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Introduction

Alex Langford[1], Satoshi Ohtake[1], David Lechuga-Ballesteros[2], and Ken-ichi Izutsu[3]

[1] Pfizer BioTherapeutics, Pharmaceutical Sciences, 875 Chesterfield Parkway West, Chesterfield, MO 63017, USA
[2] AstraZeneca Pharmaceuticals LP, Pharmaceutical Technology and Development, 121 Oyster Point Boulevard, South San Francisco, CA 94080, USA
[3] National Institute of Health Sciences, Division of Drugs, Tonomachi 3-25-26, Kawasaki 2109501, Kanagawa, Japan

Succeeding the inception of recombinant DNA technology in the 1970s [1], the pharmaceutical industry observed a significant shift from chemically synthesized drugs toward biologics. Biopharmaceuticals or biologics, distinct from small molecule drugs, include a wide variety of therapeutic products derived from living organisms or produced using biotechnology, e.g. recombinant proteins, vaccines, blood components, cellular therapies, and gene therapies. Biopharmaceuticals are characterized by a composition containing biological components or subunits including peptides, proteins, nucleic acids, and cells [2].

Since the US Food and Drug Administration (FDA) approved the first recombinant protein-based biologic in 1982 (recombinant insulin, Humulin®, Eli Lilly and Co., Indianapolis, IN, USA) [3] and monoclonal antibody-based therapy in 1986 [4], there has been continual growth in the number of biopharmaceuticals on the market. There were only nine biopharmaceutical approvals prior to 1990; however, since the mid-1990s, the United States and European Union have seen a combined average of more than 10 new approvals each year (based on Figure 1b of [5]). A survey of biopharmaceuticals published by Walsh [5] in 2014 reported that there were 212 approved biopharmaceutical products on the market in the United States and European Union with biopharmaceuticals making up an estimated 26% of all new drug approvals. The annual sales value of biopharmaceuticals in 2013 was reported to be US$140 billion, a value noted to be greater than the gross domestic product (GDP) of 156 of 214 countries listed in the World Bank GDP database. In 2017, the highest selling biologic was adalimumab (Humira, AbbVie Inc., North Chicago, IL, USA) at over US$18 billion in annual sales [6].

In more recent years, the diversity and complexity of the biopharmaceuticals in development has continued to increase. Protein-based therapeutics remain common, but the breadth of compounds the industry is currently faced with manufacturing has expanded significantly. Some examples of the products currently in development and on the market include antibody drug conjugates (ADCs),

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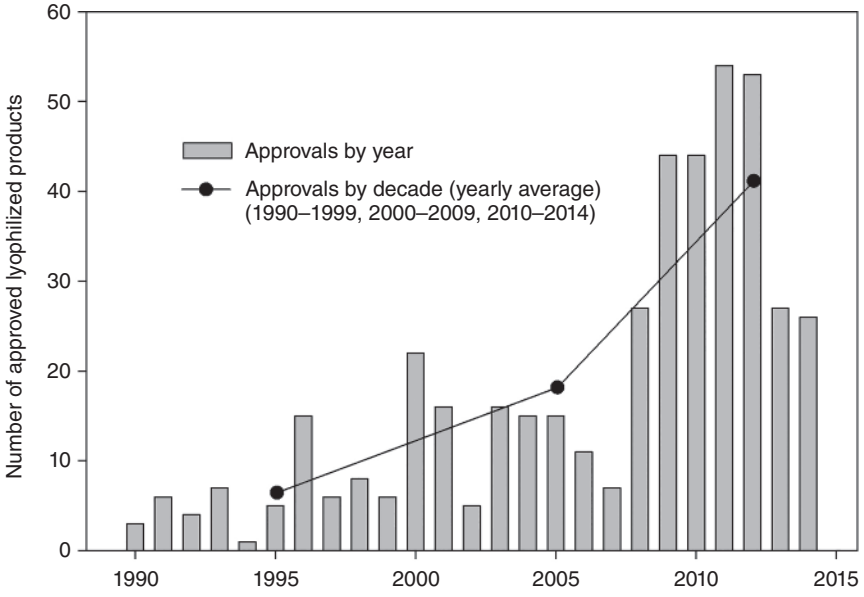

Figure 1.1 Number of FDA-approved lyophilized drugs by year and decade of approval. Source: Adapted with permission from Ref. [8].

multivalent polysaccharide conjugate vaccines, live attenuated vaccines, cellular therapies, and gene therapies.

