CHAPTER 1

AN OVERVIEW

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U.S. law defines a drug as any substance, other than a food or device, either (1) intended for use in the diagnosis, cure, relief, treatment, or prevention of disease or (2) intended to affect the structure or function of the body. The mission of pharmaceutical scientists is to continue developing safer and more effective new drugs to conquer various human diseases. However, successfully developing new medicines for patients requires significant collaboration of many interdisciplinary sciences, including:

- molecular biology;
- medicinal chemistry;
- pharmacology;
- toxicology;
- preformulation;
- formulation;
- clinical evaluation;
- synthetic chemistry;
- quality assurance/control;
- regulatory affairs;
- sales and marketing.

The objectives of formulation and analytical scientists are to develop new drug products for human use that are chemically and physically stable, bioavailable upon administration, manufacturable, cost-effective, elegant, and marketable.

Formulation and Analytical Development for Low-Dose Oral Drug Products. Edited by Jack Zheng

Pharmacologically, a drug should demonstrate its ability to:

- target the intended site or receptor (selectivity);
- remain attached to the receptor (affinity);
- show its effectiveness (efficacy);
- show its safety (adverse/side effects).

Ideally, a drug should be highly selective for its biological target, so that it has little or no effect on other physiological systems. The drug should also be very potent and effective, so that low doses of drug substance can be used, even for disorders that are difficult to treat. Finally, the drug should be administered orally, not only for patient compliance, but also for ease of production, distribution, and administration.

Drug product development is a process of transforming concept into reality. The process is not only science, but also art. After selecting a new drug candidate, drug development moves from preclinical studies to critical clinical investigation, and then to various stages of clinical and commercial product development. A drug candidate can become a drug product only when the compound is clinically efficacious and safe, and the developed product is bioavailable and stable, produces the desired pharmacological effects, and can be manufactured consistently with the identity, strength, quality, and purity it is represented to possess.

During development of an oral solid dosage form, dose strength is one of the critical product attributes that may have a significant impact on formulation and analytical development. Especially for a low-dose drug product, pharmaceutical scientists face great challenges in formulation, manufacture, analytical chemistry, and regulatory requirements.

This book addresses the challenges and strategies in developing low-dose oral solid drug products (i.e., less than 1 mg per dose unit), and aids development scientists in improving research and development productivity with a scientific and structured approach to product development. The information presented in the book is based on the extensive experience of the contributors, all of whom are actively working in the pharmaceutical industry and/or regulatory agency and have gained significant knowledge from their practical experience.

1.1 THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

Drug discovery and development is a time-consuming and unpredictable process as well as an expensive venture. Today the average cost to research and develop each successful drug is estimated to be somewhere between $1.2 billion and $1.5 billion.[1] The whole adventure is highly innovative, highly risky, highly regulated, and highly technology- and information-intensive. Typically, it takes 10–15 years to develop a safe and effective new medicine from the early stage of discovery until the drug is available to treat patients.[2] This process, as illustrated in Fig. 1.1,

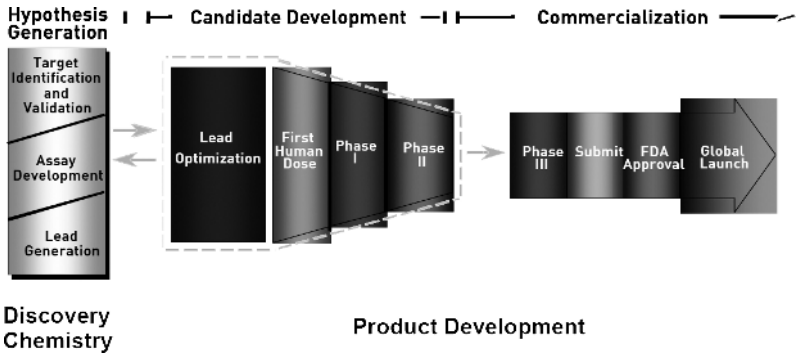

Figure 1.1 New drug discovery and development process. (See color insert.)

is normally divided into two key phases: discovery and development. During these phases, scientists have to:

- understand disease status, hypothesize "targets" that new drugs might be able to affect, and validate the targets;
- discover the molecule(s) to interact with the target hypothesized;
- assess the new compound (drug candidate) in the laboratory and clinic for safety and efficacy;
- develop the right drug product/dosage form for the intended use;
- gain regulatory approval and get the new drug into the hands of physicians and patients.

