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General Commentary

Postproduction Handling and Administration of Protein Pharmaceuticals and Potential Instability Issues

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ABSTRACT

The safety and efficacy of protein pharmaceuticals depend not only on biological activity but also on purity levels. Impurities may be process related because of limitations in manufacturing or product related because of protein degradation occurring throughout the life history of a product. Although the pharmaceutical biotechnology industry has made great progress in improving bulk and drug product manufacturing as well as company-controlled storage and transportation conditions to minimize the level of degradation, there is less control over the many factors that may subsequently affect product quality after the protein pharmaceuticals are released and shipped by the manufacturer. Routine handling or unintentional mishandling of therapeutic protein products may cause protein degradation that remains unnoticed but can potentially compromise the clinical safety and efficacy of the product. In this commentary, we address some potential risks associated with (mis)handling of protein pharmaceuticals after release by the manufacturer. We summarize the environmental stress factors that have been shown to cause protein degradation and that may be encountered during typical handling procedures of protein pharmaceuticals in a hospital setting or during self-administration by patients. Moreover, we provide recommendations for improvements in product handling to help ensure the quality of protein pharmaceuticals during use.

Introduction

In the past 2 decades, protein pharmaceuticals have become the fastest growing class of therapeutics because of their beneficial impacts in the treatment of severe and life-threatening conditions and diseases.[1] Development and manufacturing of protein pharmaceuticals is, however, challenging and requires overcoming various manufacturing hurdles such as issues with the purity of the protein product. Common impurities include protein product–related degradants (e.g., protein aggregates, fragments, and chemical degradants) and nonproduct, manufacturing process–related materials (such as process residuals; host-cell proteins/DNA; and particulates such as silicone oil droplets, glass particles, and delaminated primary packing materials or those derived from polysorbate degradation byproducts) as well as chemically degraded excipients.[2-5] Impurities within therapeutic protein products can cause severe adverse drug reactions (ADRs) in patients. ADRs can be acute[6-10] or more long term, as it is usually the case for unwanted immunogenicity,[11,12] and may result in compromised safety and efficacy.[13-15]

Aggregation and chemical degradation of proteins have been reported to enhance their immunogenicity upon administration.[16-29] Neutralizing antibodies can reduce the efficacy of therapeutic proteins[7,30-33] and sometimes cross-react with essential endogenous proteins to cause severe ADRs.[34] Physical aggregation and chemical degradation can occur throughout the life of a protein product, and even modest environmental stresses can cause extensive damage. The pharmaceutical biotechnology industry has made great strides in improving bulk and drug product manufacturing processes, and the cumulative outcome of these efforts has been significant and

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continues to improve/preserve the quality of protein products in all steps of production, storage, and transportation. Despite these improvements, once the protein product is released and shipped by the manufacturer, there is potentially little control over the many factors that may affect the structural integrity and quality of these environmentally sensitive protein products. Therefore, they may be damaged by various types of (mis)handling. It is plausible that even accepted routine handling of protein drugs in a clinical setting or in patients' hands may cause product degradation that remains unnoticed but potentially compromises the safety and efficacy of the product. For example, when preparing protein products for intravenous (IV) administration, protein particles can result from the numerous stresses generated during routine handling, and foreign materials can contribute to the particle loads delivered to patients.[35,36] Recent reports on the handling of protein drugs in hospital pharmacies and patients' hands suggest that these handling practices can potentially compromise the stability of protein pharmaceuticals.[37,38] In recognition of such problems, a conference session entitled "Fragile—handle with care" at the 2017 American Association of Pharmaceutical Scientists Annual Meeting was devoted to discussing the gap between the drug developer's understanding of real-world conditions and handling of their protein pharmaceuticals and the end user's understanding of the importance of proper handling of these drugs and the reasons behind it.

This commentary aims to address the potential risks associated with handling of protein pharmaceuticals after release and shipping by the manufacturer, that is, at the hospital pharmacies, in trained health care personnel's hands, or during patient self-administration. In this context, we first briefly discuss the different environmental stress factors that could be experienced as part of routine handling and administration procedures and how they could lead to compromised protein stability. We focus on the environmental stress factors that have been widely investigated in the past decade and proven to be detrimental to protein structural integrity and stability. The second part of the commentary contains remarks and recommendations for different units of the involved community for improvements in routine product handling, which may lead to a more reliable, controlled, and safer use of protein pharmaceuticals immediately before administration.