As the biopharmaceutical industry continues to evolve, advances in technologies will be required to address the challenges of speed to market, reducing developmental costs, improving storage stability, maintaining high product quality, and enhancing end-user convenience. The dehydration of material provides advantages that are able to address some of these challenges. While many biological materials contain high water content (typically ≥80%, w/w), the removal of water confers benefits such as ease of handling and storage, reduction in transportation costs, and improved stability [7]. For these reasons, the number of approved pharmaceutical products requiring lyophilization has significantly increased over the last two decades, as demonstrated by the increasing number of FDA-approved products that are freeze-dried (Figure 1.1). Furthermore, it was reported that the percentage of all approved injectable/infusible drugs that were lyophilized increased from only 12% between 1990 and 1998 to greater than 50% between 2013 and 2015 [8]. An increase in the number of biological therapy approvals by the FDA has been accompanied with a parallel increase in the overall number of approved drugs.

Whether it is the ancient use of sun and air drying as a means of food preservation, a primitive form of lyophilization used by the Incan Empire centuries ago using radiation from the sun and reduced pressure at high altitudes [9], or any advanced drying technology used in modern manufacturing processes across the globe, the basic principles of drying remain the same. Drying is the process of dehydration or the removal of water from a solution or suspension to form a

solid. During the drying process, an energy source transfers heat to the solution through conduction, convection, and/or radiation to vaporize water. An aqueous solution is dried by two fundamental processes to remove either bound or unbound water (i.e. bulk water). The first process is the evaporation of surface moisture from the transfer of heat, or other forms of energy, to the wet feed. The second process is the transfer of internal moisture to the product surface where it can then evaporate following the first process [10]. Chapter 2 expands on the various ways in which these principles have been applied throughout history.

Since the dawn of modern engineering, drying has continued to mature, and now hundreds of dryer types are available for industrial applications. Chapter 2 provides a review of the current applications of drying technologies in industries other than pharmaceuticals, such as the food, agriculture, and textile industries. While many drying technologies in these industries are considered well established, the need for significant improvements to existing processes remains with respect to efficiency and control. The process efficiency of dryers has been reported to range from under 5% to approximately 35% on the high side due to (i) the high latent heat of vaporization of water and (ii) the inefficient heat transfer of convection (a common method of heat transfer in industrial dryers) [10]. The rate of drying is largely based on the amount of heat transferred to the wet feed through conduction, convection, and/or radiation. Additionally, it can be altered by changing factors such as the type of energy source used and/or application of forced air or a vacuum.

Traditional methods of commercial drying are limited either by their high production costs (e.g. freeze-drying) or severe reduction in product quality due to long exposure times at high temperatures (e.g. hot air drying). For biopharmaceuticals, the maintenance of high product quality is a crucial consideration for an optimized drying process. In general, a higher drying temperature will negatively impact product quality though reduce overall processing time. Often, loss of a drug substance and/or drug product batch has such a significant impact on developmental cost and/or clinical timelines that very conservative drying temperatures (i.e. lower temperatures) are utilized early in development. These lower drying temperatures often maintain product quality but require significantly longer processing time. In addition, a greater deviation of the processing temperature from ambient typically requires greater energy consumption. Thus, finding the optimum drying temperature is the most common problem encountered in developing an efficient drying process.

Historically within the pharmaceutical industry, engineers and scientists have been very limited in their use of drying technologies. The need to preserve high product quality of labile biomolecules and maintain aseptic processing has severely reduced the number of methods used in the industry. The gold standard for the drying of biopharmaceuticals is freeze-drying as evidenced by the significant number of freeze-dried biomolecule products on the market [11]. Due to its prominence in the field, the first drying technology to be reviewed in this book is freeze-drying (Chapter 6). In addition, there are several supplemental resources on this topic recommended for further reading [12–14]. Even though the freeze-drying process is common and relatively well established, it has several shortcomings, including high energy consumption,

long drying times, low process efficiency, formulation limitations (i.e. challenges with low collapse temperature excipients such as salts), and incompatibility with continuous manufacturing. The efficiency of fully loaded laboratory- and production-scale lyophilizers was reported to range from 1.5% to 2% as calculated by Alexeenko [15]. While higher process efficiency is possible through other drying technologies, consideration of alternative drying methods depends on several factors such as the physical properties of the product, application of the product, type of energy source available, container closure system, and scalability of the equipment. Chapter 12 reviews the desired characteristics of a novel drying technology and requirements for implementation into the current manufacturing environment.