1.1.1 The Discovery Phase

Before discovering any new drug, scientists strive to understand the disease needing treatment and unravel the underlying cause of the condition. To do this, they investigate:

- how the genes are altered;
- how that alteration affects the proteins they encode;
- how those proteins interact with each other in living cells;
- how those affected cells change the specific tissue they are in;
- how the disease affects the patient.

This knowledge is the critical foundation for hunting a new medicine and treating the disease.

In 2001, scientists completed the sequencing of the human genome. They found that the genome of *Homo sapiens* consists of 24 distinct chromosomes (22 autosomal and the sex-determining X and Y chromosomes). There are approximately 3 billion

DNA base pairs containing an estimated 20,000–25,000 genes.[3,4] Each gene codes for a protein, and these proteins carry out all the functions of the human body, laying out how it grows and works. These genes and proteins can also be involved in disease. Hence, scientists are able to understand the inner workings of human disease at both the tissue level and the molecular level.

Once scientists understand the underlying cause of a disease, they can select a "target" for a potential new drug. A target is generally a single molecule, such as a gene or protein, which is involved in a particular disease state. Scientists call this earliest step in drug discovery "target identification."

After identifying a potential target, scientists must demonstrate that it actually is involved in the disease and that a drug can act on it. This process is called "target validation." Target validation is a crucial step in the drug discovery process that helps scientists minimize research paths that look promising, but that ultimately lead to dead ends. Target validation involves proving that DNA, RNA, or a protein molecule is directly involved in a disease process in vitro and in vivo, and that it can be a suitable target for a new therapeutic drug. Scientists use several methods to validate a target.

One type of target validation uses computer models. They are a fast, relatively cheap option for initial screening of both targets and potential drugs. The models usually focus on how the two types of candidate structures interact with each other.[5] Sense reversal is another route to target validation. It hinges on disrupting gene expression to reduce the amount of the corresponding protein, thereby identifying the physiological role of the target. Examples of this technique include gene knockouts, antisense technology, and RNA interference (RNAi).

One disadvantage of doing target validation at the genetic level, however, is that many genes produce several different protein isoforms that can have subtly different functions. Post-translational modifications can also give protein variations. To address these issues, a developing approach in target validation, proteomics, focuses on manipulating the activity of the potential target protein itself. Proteomics investigates and manipulates the protein make-up of a cell so it is easier to distinguish and target just one specific form of a protein.

In vivo target validation involves more complicated experiments in animal models of diseases.[5] However, animal models for certain diseases, such as psychiatric illnesses, are extremely difficult to develop. The alternative is to use gene knockouts, in which genes are deleted or disrupted to halt their expression in vivo. This can be a powerful method of predicting drug action. This method is based on the assumption that knocking out the gene for the potential target has the same effect as administering a highly specific inhibitor of the target protein in vivo. Once the target is validated, it can then be used for screening potential new drug candidates.

Scientists screen thousands of compounds (either by synthesizing or choosing from libraries) to find a molecule, or "lead compound," that may interact with the target to alter the disease course. De novo and high-throughput screening are methods commonly used to find a lead compound.[6,7] Promising lead candidates are called "hits." Hits go through a series of tests to provide an early assessment of the safety, efficacy, and pharmacokinetic properties.

Lead compounds that survive the initial screening are then "optimized" or altered to improve their drugability and developability (that is, they are developed to achieve better physicochemical and biopharmaceutical properties and more effective and safer profiles in animals). Scientists make and laboratory-test hundreds of different variations or "analogs" of the initial lead compounds to evaluate the structure–activity relationship (SAR) of the hits.

New techniques have revolutionized the ability of scientists to optimize potential drug molecules. These new techniques include magnetic resonance imaging, X-ray crystallography, and powerful computer modeling capabilities. These tools allow scientists actually to "see" the target in three dimensions. This allows them to design potential drugs to bind more powerfully to the active sites of the target where they can be most effective.

After optimization, scientists test the lead compounds in more sophisticated models including pharmacokinetics, pharmacodynamics, and toxicity. The optimal molecule selected from these assessments is then declared a new drug candidate and moves on to the next phase (development). If a program is successful, it may take a total of 3–6 years from target selection and validation through lead generation, lead optimization, and preclinical evaluation in animals to candidate selection for a potential new medicine.

In recent years, biologists have explored more therapeutic targets related to human diseases (for example, nuclear hormone receptor resources). This exploration led to the discovery of many drug candidates that are more highly specific and more active, and, consequently, can be delivered in lower doses than before. Examples include ligands for peroxisome proliferator-activated receptor, thyroid hormone receptor, mineralocorticoid receptor, and glucocorticoid receptor. The clinically efficacious dose for these compounds could be as low as a few milligrams or even micrograms. As expected, this leads to more challenges to pharmaceutical scientists during product development.

1.1.2 The Development Phase

A potential new drug candidate faces a well-defined clinical and product development process that has been refined over several decades. The development phase of a new drug product usually consists of two main activities: clinical evaluation (safety and efficacy), and product development (drug substance and dosage form). As shown in Table 1.1, the process can last as long as 7–9.5 years and the cost can be approximately 50% of the entire expense for development of a new medicine.[8] At this stage, some programs would be terminated for various reasons, such as lack of clinical efficacy, clinical toxicity, or drug developability.

Clinical investigations are clearly the most critical and demanding stage in the new drug development phase. When a drug company believes it has sufficient preclinical testing data to show that a new drug candidate is adequately safe for initial small-scale clinical studies, the company assembles and submits an investigational new drug (IND) application in the United States or a clinical trial application (CTA) in the European Union. The IND or CTA is the prerequisite for a company to obtain

TABLE 1.1 Clinical Evaluation and Drug Product Development Process for a New Drug Candidate

Attributes	Clinical Evaluation and Drug Product Development (IND)			NDA Submission and Approval	Process Validation and Launch
Length	6–7 years			0.5–2 years	0.5 year
No. of compounds	20	4	1–2	1	1
Percentage of total expense	5.8	11.7	25.5	6.9	
Clinical development	Phase I	Phase II	Phase III		
	• 20–100 healthy volunteers. • SDSS/MDSS • Safety and pharmacokinetic profiles	• 100–500 patients • Proof-of-concept • Efficacious dose range finding • Possible short-term side effects	• 1000–5000 patients. • Efficacy and safety evaluation • Randomized, double-blind placebo-controlled studies (two required) against a standard comparator	Submit clinical data package	Develop the plan for phase IV clinical study, i.e. postmarketing surveillance

Product development	• Design API synthesis route • Develop simple formulation for phase I clinical trials • Manufacture GMP materials	• Optimize API synthetic process • Develop commercial prototype dosage forms • Develop analytical method and control strategy • Supply clinical trial materials	• Scale-up and manufacture API on large scale • Optimize/scale-up commercial dosage form, manufacturing process and finalize control strategy • Prepare three registration batches • Supply clinical trial materials	Submit chemistry manufacturing control information	• ≥3 batches produced in manufacturing sites per proposed validation protocol • Develop/implement line extension strategy
Regulatory affairs	• Review preclinical/animal testing and plan for clinical testing • Approve to test the drug candidate in humans			• Review all clinical and preclinical findings, proposed labeling and manufacturing plans • Solicit opinion of an independent advisory committee • Determine if the drug can be approved for patients to use	

regulatory permission to begin testing a new drug in human subjects. Although there is no regulation that mandates a specific clinical trial structure and design, clinical evaluation of a new drug most often proceeds in at least three phases:

- *Phase I*—phase I trials consist of the cautious use of a new drug in 20–100 normal human volunteers to gain basic safety and pharmacokinetic information. The trials include a single-dose safety study (SDSS) and multiple dose safety study (MDSS). The main goal of a phase I trial is to discover if the new drug is safe in humans. These studies help scientists determine toxicity, absorption, metabolism, elimination, and other pertinent pharmacological actions, and to find the safety dosing range. Recently, the U.S. Food and Drug Administration (FDA) endorsed "microdosing," or the "phase 0 trial," which allows scientists to test a small drug dose in fewer human volunteers to quickly weed out drug candidates that are metabolically or biologically ineffective.[8]
- *Phase II*—during phase II, the drug candidate is given to a small number of patients—100–500—who have the disease or condition under study. Phase 2 trials give additional safety data, and provide the first indication of a drug's clinical effectiveness in its proposed use. Clinical researchers strive to understand some fundamental questions about the new drug: Is the drug working by the expected mechanism? Does it improve the disease condition? What are the effective dose range and dosing regime? If the new drug continues to show promise, the new drug moves into much larger phase III trials.
- *Phase III*—in phase III trials, the new drug is used in a significantly larger group of patients (about 1000–5000) who suffer from the condition that the drug is proposed to treat. This phase of clinical evaluation is key in determining whether the drug is safe and effective. It also provides the information for labeling instructions to ensure proper use of the drug. Phase III trials are both the costliest and longest trials. Hundreds of clinical sites (centers) around the United States and the world participate in the trials to get a large and diverse group of patients. Certain phase III trials, called "pivotal" trials, will serve as the primary basis for the drug approval. These studies must meet more rigorous standards, such as having a randomized, double-blind placebo-controlled study design, or having a comparator. Two pivotal clinical trials are required for a new drug application (NDA) with a regulatory agency.

