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Review

Impact of Post Manufacturing Handling of Protein-Based Biologic Drugs on Product Quality and User Centricity

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ABSTRACT

This article evaluates the current gaps around the impact of post-manufacturing processes on the product qualities of protein-based biologics, with a focus on user centricity. It includes the evaluation of the regulatory guidance available, describes a collection of scientific literature and case studies to showcase the impact of post-manufacturing stresses on product and dosing solution quality. It also outlines the complexity of clinical handling and the need for communication, and alignment between drug providers, healthcare professionals, users, and patients. Regulatory agencies provide clear expectations for drug manufacturing processes, however, guidance supporting post-product manufacturing handling is less defined and often misaligned. This is problematic as the pharmaceutical products experience numerous stresses and processes which can potentially impact drug quality, safety and efficacy. This article aims to stimulate discussion amongst pharmaceutical developers, health care providers, device manufacturers, and public researchers to improve these processes. Patients and caregivers' awareness can be achieved by providing relevant educational material on pharmaceutical product handling.

Abbreviations: ADC, Antibody Drug Conjugate; API, Active Pharmaceutical Ingredient; ASTM, American Society for Testing and Material; cGMP, Current Good Manufacturing Practice; CHMP, Committee for Medicinal Products for Human Use; CSII, Continuous Subcutaneous Insulin Infusion; CSTD, Closed System Transfer Device; DP, (Medicinal) Drug Product; Dosing Solution, Dose prepared from the drug product/ compounding/ mixture; EFPIA, European Federation of Pharmaceutical Industries and Association; EMA, European Medicines Agency; GDP, Good Distribution Practice; HCP, Healthcare providers; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMI, Innovative Medicines Initiative; ISMP, Institute for Safe Medication Practices; ISO, International Organization for Standardization; USP, United States Pharmacopeia; ISTA, International Safe Transit Organization; IV, Intravenous; mAbs, Monoclonal Antibodies; PFS, Prefilled syringe; PI/SmPC, Product Information/ Summary of Product Characteristic; PTS, Pneumatic Transport System; QWP, Quality Working Party.

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Glossary / Definitions

Biologics: medicines described as "Biological Medicinal Product" by the European Medicines Agency or "Biological Product" by the Food and Drug Administration of the United States.

Protein-Based Biologics: protein-derived group of medicines.

Post-manufacturing handling: conditions and processes of medicinal drug products from the transport to the preparation of drug product and administration to the patient.

Mechanical stresses: can indicate two different stresses. (1) Mechanical agitation: describes agitation, vibration, shaking, mixing and other mechanical movements, (2) mechanical shock: describes fast kinetic events including sudden acceleration/deceleration such as during dropping and falling, cavitation may occur.

Thermal stress: includes all temperature excursions outside (above or below) the recommended drug product or prepared dosing solution storage and handling range.

Light exposure and photodegradation: includes situations where the drug product is exposed to light. Photodegradation indicates light induced degradation that impact DP quality.

Introduction

Protein-based biologics are a class of biological medicinal products that have rapidly grown in market approvals in the last few decades, resulting in more than 180 new biopharmaceutical active ingredients (API) approved for use in the United States and the European Union between 2018 and 2022.[1,2] These drug products (DPs) include modalities such as antibody drug conjugates (ADCs), fusion-proteins, and monoclonal antibodies (mAbs), the latter representing more than 50 % of the currently approved products.[1,2] Compared to solid dosage forms of synthetic medicinal products, biologics are typically more sensitive to stresses such as temperature excursions, change of state (freezing and thawing), light exposure, and mechanical agitation and shock. