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Ram Sasisekharan
Sau L. Lee
Amy Rosenberg
Larry A. Walker *Editors*

The Science and Regulations of Naturally Derived Complex Drugs

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Ram Sasisekharan · Sau L. Lee ·
Amy Rosenberg · Larry A. Walker
Editors

The Science and Regulations of Naturally Derived Complex Drugs

Editors
Ram Sasisekharan
Department of Biological Engineering
Koch Institute of Integrative Cancer Research
Massachusetts Institute of Technology
Cambridge, MA, USA

Amy Rosenberg
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, USA

Sau L. Lee
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, USA

Larry A. Walker
Director Emeritus
National Center for Natural Products Research, School of Pharmacy
University of Mississippi
Oxford, MS, USA

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Chapter 1
Evolving Challenges in Developing Naturally-Derived Complex Mixtures into Drugs: U.S. Experience and Perspective

Adam C. Fisher and Sau L. Lee

Abstract Naturally-derived complex mixture drugs are the drugs derived from natural sources with highly heterogeneous molecular components. In such drugs, the composition of molecules in a population may be variable and it may even be difficult to define all components of a mixture. Even active components can be unknown or poorly characterized. As compared to traditional homogeneous drugs, these complex mixture drugs can face unique challenges during development and throughout the drug product lifecycle. As the understanding and science surrounding the analysis of these drugs advances, so too do the approaches to development. Scientific and regulatory approaches for these drugs may take into account prior human experience, current capabilities in characterization, ability to control raw material and manufacturing, therapeutic consistency, pharmaceutical equivalence, and bioequivalence. As more advanced analytics are developed and implemented, the ability to ensure the quality, safety, and efficacy of complex mixture drugs improves. This chapter introduces the major themes of development for these drugs including regulatory frameworks, biological activity, characterization, raw material and manufacturing control, impurities and immunogenicity, and clinical considerations. The challenges in developing natural-derived complex mixture drugs illustrate lessons of the past that can inform drug development in the future.

Keywords Drug development · Complex mixtures · Naturally-derived · Quality control · Equivalence

1.1 Introduction

Drugs derived from natural sources are some of the oldest medicines known to man. Naturally-derived drugs are sourced from raw materials of biological origin found in nature. Prior to 1869 and the discovery of the first synthetic drug, chloral hydrate, nearly all medicinal drugs came from natural sources such as plants and

A. C. Fisher · S. L. Lee (✉)
Office of Pharmaceutical Quality, CDER/FDA, Maryland, USA
e-mail: sau.lee@fda.hhs.gov

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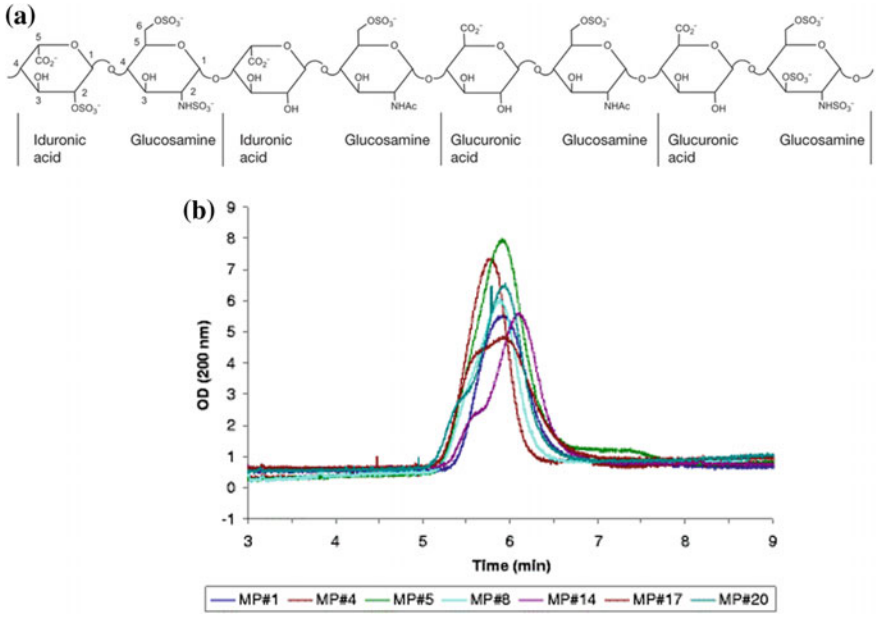

Fig. 1.1 Complexity of heparin . **a** Heparin is a mixture of oligosaccharides obtained from animal tissues, typically porcine intestinal mucosa. The manufacturing process of heparin involves several basic steps, including preparation of the animal tissue, extraction of heparin from the animal tissue, recovery of raw or crude heparin, purification of heparin, and recovery of purified heparin. Repeating disaccharide building blocks in heparin are composed of glucosamine and a uronic acid (either iduronic or glucuronic acid) with the linkage sequence: ([1–4] α-D-glucosaminyl–[1–4] β-D-hexuronosyl)$_n$. The chemical diversity of disaccharide building blocks arises not only from two different uronic acid components (iduronic or glucuronic acid), but also from different modifications at four possible positions of the disaccharide building blocks. For example, the second carbon (C2) of the uronic acid and C3 and C6 of the glucosamine can be O-sulfated. In addition, C2 of the glucosamine can be N-acetylated or N-sulfated. The different arrangements of these chemically diverse disaccharide building blocks give rise to the distribution of disaccharide building block sequences throughout heparin chains. Figure adapted from [5]. **b** A plot showing both the complexity and variability of heparin via the overlay of capillary electrophoresis data from heparins from seven different sources collected by the FDA in 2009. Figure adapted from [6]

fungi [1]. Notably, one of the earliest known medicines, dating to ~3000 BC, was the juice of *Papaver somniferum* (opium poppy plant) which contained morphine [2]. As there was limited technical ability to highly purify any one component from a natural source, nearly all historical drugs were mixtures of some fashion. Thus, closely related to naturally-derived drugs are complex mixture drugs, which contain a heterogeneous population of multiple molecular components with intra- or intermolecular heterogeneity (see Fig. 1.1 for an example). In these cases, the composition of individual molecules in a population may be variable, and it is often difficult to define all chemical components of the mixture. In some cases, even the active component(s) can be unknown or poorly characterized.