The formulation, manufacturing process, analytical development, and long-term toxicology studies in animals are parallel to the clinical investigation (Table 1.1). Clinical trial materials should be developed, manufactured, tested, and released before conducting a phase I clinical trial. Process chemists may redesign the synthetic route for the drug candidate to meet the requirements of large-scale production in a pilot plant. Preformulation scientists complete the activities of salt selection,

polymorphism studies, and physicochemical characterization. Formulation scientists develop less time-consuming formulations, such as drug-in-bottle or drug-in-capsule, for the first human dose (FHD) clinical trials.[9]

If a drug candidate survives phase I trials, the process chemists start to optimize the synthetic process for the drug substance and the formulation scientists develop near-market-image dosage forms for phase II clinical trials. Preliminary control strategies for both drug substance and drug product are developed.

Following successful phase II clinical trials, the manufacture of the drug substance is scaled up to meet commercialization needs. In addition, the prototype formulation and process is optimized and scaled up to greater than one-tenth of the commercial batch size.

The optimized formulation then is prepared for phase III pivotal clinical trials. Followed by manufacturing process optimization and scale-up, the three batches of the drug product are manufactured for primary stability evaluation at product launch sites. The information on the manufacture, scale-up, control, and stability is used for product registration with regulatory agencies.

During development, pharmaceutical scientists work to achieve an ideal drug product—one that is bioavailable after administration; physically/chemically stable through its shelf-life; and able to be manufactured reproducibly and reliably with high quality.

Upon completion of preclinical, clinical, and drug product development, the drug company submits to the FDA for approval an NDA containing a meticulous, well-indexed, comprehensive, and readable document. The document should satisfy the requirements of the Food, Drug, and Cosmetic Act and the code of Federal Regulations (CFR) used by the FDA in the review and approval of safe and effective drug products in the United States. The FDA's NDA review process may last approximately two years. Multiple review teams are involved in the review process including:

- clinical reviewer;
- pharmacology/toxicology reviewer;
- chemistry reviewer;
- statistical reviewer;
- microbiology reviewer;
- biopharmaceutics reviewer.

The NDA filing also triggers a division request for FDA field offices to conduct a preapproval inspection of the manufacturing facilities of the drug company (sponsor). During this check, FDA inspectors exam a sponsor's production facilities to audit sponsor statements and commitments made in the NDA against actual manufacturing practices employed by the sponsor.

During the drug review process, the FDA may seek advice and comment from the members of its drug advisory committees. The expert committees provide the agency with independent, nonbinding advice and recommendations.

At the end of the review process, the agency issues one of three letters: approval, approvable, or not-approvable. An approval letter means that the agency formally approves the new drug for marketing. An approvable letter most likely indicates that the sponsor must make certain revisions or submissions to the NDA, and probably submit final printed labeling before the agency grants marketing authorization. A not-approvable letter states that the agency cannot approve the NDA and identifies the relevant deficiencies.

The development phase for low-dose drug products is similar to any other drug product. At a minimum, the drug product developed should be clinically efficacious, safe, and chemically/physically stable no matter how low the dose strength. Needless to say, scientists who work in chemistry, manufacture, and control (CMC) encounter even more challenges. Therefore, this book focuses on strategies and solutions to the challenges from both theoretical and practical aspects.

1.2 CHALLENGES AND STRATEGIES IN DEVELOPMENT OF LOW-DOSE DRUG PRODUCTS

Over the last 15 years, the pharmaceutical industry has discovered and developed increasingly more low-dose drug products. Table 1.2 shows some low-dose drug products from the *Physician's Desk Reference*.[10] The dose strength of a low-dose product can be as low as 0.25 μg. Dosage forms include tablet, hard gelatin capsule, and soft elastic capsule; product types include both mono- and combo-drug substance(s). More than a few therapeutic areas use low-dose drug products.

Although development of new normal-dose and low-dose drug products follows a similar path (as discussed in the previous section), the increase in potency and decrease in dose with low-dose drug products creates increasing challenges. In particular, pharmaceutical scientists and production operators must meet the stringent regulatory standards required for formulation, manufacturing process, and analytical chemistry.