As mentioned above, drying can provide significant benefits to the stabilization of labile biomolecules. A liquid drug product formulation is often preferred due to reduced manufacturing costs and end-user convenience (i.e. no reconstitution required); however, sufficient stabilization in the liquid state often cannot be achieved. In an aqueous solution, water serves as a medium that results in significant molecular mobility and conformational perturbations and acts as a catalyst for chemical degradation that can promote instability during storage and shipping [16]. The removal of water through drying significantly retards water-mediated degradation. An early-stage clinical development strategy may be to proceed with a dried formulation as a means of quickly achieving adequate product stability without needing to develop a liquid formulation. This may be a preferred approach since many products do not make it to approval based on clinical results and the consequential reduction of up-front resources may help to reduce the company's developmental costs. That being said, smaller organizations may benefit from developing a stable liquid dosage form due to the increased cost of manufacturing a freeze-dried product. Chapter 13 presents additional details on relevant challenges in the development of liquid dosage forms and the benefits of solid-state stabilization. A drying process cannot be designed as a stand-alone entity, and the characteristics of the molecule to be processed must be considered. Chapters 3, 4, and 5 review the unique considerations when applying drying processes to small molecule active pharmaceutical ingredient (API), proteins, and vaccines, respectively.

Even though a well-designed drying procedure can often sufficiently stabilize biomolecules, drying induces new stresses to a product that are not present in a liquid formulation. From a freeze-drying perspective, these stresses include the ice–water interface, low temperature, cryo-concentration [17], freezing-induced pH shifts [18], and the removal of bulk and bound water during drying [14, 19]. It has been widely reported that the degradation of biomolecules, such as monoclonal antibodies, caused by some of these stresses can be overcome by the use of stabilizing excipients, such as disaccharides [16, 17]. Chapter 13 presents the primary considerations when developing a stable solid-state formulation in addition to discussing the key role of water in the final product. Looking toward the future, as biomolecules continue to increase in complexity (e.g. mammalian cell-based therapies), these drying-induced stresses may prove to be more problematic, and stabilizing excipients alone may not be sufficient to adequately stabilize dried

formulations. The formulation scientist may have to consider the unique benefits of next-generation drying technologies to overcome such challenges [20].

Next-generation drying technologies for biological materials include but are not limited to spray freeze-drying (Chapter 8) [21, 22], microwave drying (Chapter 9) [23, 24], foam drying (Chapter 10) [25, 26], and the use of electromagnetic/magnetic waves on freeze-drying (Chapter 11) [27]. While these "novel" drying techniques currently have limited application in the biopharmaceutical industry, many are commonly used in other industries. Benefits such as improved stabilization of biomolecules, compatibility with continuous manufacturing, and improved process efficiency compared with freeze-drying are potential reasons to evaluate these technologies. Microwave-assisted freeze-drying is an example of utilizing a hybrid of two drying methods to significantly reduce drying process time [24, 28]. For these reasons, this book will veer away from established biopharmaceutical development approaches and conventional drying processes, such as freeze-drying and spray drying (Chapter 7), to discuss and evaluate these promising next-generation technologies. Chapter 14 reviews the challenges and considerations for implementing these new technologies into the current manufacturing environment as well as discusses the potential synergy with process analytical technologies (PAT). These novel techniques are presented to the reader in hope that they will consider how to utilize them to overcome new problems and inefficiencies they encounter.

Several resources are currently available to engineers, scientists, and academics that review the fundamentals of drying and its application to various industries. However, there is currently no book that focuses solely on the application of a variety of drying technologies to biopharmaceuticals. The aim of this book is to fill this void by providing a comprehensive resource reviewing the current state and future direction of drying technologies for biopharmaceutical applications. The authors hope that this book will serve scientists and engineers in the pharmaceutical industry as well as academics, particularly in chemical engineering and pharmaceutical sciences, as a single source of information related to pharmaceutical drying technologies. Since this book presents the latest developments related to drying technologies in the field, senior leaders in the industry may find it useful for identifying improvements to current and/or new technologies to implement into their current manufacturing environment. The authors hope that the specific focus of this book on biopharmaceutical applications will enhance its effectiveness in providing a clear vision of the current and future (Chapter 15) landscape of drying in the pharmaceutical industry.

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