Before modern times, patients routinely relied on multicomponent medicines obtained from natural sources. However, the modern pharmaceutical industry largely focuses on single-component drugs, which are highly purified and very often chemically synthesized. Paradoxically, an increasing number of diseases are treated with combinations of single-component drugs [3]. The paradigm of assigning a defined biological activity to a specific compound has somewhat hindered the acceptance of multicomponent drugs in Western medicine. Eastern medicine, including traditional Chinese and Ayurvedic medicine, has been more accepting of naturally-derived mixture drugs and even acknowledges advantages in preventing or controlling complex disease mechanisms with multicomponent medicines.

Although natural products are more associated with Eastern medicine, roughly 6% of all drugs approved by the U.S. Food and Drug Administration (FDA) are natural products, either highly purified or mixtures [4]. Though many drugs can technically be considered heterogeneous, the discussion herein will focus on the scientific considerations for naturally-derived complex mixture drug substances that are derived from plants or animals without genetic modification (see Fig. 1.2 and Table 1.1). However, drugs not strictly meeting this classification may still be discussed when scientific challenges are shared. This may include, for example, glatiramer acetate,

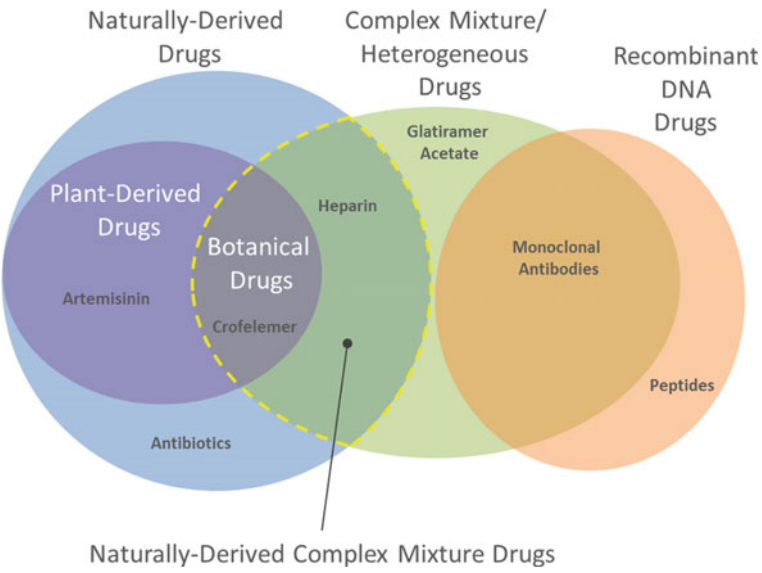

Fig. 1.2 This book focuses on the scientific considerations for developing naturally-derived complex mixture drugs (outlined with yellow dotted line) which are derived from plants or animals without genetic modification. Though many drugs that fall in all of the groupings presented share some similar scientific challenges, this book will address the challenges associated with the development of naturally-derived complex mixture drugs. Where the scientific and development issues are relevant, other types of drugs will be discussed as well. Note that the figure does not depict strict regulatory or scientific definitions and the sizes and shapes in the figure are arbitrary

which is not naturally-derived, or substances derived from recombinant DNA technology, that are considered biotechnology products and can be heterogeneous.

1.2 Evolving Regulatory Landscape

The history of regulating naturally-derived mixture drug products is nearly as complex as the drugs themselves. In 1906, comprehensive federal legislation in the USA, the Pure Foods and Drugs Act, was passed to address the safety and quality of drug products [7]. Following a 1937 incident in which 107 people were killed by Elixir Sulfanilamide, the Food, Drug, and Cosmetic (FD&C) Act of 1938 was passed to ensure that new drugs are safe before entering the market [8]. Shortly after in 1939, bovine-derived heparin became one of the first naturally-derived mixture drugs approved by the FDA [9]. A few years later in 1942, another complex mixture drug was approved (see Table 1.1). This drug was Premarin, which contains as an active ingredient a naturally-derived mixture of conjugated estrogens extracted from the urine of pregnant mares [10]. The regulation of conjugated estrogen products took many unexpected turns over the ensuing decades. In 1942, the FD&C Act required only the proof of safety of a product, not of efficacy. This was changed in 1962 with amendments to the FD&C Act, and in 1972, the FDA announced that Premarin was effective in the treatment of the symptoms of menopause and probably effective "in selected cases of osteoporosis" [11]. The circumstances changed greatly again in 1986 when the FDA announced that estrogens were effective in treating bone loss associated with osteoporosis [12]. This turned Premarin into a premier treatment for a chronic disease and with an expanding market came added scrutiny. At this point, there were numerous approved generic conjugated estrogen tablets. However, there were observed disparities between Premarin and its generics and the true complexity of the mixture (i.e., 60 or more steroidal components with biological activity) was only beginning to be uncovered [13]. In 1991, the FDA took the decisive action of withdrawing the approval of all generic conjugated estrogen tablets [14]. The debate regarding the appropriate means to approve generic conjugated estrogens raged well into the late 1990s with the FDA determining in 1997 that a generic version of Premarin would not be approved unless the active ingredients had been sufficiently defined and proven to be the same as that in Premarin [15]. Such proof was elusive as there was a limited technical ability to characterize components of the mixture, although two major components make up the majority of the mixture (estrone sulfate and equilin sulfate). It was also argued that other minor components may have potential pharmacological effects, contributing to the overall safety and efficacy of the drug. As a result, over 70 years have passed since Premarin's approval under the FD&C Act and there are presently no approved generic conjugated estrogens tablets on the U.S. market. The case of conjugated estrogens is a vivid display of how changing scientific knowledge creates regulatory challenges that can dramatically affect the lifecycle and trajectory of a complex mixture drug.