From a formulation perspective, a low-dose drug product means low drug concentration, or low drug load, which can be less than 0.01% (w/w). In other words, the low-dose formulation likely has a very high ratio of excipients to drug substance. These characteristics present many hurdles during formulation and process development, including:

- difficulty achieving content uniformity due to low drug concentration;
- low potency due to manufacturing loss;
- instability due to the huge ratio of excipients to drug substance (which increases the likelihood of incompatibility);
- chemical instability due to a micronized drug having greater surface exposure to excipients, moisture, and manufacturing equipment;
- instability due to physical transformation to a less stable solid form during manufacture or long-term storage.

TABLE 1.2 Marketed Oral Solid Low-Dose Drug Products

Brand Name	Chemical Name	Dose Strengths	Dosage Form	Indication	Pharmacological Action Mechanism	Ingredients	Manufacturer
Flomax®	Tamsulosin HCl	0.4 mg	Capsule	Benign prostatic hyperplasia	$Alpha_{1A}$ adrenoceptor antagonist	Methacrylic acid copolymer, polysorbate 80, SLS, MCC, triacetin, calcium stearate, talc	Boehriner Ingelheim
Avodart™	Dutasteride	0.5 mg	SEC	Benign prostatic hyperplasia	A selective inhibitor of both the type 1 and type 2 isoform of steroid 5α-reductase	Mono-di-glycerides of caprylic/capric acid, butylated hydroxytoluene	Glaxosmithkline (GSK)
Mavik®	Trandolapril	1, 2, 4 mg	Tablet	Hypertension	The ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor	Corn starch, croscarmellose sodium, hypromellose, iron oxide, lactose, povidone, sodium stearyl fumarate	Abbott Laboratories
Tarka®	Trandolapril/verapamil HCl	1 mg/240 mg 2 mg/180 mg 2 mg/240 mg 4 mg/240 mg	Extended release tablet	Hypertension	ACE inhibitor	Corn starch, dioctyl sodium sulfosuccinate, ethanol, HPC, HPMC, lactose, magnesium stearate, MCC, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, talc, sytnetic iron oxides, titanium dioxide	Abbott Laboratories
Catapres®	Clonidine HCl USP	0.1, 0.2, 0.3 mg	Tablet	Hypertension	Alpha-adrenoreceptor agonist	Colloidal silicon dioxide, corn starch, dibasic calcium phosphate, gelatin, glycerin, lactose, magnesium stearate, methylparaben, propylparaben	Boehriner Ingelheim (Mylan)

(*Continued*)

TABLE 1.2 *Continued*

Brand Name	Chemical Name	Dose Strengths	Dosage Form	Indication	Pharmacological Action Mechanism	Ingredients	Manufacturer
Arimidex®	Anastrozole	1 mg	Tablet	Breast cancer	A selective nonsteroidal aromatase inhibitor	Lactose, magnesium stearate, HPMC, PEG, povidone, sodium starch glycolate, titanium dioxide	AstraZeneca
Avandamet™	Rosiglitazone maleate/ met-formin HCl	1 mg/500 mg 2 mg/500 mg 2 mg/1000 mg 4 mg/500 mg 4 mg/1000 mg	Tablet	Type II diabetes	Rosiglitazone: insulin sensitizing agent; metformin: decreasing endogenous hepatic glucose production	Hypromellose 2910, lactose monohydrate, magnesium stearate, MCC, PEG 400, povidone, sodium starch glycolate	GSK
Prandin®	Repaglinide	0.5, 1, 2 mg	Tablet	Type II diabetes	Stimulating the release of insulin from the pancreas. ATP-dependent K-channel blocker	Calcium hydrogen phosphate, MCC, maize starch, polacrilin, potassium, povidone, glycerol (85%), magnesium stearate, meglumine, poloxamer	Novo Nordisk
DDAVP®	Desmopressin acetate	0.1 mg, 0.2 mg	Tablet	Central diabetes insipidus	A synthetic analog of the natural pituitary hormone 8-arginine vasopressin	Lactose, potato starch, povidone, magnesium stearate	Aventis
ACTIQ®	Fentanyl citrate USP	200, 400, 600, 800, 1200, or 1600 μg	Oral Trans-mucosal	Analgesia	Opioid mu-receptor agonist	Hydrated dextrates, citric acid, dibasic sodium phosphate, berry flavor, magnesium stearate, modified food starch, confectioner's sugar	Cephalon
AMERGE®	Naratriptan HCl	1, 2.5 mg	Tablet	Migraine	5-HT1D/1B receptor agonist	Croscarmellose sodium, hypromellose, lactose, magnesium stearate, MCC	GSK

