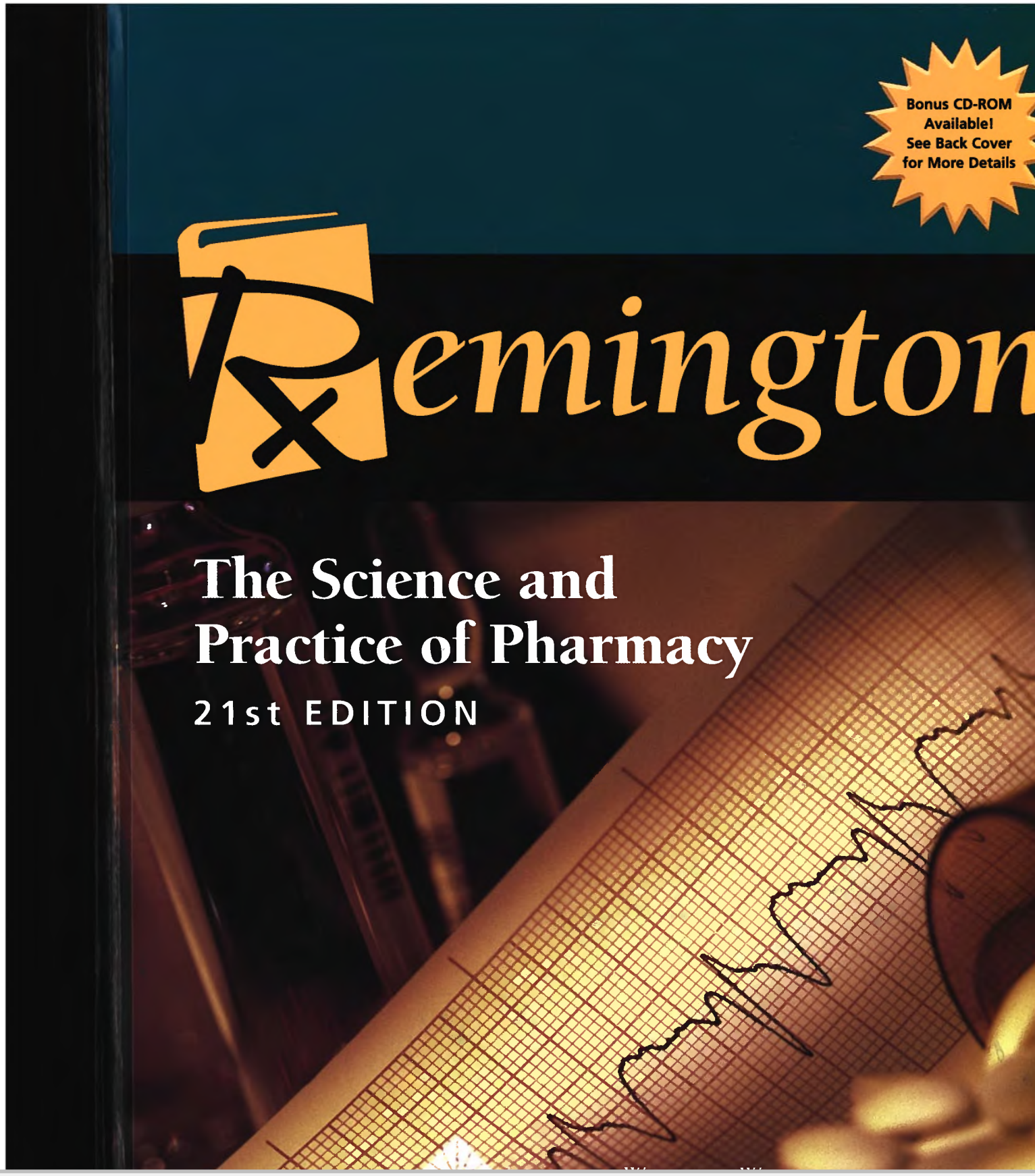

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CHAPTER 52

Stability of Pharmaceutical Products

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Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data involve selected parameters that, taken together, form the stability profile. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.

The stability of a pharmaceutical product is investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salts stability/compatibility with various solvents, buffered solutions, and excipients considered for formulation development. Optimization of a stable formulation of a pharmaceutical product is built upon the information obtained from the preformulation stage and continues during the formulation development stages.

Typically, the first formulation development stage is the preparation of a "first in human" formulation which is often a non-elegant formulation optimized for short-term dose-ranging clinical studies. The second major formulation development stage occurs to support Phase II and early Phase III clinical studies. The pharmaceutical product developed at this stage is usually the prototype for the commercial product. Therefore, the pharmaceutical product will be formulated based in part on the stability information obtain from the previous formulations and must meet stability requirements for longer-term clinical studies. The final formulation development stage is for the commercial pharmaceutical product. In addition to building on the clinical requirements of the drug, the commercial pharmaceutical product must also incorporate the commercial or the final market image of the product, which includes the container closure system. The stability of this product must be demonstrated to the appropriate regulatory agencies in order to assign an expiration date for the product.

approval, affect the safety and efficacy of the drug, and/or cause product recall.