Table 1.1 Examples of U.S. FDA approvals of complex mixture drugs[1]

Product	Description	Use	First FDA Approval
Heparin	Mixture of animal-derived (bovine/porcine) polysaccharides	Anticoagulant; prevents clots in blood vessels	1939 (Liquaemin)
Conjugated estrogens	Hormone mixture derived from the urine of pregnant mares	Treats symptoms of menopause and prevents osteoporosis	1942 (Premarin)
Hyaluronidase	Complex substance harboring enzymes derived from animal testes (bovine/porcine/ovine)	Increases the absorption and dispersion of injected drugs, as a tissue permeability modifier	1948 (Wydase)
Protamine sulfate	Peptide mixture from the sperm of salmon and other species of fish	Treats heparin overdose	1969 (Protamine sulfate)
Hetastarch	Starch derivative from polysaccharides (amylopectin) of natural products, including corn	Expands intravenous plasma volume	1972 (Hespan)
Menotropins	Partially characterized mixtures of gonadotropins from the urine of postmenopausal women	Treats infertility in women	1975 (Pergonal)
Bovine surfactant extract	Bovine lung extract that contains phospholipids, neutral lipids, fatty acids, and proteins	Lowers the surface tension of the mucoid layer lining the pulmonary alveoli	1991 (Survanta)
Low Molecular Weight Heparins	Depolymerized heparin molecules (bovine/porcine)	Anticoagulant; prevents clots in blood vessels	1993 (Enoxaparin/lovenox)
Pentosan Polysulfate	Polysaccharide mixture derived from beechwood	Treats bladder pain or discomfort associated with interstitial cystitis	1996 (Elmiron)
Glatiramer acetate[2]	Mixture of synthetic peptides	Treats relapsing forms of multiple sclerosis	1996 (Copaxone)
Omega-3-acid ethyl esters	Fatty acid ester mixture from multiple fish species	Reduces triglyceride levels in patients with severe hypertriglyceridemia	2004 (Lovaza)
Sinecatechins	Partially purified extract of green tea (*Camellia sinensis*) leaves	Treats external genital and perianal warts	2006 (Veregen)

(continued)

Table 1.1 (continued)

Product	Description	Use	First FDA Approval
Pancrelipase	Mixture of animal-derived (bovine/porcine) pancreatic enzymes	Treats exocrine pancreatic insufficiency	2009 (Creon)
Crofelemer	Oligomeric proanthocyanidin mixture from crude the flowering plant *Croton lechleri*	Relieves non-infectious diarrhea in adult patients with HIV/AIDS	2012 (Fulyzaq)

[1]Excludes: substances derived from fermentation and bacteria such as teicoplanin, substances derived from recombinant DNA technology, and PEGylated proteins
[2]Not naturally-derived, synthesized chemically

The regulatory approach for evaluating complex mixture products has evolved with time and has depended on the state of scientific knowledge at the time and, to a large extent, the ability to analyze the physicochemical properties of heterogeneous molecules. Take for example the case of pancrelipase, which is a porcine pancreas derived concentrate of pancreatic enzymes normally produced by the human pancreas. It is principally used to improve the digestion of fats, but also digests proteins, and carbohydrates in patients who do not produce sufficient levels of pancreatic enzymes, for example, due to cystic fibrosis [16]. Products containing pancrelipase were available prior to the FD&C Act in 1938 and were generally not regulated as new drugs, thus remaining available without regulatory approval for a considerable time. However, the FDA became aware that these unapproved products were causing problems for patients due to variability in the amounts of therapeutic enzymes. In 1990s, the FDA proposed rulemaking for pancrelipase products and concluded that: (i) an over-the-counter monograph would not be sufficient to regulate these as drug products; (ii) standardized enzyme bioactivity for each product would be necessary; and (iii) continuous physician monitoring of patients would be necessary to ensure safety and efficacy [17]. As a result, the FDA declared in 2004 that pancreatic enzyme products would be considered new drugs and should be available by prescription. This required manufacturers to obtain marketing approval of their pancrelipase products [18]. The first approved pancrelipase product in the USA to reach the market after the FDA declaration was Creon in 2009, over 70 years after passage of the FD&C Act [18].

As illustrated in the examples of pancrelipase and conjugated estrogen products, it is clear that the regulatory and scientific challenges surrounding complex mixture drugs are distinct from those of single-component drugs. These challenges span the drug product lifecycle (Fig. 1.3) which covers, in the context of this chapter, a period spanning early drug discovery to the first clinical trial to the approval of generic products. These challenges also change with evolving technology, an observation particularly pertinent in the current era of advanced analytics, omics, big data, and

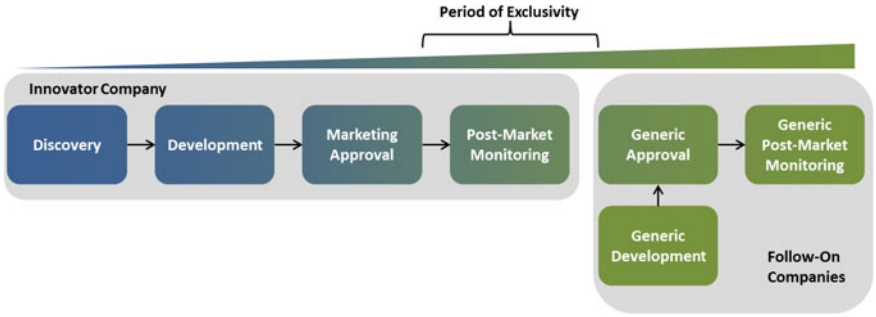

Fig. 1.3 Lifecycle of a drug product

data integration. The discussion below will provide a more in-depth overview of the scientific and regulatory challenges that can be encountered during different stages of the drug product lifecycle.

1.3 Challenges in Bringing Naturally-Derived Complex Mixtures to Market

The path for introducing a new drug product into the U.S. market typically begins with an Investigational New Drug Application (IND) which is a request to administer an investigational drug to humans in a clinical study context. During successive phases of IND studies, the clinical performance of the drug regarding safety and efficacy is elucidated. Once sufficient evidence is gathered to support the safety and efficacy of proposed drug product, a New Drug Application (NDA) that includes full information on chemistry, manufacturing and controls (CMC), bioavailability, packaging and labeling for both physician and consumer, and the results of any additional toxicological studies can be submitted to the FDA for the purpose of seeking regulatory approval to market the drug. Naturally-derived mixtures are expected to meet the same standards for safety, efficacy, and quality as single-component drugs. Thus, the general requirements and procedures for single-component drugs are applicable to naturally-derived mixtures. However, the unique characteristics of naturally-derived mixtures can pose challenges in different stages of the development program, and therefore, the scientific and regulatory issues surrounding developing naturally-derived mixtures into new drugs warrant special consideration.

