologic properties may affect product quality and performance.

Practical Focus

Quantitative Change in Excipients

A manufacturer would like to increase the amount of starch by 2% (w/w) in an immediate-release drug product. Would you consider this change in an excipient to be a Level 1, 2, or 3 change?

The FDA has determined that small changes in certain excipients for immediate-release drug products may be considered Level 1 changes (see). lists the changes in excipients, expressed as percentage (w/w) of the total formulation, less than or equal to the following percent ranges that are considered as Level 1 changes. According to this table, a 2% increase in starch would be considered a Level 1 change.

Table 16.6 Level 1—Allowable Changes in Excipients

Excipient	Percent Excipient (w/w) out of Total Target Dose Form Weight
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Calcium stearate	±0.25
Magnesium stearate	±0.25
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film coat	±1

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency.

Source: FDA Guidance: Immediate release solid oral dosage forms: Scale-up and postapproval changes (1995).

The total additive effect of all excipient changes should not be more than 5%. For example, a drug product containing the active ingredient lactose, mirocrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (eg, lactose increases 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the Level 1 range.

It should be noted that a small change in the amount of excipients is less likely to affect the bioavailability of a highly soluble, highly permeable drug in an immediate-release drug product compared to a drug that has low soluble and low permeability.

Changes in Batch Size (Scale-up/Scale-down)

For commercial reasons, a manufacturer may increase the batch size of a drug product from 100,000 units to 5 million units. Even though similar equipment is used and the same Standard Operating Procedures (SOPs) are used, there may be problems in manufacturing a very large batch. This problem is similar to a chef's problem of cooking the main entrée for two persons versus cooking the same entrée for a banquet of 200 persons using the same recipe. The FDA has generally considered that a change in batch size greater than 10-fold is a Level 2 change and requires the manufacturer to notify the FDA and provide documentation for all testing before marketing this product.

PRODUCT QUALITY PROBLEMS

The FDA and industry are working together to establish a set of quality attributes and acceptance criteria for certain approved drug substances and drug products that would indicate less manufacturing risk. summarizes some of the quality attributes for these products. However, all approved drug products must be manufactured under current Good Manufacturing Practices.

Table 16.7 Quality Attributes and Criteria for Certain Approved Drug Substances and Drug Products

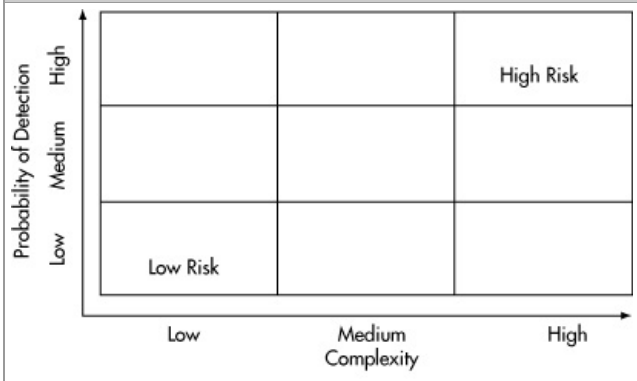
Drug Substances		Drug Products	
Attribute	**Criteria**	**Attribute**	**Criteria**
Chemical structure	Well characterized	Dosage form	Oral (immediate release), simple solutions, others
Synthetic process	Simple process	Manufacturing process	Easy to manufacture (TBD)
Quality	No toxic impurities; adequate specifications	Quality	Adequate specifications
Physical properties	Polymorphic forms, particle size are well controlled	Biopharmaceutic Classification Systems (BCS)	Highly permeable and highly soluble drugs
Stability	Stable drug substance	Stability	Stable drug product (TBD)
Manufacturing history	TBD	Manufacturing history	TBD
Others	TBD	Others	TBD

TBD, to be defined.

Adopted from Yuan-yuan Chui, CMC Initiative: Risk-based CMC reviews, *PhRMA-Dialog*, October 27, 2000 (http://www.fda.gov/cder/ondc/).