Handling of Protein Pharmaceuticals, Stress Factors, and Stability Concerns

During normal handling in clinical settings, protein therapeutics that are formulated for IV administration are typically prepared in the pharmacy (e.g., reconstituted from a lyophilized formulation, drawn into a syringe, injected into a bag of IV solution, and mixed), transported to the patient's floor (e.g., via a pneumatic tube or traditional hand-carried hospital trolleys), placed in temporary storage, and eventually administered to the patient. Alternatively, protein therapeutics that are formulated for subcutaneous injections are often handed over to a patient at the pharmacy, transported by patients to their homes, stored (e.g., in a refrigerator), and eventually injected subcutaneously by the patients themselves or by a caregiver. The pharmacist and a health care worker generally give recommendations to patients for proper storage and use. Furthermore, patients have access to the patient information leaflet[39] that includes descriptions of the optimal conditions for storage and use.

Each of the aforementioned steps, even when followed strictly, can expose proteins to various stresses that may cause product degradation as well as contamination. Contaminants (e.g., cellulose, dust, bacteria, virus) are of extraneous origin and, in principle, should not be present in a product or introduced during routine handling. However, extreme care should be taken to protect the product during handling at steps where it may become exposed to the external environment, such as during transfer from a vial to an IV bag. This commentary focuses on protein product—related impurities rather than these foreign matter contaminants.

It is noteworthy that in general, there appears to be a lack or an insufficient level of strict procedures for handling of protein pharmaceuticals in hospital pharmacies from a protein stability point of view. There is also more obviously a relative lack of control over the patients' handling and treatment of the protein product during at-home use. In a recent observational study performed in a hospital, some of authors have documented several incidents during the process of compounding at the pharmacy and transport of the drug to patients which could jeopardize the quality of protein pharmaceuticals. For instance, observations included vigorous manual agitation of a vial that contained a liquid formulation of a protein pharmaceutical causing formation of foam in the vial, repeated back and forth movement of a syringe plunger resulting in foaming in a syringe, nonuniform processes for injection of drug into infusion bags, and careless handling of IV bags to the patient's section by a nurse who was unaware of the contents of the IV bags.[37] In other observations in a different hospital, some of the authors identified the transportation of the protein pharmaceutical—containing IV bags with a pneumatic tube system to be of concern with respect to the stability of the proteins. In addition, discussions with pharmacists from a number of hospitals corroborate the abovementioned observations, the general lack of awareness, and the lack of suitable procedures for handling of protein pharmaceuticals in hospital pharmacies (let alone situations where a cold supply chain is not available or properly maintained in both developed countries and many developing parts of the world, a topic that has been widely reviewed with temperature-sensitive vaccines[40]). Furthermore, special cases such as issues with repackaging of a drug product for off-label use (as for an antivascular endothelial growth factor drug, Avastin) and complications with the effects of handling on aggregation and potential contamination have been reported and deserve further attention.[41,42]

One can envision that such concerns are similarly valid for protein pharmaceuticals provided to patients for self-administration at home. The scientific community has raised this concern, and a few publications have reported that home storage temperatures often deviate from the recommended temperature range.[38,43] Obviously, it is more difficult to gather information about other stress parameters, and it is not known how patients may treat protein pharmaceuticals with respect to mechanical shocks, light exposure, and various combinations of these stress factors.

In this next section of the commentary, we summarize the environmental stress factors that have been shown to cause protein degradation and could be encountered during typical handling procedures and mishandling of protein pharmaceuticals in a hospital setting or in patients' or caregivers' hands.

Mechanical Stresses and Contact With Interfaces

Mechanical stress is arguably the most common type of stress that a protein drug product may be exposed to in the compounding and transportation processes in a hospital or in a patient's hands during at-home use. A certain level of stability against mechanical stresses is a must-have property for protein pharmaceutical products. To this end, great care is taken in formulation design to add excipients (e.g., nonionic surfactants) that decrease a protein's susceptibility to mechanical stresses[44] as well as in the design of manufacturing processes to reduce protein damage that can arise during formulation/filling processes and during transportation of containers holding protein solutions. In hospital and home environments, however, generated mechanical forces and surface