1.3.1 Prior Human Experience

The amount of information needed to support an IND for a particular drug depends on several factors, including the extent of previous human-use experience and past clinical studies, the known or anticipated risks, and the development phase. Despite the fact that most naturally-derived mixtures are highly complex due to their heterogeneous nature, some of these mixtures were discovered long ago for medicinal use and/or have a substantial record of prior use by humans. The appropriate use of information pertaining to prior human experience with an investigational drug can play a significant role in the early development of products containing naturally-derived mixtures by reducing the need for new data to support the drug's safety for early phase clinical studies (e.g., a Phase I clinical study). For example, if the investigational drug is a naturally-derived mixture present in a dietary supplement that is legally marketed in the USA with no known safety issues, toxicity and CMC data needed to support the initiation of early phase clinical studies may be reduced. However, for products that are only available in foreign markets (e.g., traditional Chinese medicine or herbal medicine), the use of prior human experience to support early phase drug development may not be appropriate if data have not been acquired in a rigorous manner to bridge historical use to the clinical context. Such an analysis may not be straightforward and generally includes comparing the amount of raw material to the dose proposed in the clinical study, comparing the quality of the drug with that in traditional preparations, and assessing the relevance of prior use to the clinical setting.

1.3.2 Product Characterization

For single-component drugs, identification of the active ingredient is straightforward and can be achieved early in the development by analytical means (e.g., spectroscopic or chromatographic methods). However, in a naturally-derived mixture, the chemical components are not always known and, in particular, the active component(s) may not be identified. Similarly, the biological activity may not be well characterized. As such, it can be challenging to comprehensively characterize a mixture in early phase studies from both the technical and practical standpoints [19]. However, as mentioned above, some naturally-derived mixtures have been previously marketed or tested in humans. In these cases, comprehensive characterization may not be necessary in the early phase development from a safety and risk perspective.

The amount of characterization data needed for naturally-derived mixtures will increase through later phases of clinical development. This information becomes necessary as an investigational drug product draws closer to potential marketing approval. Approval will rely on the identification of product attributes and their impact on clinical safety and efficacy. In particular, understanding the linkage of late-phase (e.g., Phase III) clinical data with product attributes assures that a sufficient

control strategy is in place to ensure marketed products deliver the same therapeutic effect as products tested in the pivotal clinical studies. Fortunately, advances in analytical technologies have made such product understanding possible. It is becoming increasingly common that at least part of the naturally-derived mixture is well characterized and that some consistently present and active components are identified in the mixture. For example, the botanical drug crofelemer contains a mixture of proanthocyanidin oligomers derived from the red latex of the plant *Croton lechleri*. This mixture of oligomers varies in composition, sequence, and length. Advanced analytical methods revealed extensive information on the components of crofelemer, though they alone were insufficient to support characterization and quality control. In this case, a clinically relevant bioassay was needed to support approval [20].

1.3.3 Raw Material Control

For naturally-derived mixtures, raw material control is necessary to ensure product quality and consistency and thus the validity and reliability of clinical data. As the characteristics of naturally-derived mixtures largely depend on the source and quality of the raw materials, it is important that the clinical study materials not differ significantly in their quality. If they do, meaningful differences in clinical outcomes may manifest in successive clinical trials. If such a discrepancy exists, this may raise questions regarding the ability to control the consistency of critical quality attributes in the product.

Raw material control is also a key component of the control strategy to ensure consistent product quality. However, it should be noted that batch-to-batch variation (e.g., variations in chemical composition) is known to exist in naturally-derived mixture products. Therefore, in setting appropriate standards and limits for quality control of raw material, the impact of such variations on the therapeutic effect of the products needs to be considered. Obtaining such knowledge will require thorough product characterization, a clinically relevant bioassay, and/or clinical investigation (e.g., Phase III clinical studies) all utilizing multiple batches of product manufactured using different batches of raw material. This type of investigation, if designed and conducted properly, helps to identify which variations are clinically relevant and the range of variability sufficient to maintain a drug product's quality and clinical performance.

1.3.4 Quality Control and Therapeutic Consistency

Adequate quality control of naturally-derived mixture products is critical to ensure that the marketed product delivers therapeutic effects consistent with product batches tested in clinical studies (i.e., therapeutic consistency). In light of the difficulties discussed above, an approach for quality control of naturally-derived mixtures needs to

be based on the totality of evidence. Specifically, in addition to conventional CMC data, the approach should include raw material control, clinically relevant bioassay(s), and clinical data pertaining to clinical performance of multiple batches of the drug product. This information will help assess the effect of product variability on clinical performance and establish clinically relevant control criteria for raw material and product quality attributes. The degree of reliance on these other data for ensuring consistency of quality depends on the extent to which the naturally-derived mixture can be characterized and quantified. The totality-of-evidence approach was adopted to ensure the consistency of product quality for both FDA-approved botanical products, Veregen and Fulyzaq [20]. More details regarding this approach are described in Chap. 10.

1.4 Challenges in Developing Generic Naturally-Derived Mixture Products

Whereas new drugs are generally required to show safety and efficacy through clinical studies, a generic drug relies on the prior findings of safety and efficacy for an innovator product and product quality similarity of generic to innovator to obtain approval. That is, clinical studies are often not required. In order to understand the challenges of developing generic complex mixture drugs, it is important to first understand a regulatory framework. In the USA, an Abbreviated New Drug Application (ANDA) seeks the approval to market a generic drug product following expiry of the market exclusivity of the innovator product. For approval, the generic drug product in the ANDA must show therapeutic equivalence to an approved reference listed drug (RLD). This requires proof of both pharmaceutical equivalence and bioequivalence. Pharmaceutical equivalence requires that the generic drug product contains the same active ingredient(s) as the RLD; be identical in strength, dosage form, and route of administration; and meet compendial or other applicable standards of strength, quality, purity, and identity [21]. Bioequivalence generally refers to the absence of a significant difference in the rate and extent to which the active ingredient in a pharmaceutically equivalent drug product becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions [21]. The fundamental premise of the ANDA approval pathway is that the generic and the innovator products can be substituted for each other and expected to have the same clinical effect and safety profile. Since naturally-derived mixtures contain many chemical components and often have poorly defined and characterized active component(s), the scientific challenges regarding approving generic versions of naturally-derived mixture products can be substantial.