ORAP®	Pimozide	1, 2 mg	Tablet	Tourette's disorder	Blockade dopaminergic receptors in the CNS	Calcium stearate, MCC, lactose anhydrous, corn starch	Gate
Lanoxicap®	Digoxin	50, 100, 200 μg	SEC	Heart failure, atrial fibrillation	Na-K ATPase inhibitor	PEG 400, ethyl alcohol, propylene glycol, purified water	GSK
Tikosyn®	Dofetilide	125, 250, 500 μg	Capsule	Maintenance of normal sinus rhythm and conversion of atrial fibrillation/ flutter	Cardiac ion channel blocker/ antiarrhythmic drug	MCC, corn starch, silicon dioxide, magnesium stearate	Pfizer
LOTRONEX®	Alosetron HCl	0.5, 1 mg	Tablet	For women with severe diarrhea–predominant irritable bowl syndrome	A potent and selective 5-HT3 antagonist	Lactose anhydrous, magnesium stearate, MCC, pregelatinized starch	GSK
Mirapex®	Pramipexole 2HCl	0.125, 0.25, 0.5, 1 and 1.5 mg	Tablet	Parkinson's disease	Nonergot dopamine agonist	Mannitol, corn starch, colloidal silicon dioxide, povidone, magnesium stearate	Boehriner Ingelheim
Requip®	Ropinirole HCl	0.25, 0.5, 1, 2, 3, 4, 5 mg	Tablet	Parkinson's disease	A nonergoline dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D2 and D3 dopamine receptor subtypes	Croscarmellose Na, lactose hydrous, magnesium stearate, MCC	GSK
Permax®	Pergolide mesylate	0.05, 0.25, 1 mg	Tablet	Parkinson's disease	D1 and D2 dopamine receptor agonist	Croscarmellose Na, lactose, magnesium stearate, povidone, L-methionine	Valeant Pharmaceuticals

(*Continued*)

TABLE 1.2 *Continued*

Brand Name	Chemical Name	Dose Strengths	Dosage Form	Indication	Pharmacological Action Mechanism	Ingredients	Manufacturer
Risperdal® M-TAB	Risperidone	0.5, 1, 2 mg	Orally disinte-grating tablet	Schizophrenia	A selective monoaminergic antagonist (5HT2, dopamine type 2 (D2), α1, and α2 adrenergic, and H1 histaminergic receptors	Amberlite resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, peppermint oil	Janssen Pharmaceuticals
Risperdal®	Risperidone	0.25, 0.5, 1, 2, 3, 4 mg	Tablet	Schizophrenia	A selective monoaminergic antagonist (5HT2, dopamine type 2 (D2), α1 and α2 adrenergic, and H1 histaminergic receptors	Colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, MCC, propylene glycol, sodium lauryl sulfate, corn starch	Janssen Pharmaceuticals
Decadron®	Dexametha-sone USP	0.5, 0.75, 4 mg	Tablet	Replacement therapy in adrenocortical deficiency, anti-inflammatory	A synthetic adrenocortical steroid-potent anti-inflammatory effects	Calcium phosphate, lactose, magnesium stearate, starch	Merck & Co. (Roxane Laboratories and Par)
Propecia®	Finasteride	1 mg	Tablet	Male pattern hair loss	A specific inhibitor of steroid type II 5α-reductase	Lactose monohydrate, MCC, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, Hypromellose 2910	Merck & Co.

Dostinex®	Cabergolin	0.5 mg	Tablet	Hyperprolactin-emic disorders	A dopamine receptor (D2) agonist in CNS	Leucine USP, lactose	Pfizer
ProSom™	Estazolam	1, 2 mg	Tablet	Insomnia		Lactose, povidone, colloidal silicon dioxide, stearic acid, sodium starch glucolate	Abbott Laboratories
Xanax®	Alprazolam USP	0.25, 0.5, 1, 2 mg	Tablet	Anxiety disorder	Binding at stereo specific receptor/CNS active agent	Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, sodium benzoate	Pfizer (Mylan)
Hivid®	Zalcitabine	0.375, 0.75 mg	Tablet	HIV	A synthetic nucleoside analog (DNA replacement)	Lactose, MCC < croscarmellose Na, magnesium stearate, hypromellose, PEG, polysorbate 80	Roche
Klonopin®	Clonazepam	0.5, 1, 2 mg	Tablet	Panic disorder		Lactose, magnesium stearate, MCC, corn starch	Roche
Klonopin® Wafers	Clonazepam	0.125, 0.25, 0.5, 1 mg	Orally disinte-grating tablet	Panic disorder	Gamma aminobutyric acid (GABA) enhancement	Gelatin, mannitol, methylparaben sodium, propylparaben sodium, xanthan gum	Roche
Kytril®	Granisetron HCl	1 mg	Tablet	Nausea and vomiting	A selective 5-HT3 receptor antagonist	Hypromellose, lactose, magnesium stearate, MCC, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium oxide	Roche
Agrylin®	Anagrelide HCl	0.5, 1 mg	Capsule	Thrombo-cythe-mia and myelo-pro-liferative disorders	Inhibition of cAPM phosphodiesterase, ADP-collagen-induced platelet aggregation	Anhydrous lactose, crospovidone, lactose monohydrate, magnesium stearate, MCC, povidone	Shire