Drug substances and drug products that have more quality risk are generally those products that are more complex to synthesize or manufacture (). For example, biotechnology-derived drugs (eg, proteins) made by fermentation may have more quality risk than chemically synthesized small molecules. Extended-release and delayed-release drug products may also present a greater quality risk than an immediate-release drug product. Drug products that have a very small ratio of active drug substance to excipients are more difficult to blend uniformly and thus may have a greater quality risk. Good Manufacturing Practices and control of the critical manufacturing operations help maintain the quality of the finished product. Complex operations can have consistent outcome quality as long as the manufacturer maintains control of the process and builds in quality during the manufacturing operations.

Figure 16-2.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

General principles to define low-risk drugs.

(,)

Practical Focus

BSE in Gelatin

Gelatin may be produced from bones and hides obtained from cattle. In the early 1990s, the FDA became concerned about transmissible spongiform encephalopathies (TSEs) in animals and Creutzfeldt-Jakob disease in humans. In 1993, the FDA recommended against the use of materials from cattle that had resided in, or originated from, countries in which *bovine spongiform encephalopathy* (BSE, or "mad cow disease") had occurred. The FDA organized a Transmissible Spongiform Encephalopathies Advisory Committee to help assess the safety of imported and domestic gelatin and gelatin by-products in FDA-regulated products with regard to the risk posed by BSE. The FDA published a Guidance to industry concerning the sourcing and processing of gelatin used in pharmaceutical products to assure the safety of gelatin as it relates to the potential risk posed by BSE (www.fda.gov/opacom/morechoices/industry/guidance/gelguide.htm).

Gelatin Capsules Stability

Soft and hard gelatin capsules show a decrease in the dissolution rate over time in simulated gastric fluid (SGF) with and without

pepsin or in simulated intestinal fluid (SIF) without pancreatin. This has been attributed to pellicle formation. When the dissolution of aged or slower-releasing capsules was carried out in the presence of an enzyme (pepsin in SGF or pancreatin in SIF), a significant increase in dissolution was observed. In this setting, multiple dissolution media may be necessary to assess product quality adequately.

Excipient Effects

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved immediate-release solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving immediate-release product.

When new excipients or atypically large amounts of commonly used excipients are included in an immediate solid dosage form, additional information documenting the absence of an impact on bioavailability of the drug may be requested by the FDA. Such information can be provided with a relative bioavailability study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (eg, polysorbate 80) and sweeteners (eg, mannitol or sorbitol) may be problematic.

POSTMARKETING SURVEILLANCE

Pharmaceutical manufacturers are required to file periodic Post-Market Reports for an approved ANDA to the FDA through its *Postmarketing Surveillance Program*. The main component of the requirement is the reporting of adverse drug experiences. This is accomplished by reassessing drug risks based on data learned after the drug is marketed. In addition, labeling changes may occur after market approval. For example, a new adverse reaction discussed by postmarketing surveillance is required for both branded and generic drug products.

FREQUENTLY ASKED QUESTIONS

1. Three batches of ibuprofen tablets, 200 mg, are manufactured by the same manufacturer using the same equipment. Each batch meets the same specifications. Does meeting specifications mean that each batch of drug product contains the identical amount of ibuprofen?

2. What should a manufacturer of a modified-release tablet consider when making a qualitative or quantitative change in an excipient?

LEARNING QUESTIONS

1. For solid oral drug products, a change in the concentration of which the following excipients is more likely to influence the bioavailability of a drug? Why?

Starch

Magnesium stearate

Microcrystalline cellulose

Talc

Lactose

2. How does the polymorphic form of the active drug substance influence the bioavailability of a drug? Can two different polymorphs of the same active drug substance have the same bioavailability?

REFERENCES

CMC Initiative: Risk-based CMC Reviews, PhRMA-Dialog, Oct 27, 2000 (www.fda.gov/cder/ondc/)

FDA, CDER Report to the Nation: 2001 (www.fda.gov/cder/reports/rtn/2001/rtn2001-3.htm)

FDA Guidance for Industry: Changes to an Approved NDA or ANDA, FDA/CDER, November 1999 (www.fda.gov/cder/guidance/index.htm)

Risk-Based CMC Review; Advisory Committee for Pharmaceutical Sciences, FDA, Oct 21, 2002