1.4.1 Pharmaceutical Equivalence

Demonstration of pharmaceutical equivalence for naturally-derived mixtures presents two key scientific challenges. The first challenge is determining if products contain the same active ingredient as the innovator product (i.e., the active ingredient sameness determination). Due to structural complexity and potentially insufficient knowledge of the active component(s), the amount of characterization data required to demonstrate active ingredient sameness for naturally-derived mixture products can be demanding. As the innovator manufacturing process and its conditions are generally unknown to a generic manufacturer, differences between manufacturing processes may manifest in drugs with differing attributes, potentially impacting product safety and efficacy. For this reason, it is critical to comprehensively characterize the entire mixture, particularly any known active components and structural signatures that reflect key attributes of the raw material and manufacturing process. Additionally, a bioassay may provide critical support for sameness if one is feasible, available, and informative. As described earlier, the innovator products exhibit a certain degree of batch-to-batch variability. Therefore, demonstrating active ingredient sameness between the generic and innovator products requires comprehensive characterization of multiple representative batches of the innovator product to assess the inherent variability and to establish quantitative equivalence criteria. An emerging scientific paradigm to establish active ingredient sameness is to develop a framework that provides a mathematical description or model of the entire mixture by incorporating measurements of key attributes from diverse and orthogonal analytical datasets as constraints on the model. Orthogonal measurements include diverse analytical data and characterization of different subpopulations or "levels" of the mixture. In this way, the same mixture attribute can be quantified in an unbiased manner. The active ingredient sameness characterization of naturally-derived mixtures relies on orthogonal, high-resolution methods (and the emerging concept of a mathematical model of the mixture), as no individual test is likely to provide sufficient information The main challenge associated with characterization is determining whether the combination of analytical and biological assays is sufficient to establish sameness. If designed properly, multiple orthogonal methods collectively can provide sufficient evidence of sameness, when both a proposed generic and an innovator product are each subject to the same appropriate battery of tests. The design of these methods can be guided based on the state of a priori knowledge of the chemical heterogeneity of the active ingredient mixture including starting material and manufacturing process. As an example, in the case of enoxaparin, the heterogeneity arises from variations in the starting material and modifications introduced by the manufacturing process. This is reflected in the evaluation and approval of generic enoxaparin (a low molecular heparin) in the USA. For a low molecular weight heparin, the FDA requires equivalence of: (i) physicochemical properties, (ii) heparin source material and mode of depolymerization, (iii) disaccharide building blocks, fragment mapping and sequence of oligosaccharide species, (iv) biological and biochemical assays, and (v) in vivo pharmacodynamic profile [5]. For more discussion

of the development of generic low molecular weight heparin, please see Chap. 9. Another example is the case of glatiramer acetate where the starting material is well defined and the heterogeneity arises from the kinetics of polymerization and depolymerization/deprotection events. For the approval of generic glatiramer acetate, the FDA requires, among other things, generic manufactures to demonstrate sameness in process signatures related to the polymerization and depolymerization events.

The second challenge is to ensure comparability of quality (e.g., purity) of the generic to the innovator product, such that the generic product would not pose a greater safety (e.g., immunogenicity) risk than the innovator product. Control of product- and process-related impurities is critical to the safety, efficacy, and quality of all types of drugs in each phase of the lifecycle. For complex mixture generics, this concern is particularly important as the requirement of interchangeability precludes any unexpected immune response to a generic product. The primary concern with respect to impurities in naturally-derived mixtures is often related to difficulties surrounding impurities associated with raw materials and final products. These can, at times, be hard to detect and therefore control in specifications. However, as with all types of drugs, naturally-derived mixture drugs should be closely evaluated for levels of impurities including aggregates, leachates, and process-related impurities. These impurity levels can be controlled in process/product development and during manufacturing. Aggregation, in particular, is a product-specific concern with the propensity to aggregate varying considerably between different types of drug products. It is critical to control aggregates of complex mixture products because they can have a potentially profound effect on the immunogenicity of a drug product [22]. As with other impurities, the levels of aggregates can be assessed using orthogonal techniques to ensure that the amount of aggregation in the generic product will be no different qualitatively or quantitatively than in the innovator product under similar and relevant testing conditions.

The level of immunogenicity risk can be product-specific as well and therefore the approach to address such a risk needs to consider both the underlying mechanism(s) responsible for the immune response and the consequences of the immune response. For example, immunogenicity is a strong concern for heparin and low molecular weight heparin (LMWH) products as a potentially fatal adverse event, heparin-induced thrombocytopenia (HIT), can occur when a patient produces antibodies to the complex of platelet factor (PF4) bound to heparin [23, 24]. As impurities have the potential to impact the formation of such complexes [5, 25], studies are needed to show that a proposed LMWH generic product is free of such impurities. Complementary approaches can provide further support: testing raw/source material for the presence of impurities (e.g., nucleic acids, proteins, and lipids) and assessing the capability of the manufacturing process to remove impurities. As the example of LMWH shows, as the understanding of immunogenicity risk for specific products evolves, so too will the methods for evaluating such.

1.4.2 Bioequivalence

In the USA, establishing bioequivalence can be relatively straightforward if the generic product is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients as the innovator product. In such cases, bioequivalence studies may not be necessary and a waiver of in vivo studies may be granted, even for complex mixtures (e.g., heparin and glatiramer acetate). For orally administered drugs intended for systemic action, bioequivalence can generally be established based on drug concentration in a relevant biological fluid (e.g., plasma or blood) after administration of the test and reference products to healthy subjects at the same dose under similar conditions. In this pharmacokinetic approach, two drug products are considered bioequivalent if the geometric mean test/reference ratios of (i) area under the curve (AUC) and (ii) peak plasma concentration ($C_{\max}$) have 90% confidence intervals that both fall within the limits of 80–125% [26].