Much has been written about the development of a stable pharmaceutical product. Comprehensive treatments of all aspects of pharmaceutical product stability has been published by Lintner,[1] Connors et al,[2] and more recently Carstensen[3]. This chapter will outline the appropriate steps from preformulation to drug approval to assure that the pharmaceutical product developed is stable. Requirements for compounded products will also be discussed.

The USP defines the stability of a pharmaceutical product as "extent to which a product retains, within specified limits, and throughout its period of storage and use (ie, its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture." There are five types of stability that must be considered for each drug.

Type of Stability	Conditions Maintained Throughout the Shelf-Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

Stability of a drug also can be defined as the time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level. Expiration date (time)

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placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both the dry mixture and the reconstituted product. Tamper-resistant packaging is to be used where applicable.

One type of time-related stability failure is a decrease in therapeutic activity of the preparation to below labeled content. A second type of stability failure is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The numbers of published cases reflecting this second type are few. However, it is possible, though remote, for both types of stability failures to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a stability failure may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or recalled from the market appreciably earlier than actually is necessary) and the Type 2 or beta error (setting the date too late so that the failure occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly define the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf-life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

REGULATORY REQUIREMENTS

Stability study requirements and expiration dating are covered in the Current Good Manufacturing Practices (cGMPs),[4] the USP,[5] and the FDA guidelines.[6]

GOOD MANUFACTURING PRACTICES—The GMPs[4] state that there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine appropriate storage conditions and expiration dating. The latter is to ensure that the pharmaceutical product meets applicable standards of identity, strength, quality, and purity at time of use. These regulations, which apply to both human and veterinary drugs, are updated periodically in light of current knowledge and technology.

COMPENDIA—The compendia also contain extensive stability and expiration dating information. Included are a discussion of stability considerations in dispensing practices and the responsibilities of both the pharmaceutical manufacturer and the dispensing pharmacist. It now is required that product labeling of official articles provide recommended storage conditions and an expiration date assigned to the specific formulation and package. Official storage conditions as defined by the USP 26[5] are as follows: *Cold* is any temperature not exceeding 8°C, and *refrigerator* is a cold place where the temperature is maintained thermostatically between 2 and 8°C. A *freezer* is a cold place maintained between −25 and −10°C. *Cool* is defined as any temperature between 8 and 15°C, and *room temperature* is that temperature prevailing in a working area. *Controlled*

established to harmonize with international drug standards of forts. The usual or customary temperature range is identified as 20 to 25°C, with the possibility of encountering excursions in the 15 to 30°C range and with the introduction the mean kinetic temperature (MKT).

The mean kinetic temperature is calculated using the following equation:

$$T_k = \left[-In\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_{n-1}} + e^{-\Delta H/RT_n}}{n} \right)^{\frac{\Delta H/R}{}} \right]$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1}; R is the universal gas constant, 8.3144×10^{-3} kJ· mole^{-1}· degree^{-1}; T_1 is the value for the temperature (in degrees Kelvin [°K]) recorded during the first time period, T_2 is the value for the temperature recorded during the second time period, eg, second week; T_{n-1} is the value of the second to last time period, and T_n is the value for the temperature recorded during the nth time period. Typically, the time period is in days or weeks. The mean kinetic temperature determines the thermal exposure of a material. This allows an acceptable estimation to assess if a temperature excursion (or series of excursions) adversely affected a material.

FDA Guidelines provide recommendations for:

1. The design of stability studies to establish appropriate expiration dating periods and product storage requirements
2. The submission of stability information for investigational new drugs, biologicals, new drug applications, and biological product license applications

Thus, the guidelines represent a framework for the experimental design and data analysis as well as the type of documentation needed to meet regulatory requirements in the drug-development process.

Table 52-1. Stability Protocols

CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
Long-term testing 25°C ± 2°C/60% ± 5% RH	12 mo
Accelerated testing 40°C ± 2°C/75% ± 5% RH	6 mo
Alternate testing[a] 30°C ± 2°C/65% ± 5% RH	12 mo

[a]Required if *significant change* occurs during 6-mo storage under conditions of accelerated testing.

Example Stability Pull Schedule for a Solid Oral Dose for Zone I and II

STORAGE CONDITIONS	DURATIONS (MONTHS)								
	0	1	3	6	9	12	18	24	
25°C/60% RH	R*		X	X	X	X, Y	X	X	X
30°C/65% RH			O	O	O	O			
40°C/75% RH		X	X	X, Y					

*From Release testing if testing is within 30 days of stability set down.

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