(*Continued*)

TABLE 1.2 *Continued*

Brand Name	Chemical Name	Dose Strengths	Dosage Form	Indication	Pharmacological Action Mechanism	Ingredients	Manufacturer
Synthroid®	Levothyroxine sodium	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 μg	Tablet (USP)	Hypothyroidism, pituitary TSH suppression	Thyroid receptor agonist	Acacia, confectioner's sugar, lactose monohydrate, magnesium stearate, povidone, talc	Abbott Laboratories
Cytomel®	Liothyronine Na (T3)	5, 25, 50 μg	Tablet	Hupothyroidism, euthyroid goiters	Hormone, TSH suppressant	Calcium sulfate, gelatin, starch, stearic acid, sucrose, talc	King Pharmaceuticals
Hectorol®	Doxercal-ciferol	0.5, 2.5 μg	SEC	Secondary hyperparathyroidism	Vitamin D2 analog to regulate blood calcium	Fractionated triglyceride of coconut oil, ethanol, and butylated hydroxyanisole	Bone Care International
Rocaltrol®	Calcitriol	0.25, 0.5 μg	SEC	Secondary hyperparathyroidism and resultant metabolic bone disease, hypocalcemia	A synthetic vitamin D analog	A fractionated triglyceride of coconut oil	Roche
PLAN B®	Levonorgestrel	0.75 mg	Tablet	Emergency contraceptive	A synthetic progestogen	Colloidal silicon dioxide, potato starch, gelatin. Magnesium stearate, talc, corn starch, lactose monohydrate	Barr Laboratories
Seasonale®	Levonorgestrel/ ethinyl estradiol	0.15 mg/0.03 mg	Tablet	Oral contraceptive	Inhibition of ovulation	Anhydrous lactose, HPMC, MCC, PEG, magnesium stearate, polysorbate 80, titanium dioxide	Barr Laboratories

Yasmin®	Drospirenone/ ethinyl estradiol	3 mg/0.03 mg	Tablet	Oral contraceptives	Suppression of gonadotropins	Lactose monohydrate, corn starch, modified starch, povidone 25000, magnesium stearate, HPMC, Macrogol 6000, talc, titanium dioxide, ferric oxide pigment, yellow NF	Berlex
Cenestin®	Synthetic conjugated estrogens A (a blend of nine synthetic estrogenic substances)	0.3, 0.45, 0.625, 0.9, 1.25 mg	Tablet	Estrogen replacement therapy	Estogen receptors (two nuclear receptors identified)	Ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, PEG, polysorbate 80, pregelatinized starch, titanium dioxide, triethyl citrate	Duramed Pharmaceuticals
VAGIFEM®	Estradiol	25 μg	Vaginal tablet	Atrophic vaginitis	Estrogen receptor agonist	Hypromellose, lactose monohydrate, maize starch, magnesium stearate	Novo Nordisk
Ortho Micronor®	Norethindrone	0.35 mg	Tablet	Prevent conception	Suppressing ovulation/ progestin receptor	Lactose, magnesium stearate, povidone, starch	Ortho-McNeil
Estratest® H.S.	Esterified estrogens/ methyltesto-sterone	0.625 mg/1.25 mg	Capsule	Vasomotor symptoms from menopause	Estrogen/testosterone receptor	Acacia, calcium carbonate, citric acid, colloidal silicon dioxide, gelatin, lactose, magnesium stearate, MCC, glaze, povidone, sodium benzoate, sodium bicarbonate, carboxymethylcellulose sodium, sorbic acid, starch, talc, titanium dioxide, tribasic calcium phosphate, alcohol denatured 3A	Solvay Pharmaceuticals

(*Continued*)