The establishment of bioequivalence becomes much more challenging for other means of delivery (e.g., oral and topical) and for less characterized mixtures (e.g., botanicals). Even for systemically acting mixtures, it is often not possible to apply the pharmacokinetic approach to establish bioequivalence for these mixtures, due to the difficulty in identifying the active component(s) and measuring it in a relevant biological fluid. In some cases, a pharmacodynamics endpoint may suffice, but the mechanism of action needs to be understood to ensure the clinical relevance of the endpoint. It can be hard to define mechanism of action in the absence of proper in vitro and in vivo models for the disease. In some cases, a clinical endpoint may be necessary, but clinical endpoints are generally variable and less sensitive and therefore may require large patient populations. For example, pentosan polysufate (PPS) is a naturally-derived mixture of sulfated xylan polysaccharides from the bark of the beechwood tree indicated for the relief of bladder pain associated with interstitial cystitis. There is currently no analytical method sensitive enough to measure the PPS active ingredient (or surrogate) in a biological fluid. For this reason, the FDA presently recommends a bioequivalence study with a clinical endpoint (i.e., proportion of subjects reporting "treatment success") for the development of generic PPS solid oral dosage forms [27]. However, such a clinical endpoint bioequivalence study may not be practical or feasible (e.g., requiring a large number of patients). Therefore, more research is needed to find a more efficient approach to demonstrate bioequivalence for this complex drug product. Overall, it is clear that bioequivalence of complex mixture drugs needs careful scientific consideration and the appropriate means to establish bioequivalence may best be considered on a case-by-case basis.

1.5 Future Issues Facing Naturally-Derived Complex Mixture Drugs

The challenges in developing natural-derived complex mixture drugs illustrate the unique scientific and regulatory issues surrounding these products. The lessons of the past can inform the future and there are several trends that will impact the future of these drugs. The first is the development and use of advanced analytics, omics, big data, and data integration to better characterize components of complex mixtures. This will improve the overall understanding of these drug products through better characterization, enhance quality control via better detection of active components and impurities, and increase the ability to support pharmaceutical equivalence for generics drugs, particularly with respect to active ingredient sameness. The second trend is the improved understanding of the relationship between structure and activity for individual drug products. This will impact the understanding of which components of a mixture are essential for clinical performance and bioavailability. The third is the discovery and use of validated chemical markers or biomarkers for pharmacokinetic and pharmacodynamic studies, respectively. This will allow for improved bioequivalence data and analysis. The fourth is the development of in vitro bioassays that will allow for better correlations between quality attributes and bioactivity. This will greatly aid the development of products, processes, and controls for complex mixture drugs to support not only approvals but also post-approval changes.

In conclusion, the regulation of complex mixture drugs advances in parallel with scientific and technical progress. As modern analytics, omics, big data, and data integration processes are developed and implemented, the ability to ensure the quality, safety, and efficacy of complex mixture drugs improves. This book focuses on the major themes of complex mixture drug development introduced in this chapter including regulatory frameworks, biological activity, characterization, raw material and manufacturing control, impurities and immunogenicity, and clinical considerations. In learning the lessons of history and surveying the changing state of science, it is clear that complex mixture drugs will continue to bring unique scientific and regulatory challenges.

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Chapter 2
Regulatory Landscapes for Approval of Naturally-Derived Complex Mixture Drugs

Larisa C. Wu, Andre Raw, Werner Knöss, Michael Smith, Wei-Dong Zhang, Y. S. Bedi, Elaine Gray and Barbara Mulloy

Abstract The chapter contains brief surveys of current approaches used in countries around the world in the regulation of naturally-derived complex drugs. There is a marked diversity in the scientific and regulatory approaches in different regions, depending on history, the recognition and integration of traditional medicine systems, the evolution of regulatory bodies, and government regulatory philosophies. In the USA, there is a sharp regulatory distinction between drug and non-drug entities, based primarily on whether or the intended use is for treatment, prevention, or mitigation of disease states; for example, an herbal preparation may be registered as a botanical drug conforming to drug laws and guidelines, or it may be marketed essentially in the form of a dietary supplement. However, in many countries such as Europe, there is a particular regulatory class "herbal medicinal products" with

L. C. Wu (✉) · A. Raw
Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
e-mail: larisa.wu@fda.hhs.gov

W. Knöss
Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany

M. Smith
National Center for Natural Products Research, University of Mississippi, University, MS, USA

M. Smith
National Institute for Complementary Medicine, Western Sydney University, Sydney, Australia

W.-D. Zhang
Lab of Natural Products, School of Pharmacy, Second Military Medical University, Shanghai 200433, China

Y. S. Bedi
CSIR-Indian Institute of Integrative Medicine, Jammu 180001, Jammu and Kashmir, India

E. Gray
National Institute for Biological Standards and Control, Blanche Lane, Potters Bar, Herts EN6 3QG, UK

B. Mulloy
Institute of Pharmaceutical Science, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK

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some specific regulations within the framework for medicinal products. Countries such as Australia and Canada have developed a more comprehensive and tailored approach developing regulatory frameworks working off the therapeutic good/drug model that captures most herbal and traditional medicines on the market. In Asia, the regulatory approaches provide a special framework for the traditional systems of medicine, such as Ayurveda or traditional Chinese medicine (TCM). Interestingly in India, there is the development of hybrid categories, wherein some products from traditional medicine can be modified or specially formulated and marketed. In these subchapters, the heterogeneous environments, histories, and regulatory intents are captured and reflected for the USA, Europe, Canada, Australia, China, India, and World Health Organization and National Institute for Biological Standards and Control. However, these subchapters are instructive for background and context in the book's treatment of the regulation of naturally-derived complex mixture drugs in this age of globalization.

Keywords Regulation · Naturally-derived complex drugs
Traditional medicine systems · Herbal medicinal products · Botanical drugs
Market authorization

2.1 The US Regulatory Framework and Standards for Naturally-Derived Complex Mixture Drugs[1]

Larisa C. Wu and Andre Raw

2.1.1 Regulatory Approaches for Complex Mixture Drugs

Complex mixture drug substances are heterogeneous mixtures of multiple chemical components that can be synthetic, semi-synthetic, or naturally-derived (from plants, algae, macroscopic fungi, animals of animal parts, and/or minerals).

Common characteristics of complex mixture drug substances include:

- Crude extracts or mixtures that may have undergone varying degrees of chemical modification and/or purification,
- Heterogeneous mixtures containing multiple chemical constituents,
- One or more active constituents are responsible for the physiological or pharmacological action of the mixture.

Marketing drug applications for complex heterogeneous mixtures (either naturally derived or chemically synthesized) are submitted to the FDA in the form of new drug

[1] The views and opinions expressed in this section are those of the authors only, and do not necessarily reflect the views and policies of FDA.

applications (NDAs), abbreviated new drug applications (ANDAs), and reviewed by the FDA's Center for Drug Evaluation and Research (CDER). As for other drug products, the statutory and regulatory framework of a complex heterogeneous mixture is generally determined by the type of studies provided in the application, as dictated by the type of the active ingredient(s) used in the product. Complex mixture drugs have been approved by FDA under current regulatory pathways as NDAs (e.g., heparins, low molecular weight heparins, pentosan polysulfate, crofelemer, and conjugated estrogens), and ANDAs (e.g., heparin, enoxaparin, and glatiramer acetate).

When an application for a heterogeneous mixture product is submitted for review and approval to the FDA, it is the responsibility of the applicant or manufacturer to provide evidence that the product is safe, effective, and of high quality. CDER then assesses all data to conclude whether adequate evidence has been established with regard to safety, efficacy, risk–benefit profile, proposed labeling, and quality. Generally, the same standards as for small molecule drugs apply for the demonstration of safety and effectiveness of complex mixture drugs, and the applicants of complex mixture drug applications should comprehensively provide all clinical and nonclinical drug development efforts. Nevertheless, demonstration of quality in complex mixture drugs constitutes a real scientific and regulatory challenge when compared to small-molecule drugs. This is due to the uncertainty of its constituents, a complex mixture drug poses multiple technical challenges for quality control to determine its identity and ensure consistency of its strength and quality. In addition, it is also critical to ensure that the therapeutic effect for marketed batches of a complex mixture drug product is consistent to the one demonstrated in batches used in the pivotal clinical studies performed during drug development [1]. The following information will focus on regulatory and scientific considerations to address challenges in demonstrating and assessing the quality of complex mixture drug products.

2.1.2 Pharmaceutical Quality of Complex Mixture Drugs

FDA developed a consistent approach to assess the quality of the complex mixture drug products and its impact on safety and efficacy. FDA also issued related guidance for new botanical drugs [1] and product-specific generic drugs [2], which describe general scientific and regulatory concepts that may be applicable to complex mixture drugs.

Similar to a drug application submitted for a small molecule drug product, the pharmaceutical quality/chemistry, manufacturing and controls (CMC) section in an application for a complex mixture presents a rigorous account of drug substance/product characterization, drug product design, manufacture and packaging, drug substance/product specifications, microbiology, container closure system, and stability. As general recommendations on the pharmaceutical quality or CMC information that should be included in a drug application have been discussed elsewhere [3], this section focuses on unique quality characteristics of the complex mixtures drug substances and their respective drug products.

For complex mixtures drugs, the structure of active ingredients and/or related impurity profile are more intricate than in chemically synthesized small molecule drugs and generally cannot be characterized easily by single analytical means. As a result of this complexity, a "totality-of-evidence" approach is applied, where the quality control of complex mixture drugs may not solely rely on analytical testing and manufacturing control, but also on control of raw materials from natural sources, clinically relevant biological assay(s), and/or other non-CMC data (including clinical data on the dose–response generated based on multiple batches of the drug product) to overcome the limited ability to characterize the entire mixture [4], in order to ensure batch-to-batch consistency with respect to quality and thereby therapeutic effect. It is important that these unique quality characteristics are investigated and described in detail in a complex mixture drug application, so that FDA reviewers can thoroughly assess any related scientific matter that may have a bearing on drug product safety and performance.

2.1.2.1 Raw Material Control

Adequate raw material controls ensure that therapeutically consistent complex mixture drugs are manufactured, and the non-related substances are controlled. In this regard, an appropriate control of the raw materials refers to the origin, source, and location of the starting materials which may dictate the identity and activity of a complex mixture. Still, seasonal and diurnal variations, differences in materials coming from slightly different sources or species, contribute to micro-heterogeneity, and biological variations are possible. Raw material controls and collection for manufacturing therefore should employ good agricultural and collection practices (CAGPs) and/or good manufacturing practices (cGMPs) to minimize variability, and as well as the risks for material contamination and deterioration. In addition, qualitative and quantitative testing of key attributes of starting materials, including chemical identification by a spectroscopic or chromatographic method and authentication by a fingerprinting method, may be needed to ensure control over these sources of variability.

2.1.2.2 Quality Control by Chemical Testing and Manufacturing Control

Generally, due to its heterogeneity, identification and full characterization of individual components in a complex mixture are not a trivial task. Therefore, an application for a complex mixture drug should detail all pertinent physical and chemical properties and spectroscopic and/or chromatographic tests (e.g., HLPC, CD, IR, UV, NMR, and MS) performed to demonstrate the identity, purity, quality, strength, potency, and stability of all components considered active ingredients, as well as those considered impurities. Nevertheless, the manufacturer should evaluate currently available technologies, and if needed, develop orthogonal analytical methods to provide adequate

identification and quantification of the individual active ingredients in a complex mixture drug. When the individual active constituents are not known and/or the complex mixture cannot be fully characterized, the manufacturer may alternatively select a characteristic profile of chemical constituents (i.e., "fingerprint"), to ensure batch-to-batch consistency, as well as ensure that changes in the quality of the raw material(s) and/or manufacturing conditions do not impact the active ingredients [1].

In this regard, attempts to identify and characterize minor components in the complex mixture should be made in the context of existent orthogonal analytical techniques. Minor components in the complex mixture can be generally treated as part of the active ingredients, even if their contribution to the intended physiological and pharmacological action(s) of the complex mixture is unclear.

In addition, the manufacturing process (usually comprised of multiple steps including extraction, purification, and/or digestion/hydrolysis) is a crucial determinant of the complex mixture's identity; therefore, robust manufacturing process controls need to be employed.

Non-related substances in a complex mixture, such as those intended to be removed by the manufacturing process or known to adversely affect the safety profile of the complex mixture (e.g., adventitious agents, residual solvents, and product- and process-related substances with known adverse effects) should be excluded from the drug substance. Specific impurities that fall into this class are linked to safety risks and are characterized, qualified, and quantified [5].

Lastly, release specifications/acceptance criteria should be established based on clinical batches (or comparisons with the referenced product, if applicable) rather than production capabilities, in an effort to establish a relationship between the identity of the active ingredient(s) and the effectiveness of the complex mixture drug. Moreover, analytical methods should be able to detect any differences in critical quality attributes of a complex mixture drug among multiple batches.

2.1.2.3 Biological Assay

Due to the complex nature of complex mixture drugs, establishing their identity may not be possible by relying on chemical testing alone, in many cases, a characterization of relative potency and activity by a biological assay may be required. Generally, appropriate functional testing by in vitro biochemical assays is expected based on a known or intended mechanism of action, but phenotypic assays are also possible when the mechanism of action is unknown. Importantly, due to the variability of the biological assays, the potency and activity of the tested complex mixture drug should be evaluated relative to a suitable reference standard or material. It is important for the manufacturer to ensure that the assay performs in a reproducible and predictable manner [1].