TABLE 1.2 *Continued*

Brand Name	Chemical Name	Dose Strengths	Dosage Form	Indication	Pharmacological Action Mechanism	Ingredients	Manufacturer
Femtrace®	Estrodiol acetate	0.45, 0.9, 1.8 mg	Tablet	Vasomotor symptom from menopause	Estrogen receptor	Povidone, lactose monohydrate, MCC, croscarmellose Na, silicon dioxide, magnesium stearate	Warner Chilcott
Alesse®-28	Lenonorgestrel and ethinyl estradiol	0.10 mg/0.02 mg	Tablet	Oral contraceptives	Estrogen/progestin receptor	Cellulose, hypromellose, lactose, magnesium stearate, polacrilin potassium	Wyeth
Lo/Ovral®-28	Norgestrel and ethinyl estradiol	0.3 mg/0.03 mg	Tablet	Oral contraceptives	Estrogen/progestin receptor	Cellulose, lactose, magnesium stearate, polacrilin potassium	Wyeth
Ovrette®	Norgestrel	0.075 mg	Tablet	Oral contraceptive	progestin receptor	Cellulose, lactose, magnesium stearate, polacrilin potassium	Wyeth
Premarin®	Conjugated estrogens USP	0.3, 0.45, 0.625, 0.9, 1.25 mg	Tablet	Vasomotor symptom from the menopause	Estrogen receptor	Calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, hypromellose, glaze, PEG, stearic acid, sucrose, tinanium dioxide	Wyeth

Low potency, the most common issue for a low-dose drug product, is most likely related to platform-dependent manufacturing loss. Physical properties of the drug substance (particle size, shape, and density) and poor mixing of trace amounts of drug substance with excipients can cause lack of content uniformity. Product instability can be associated with impurities in excipients, physical transformation of drug substance to a less stable form during manufacture, and nonoptimal container-closure systems. Thus, formulation design, optimization, and selection of manufacturing platform become a different set of challenges for a low-dose drug product in comparison with a conventional drug product.

There are also enormous challenges for analytical chemists in analytical method development, method validation, and control of product quality. It can be very difficult to develop robust methods for assaying trace amounts of drug substance and impurities in dosage forms, resolving testing interferences of impurities from excipients, and determining the residue of drug substance on manufacturing equipment after cleaning. Extraction of trace amounts of drug from the formulation matrix and maintaining drug stability in the testing medium can also be very challenging. Analytical chemists have to make extra efforts to improve the method sensitivity and selectivity of the equipment used. For example, higher sensitivity for impurity testing using high-pressure liquid chromatography (HPLC) can be obtained from the following approaches:

- sample preparation (derivatization and preconcentration techniques);
- enhanced detection systems (electrochemical/fluorescent detector, mass spectrometry);
- large volume injection loop.

For in vitro dissolution methods, a small volume vessel using 100 mL of medium can also offer a significant sensitivity gain. Nevertheless, equipment modification may be needed to develop analytical methods for low-dose drug products.

In addition to technical challenges in formulation and analytical development, developing a containment strategy is another issue as the exposure limits for highly potent compounds become increasingly low. Product development areas, manufacturing areas, and analytical laboratories can encounter containment control issues. Containment control in pharmaceutical manufacturing and R&D processes is very important in minimizing exposure potential for workers involved in the process, controlling migration of materials for potential cross-contamination, and preventing any leakage of materials from environmental contamination in water and air.

Therefore, the book will cover a wide range of issues associated with low-dose drug product development, including drug substance, formulation design, manufacturing process, analytical control, regulatory consideration, and containment. Together, this book will result in overall scientific understanding of "state-of-the-art" low-dose oral drug product development. Our approach is to teach graduate students, pharmaceutical scientists, process engineers, process chemists, analytical

chemists, and regulatory scientists what to do and how to do appropriate CMC activities. However, this book covers only oral solid dosage forms for low-dose drug products. Solution and soft-elastic capsule formulation development of low-dose products will be, for sure, the focus and interest of other pharmaceutical scientists.

1.3 SUMMARY

Since the beginning of this decade, research and development of new medicines in today's pharmaceutical industry have faced increasing challenges. Developing low-dose drug products from candidate selection to market poses a different set of challenges to pharmaceutical scientists in comparison with developing "normal"-dose products. These challenges include continuing to improve existing processes and introducing new cutting-edge technologies, worthy of the best minds and most innovative scientists.

Regardless of the challenges, involvement in new drug product development aimed at bettering human health is one of the greatest careers. The goal of pharmaceutical scientists is to reduce product development time and control development costs effectively without compromising safety and quality. In doing this, pharmaceutical scientists help achieve the goal of providing innovative, tailored, and affordable therapies to patients as early as possible.

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