2.1.3 Conclusion

As every complex mixture drug has unique quality considerations, the portfolio of investigated attributes and employed analytical techniques for a given product needs to be determined on a case-by-case basis. It is expected that the amount of the CMC information will vary with the type of complex mixture. Although the active ingredients in these mixtures may not be unequivocally identified, a "totality-of-evidence" approach can be used to ensure the therapeutic consistency of complex mixture drugs based upon integrating controls of raw material controls, manufacturing process controls, fingerprinting identity of the mixture, and clinically relevant bioassays.

2.2 The EU Regulatory Framework for Herbal Medicinal Products and Traditional Herbal Medicinal Products[2]

Werner Knöss

2.2.1 Legislation on (Traditional) Herbal Medicinal Products in the European Union

Medicinal plants and preparations thereof have been used in Europe since ancient times. Different traditions of usage existed in current Member States of the European Union (EU) with diverse national regulations developed in the twentieth century. Nowadays, a common legislation for medicinal products has been established in all Member States of the EU [6, 7]. The legislation in the EU has taken into account the challenge of complex mixtures of natural constituents, contributing to the particular characteristics of herbal medicinal products. The EU legislation offers the option for marketing authorization of new and also well-established herbal medicinal products, but moreover, a new legislative approach was developed in 2004 to harmonize assessment and access to the market for traditional herbal medicinal products [8]. The basic concept for the assessment of herbal medicinal products with a long tradition was to combine scientific evaluation and applicable knowledge that has been accumulated from long-standing use.

[2]The views expressed in this article are the views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties. There is no conflict of interest. The data provided are based on availability in March 2017.

2.2.2 Harmonization of Assessment Throughout the European Union

The Committee on Herbal Medicinal Products (HMPC) has been established at the European Medicines Agency (EMA) in London in 2004 in order to harmonize the scientific evaluation of (traditional) herbal medicinal products in the EU [8, 9]. HMPC is one out of seven scientific committees at EMA. It is composed of 28 members with scientific expertise being delegated from each member state of the EU. Additionally, five so-called co-opted members are elected who cover special fields of expertise, currently pediatrics, general medicine, pharmacology, clinical pharmacology, and toxicology. All documents developed by the HMPC are made available at the Web site of EMA [10]. According to the general policy of EMA, agendas and minutes of the plenary meetings of the HMPC are published, and interested parties, applicants and citizens can be informed about the work of the HMPC [10].

The core task of the HMPC is to harmonize the market of herbal medicinal products and traditional herbal medicinal products in the EU. This objective is assured by developing EU monographs and list entries for herbal substances and preparations thereof as well as by publication of relevant guidance. The establishment of monographs and other guidance documents is a fully transparent process. A public call for data is the starting point for developing a monograph. A rapporteur is nominated by the HMPC and is responsible for evaluation of the external input, data in the public domain, and market overviews provided by the Member States. A draft monograph is established, and the scientific background is documented in an assessment report. Scientific discussions in Working Party on Monographs and List Entries (MLWP) and HMPC contribute to evolving the documents, and finally, both documents are published for comments together with a list of references. The input from this public consultation is taken into account for finalization of the monograph.

2.2.3 Options and Concepts for Access of New, Well-Established, and Traditional Herbal Medicinal Products to Access the Market

In the EU, an access of any medicinal product to the market in the EU requires approval after assessment of quality, safety, and efficacy by a regulatory authority. Basic definitions for herbal substances, herbal preparations, herbal medicinal products, and traditional herbal medicinal products are provided in Community Directive 2001/83/EC as amended by Directive 2004/24/EC [6]. This legislation also defines detailed requirements for the documentation which have to be provided.

There are three main options to apply for an access to the market:

- Marketing authorization for new herbal medicinal products with a full set of data,

- Marketing authorization for well-established use medicinal products based on complete bibliographic data, or
- Registration for traditional herbal medicinal products, for which efficacy is based on plausibility and long-standing use.

Well-established use is based on the existence of an authorized medicinal product in the EU for a period of at least ten years. There must be an evidence-based medicinal use, and efficacy should be proven by at least one successful clinical trial. Existing bibliographic data must cover requirements on efficacy and safety. Moreover, scientific assessment of available data includes a check of overall coherence.

The designated licensing pathway for traditional herbal medicinal products may result in a so-called registration. The concept of traditional use is based on the approach to derive safety and efficacy from the long-standing use of a traditional medicinal product. Traditional use for a period of at least 30 years (with at least 15 years of such use in the EU) is a precondition for acceptance of plausible efficacy and an acceptable level of safety. Nevertheless, additional safety data may be requested by a national regulatory authority if necessary. This approach to approve traditional herbal medicinal products is only appropriate for products which are very safe. Therefore, this approach is restricted to oral and external use or inhalation for minor complaints. Moreover, complaints requiring medical prescription, diagnosis, or supervision by a medical doctor are excluded, and traditional herbal medicinal products must comply with provisions for over-the-counter medicines.

HMPC has released about 160 monographs, 13 list entries, 18 public statements, and about 40 guidance documents [10]. Well-established use has been attributed only within nearly 30 monographs. Public statements have been developed if a monograph could not be drafted, for example, because of lack of adequate data or concerns associated with a specific herbal substance or a specific natural constituent. The guidance documents are addressing a broad set of aspects of quality, safety, and efficacy to support further harmonization among the Member States. A regular review of monographs has been initiated in order to provide a sustainable and reliable system, which is reflecting current state of scientific knowledge. Meanwhile, more than 1700 registrations for traditional herbal medicinal products have been granted by national regulatory authorities of the Member States of the EU. About one third of these registered traditional herbal medicinal products are combination products containing more than one active substance. They address a broad spectrum of therapeutic areas, demonstrating that the system is very well-accepted and also used by the pharmaceutical industry. Therapeutic areas frequently targeted are, for example, cough and cold, gastrointestinal disorders, and mental stress.

2.2.4 Administrative Procedures

The following procedures for marketing authorization or registration of (traditional) herbal medicinal products in the EU have been legally established [10, 11]. They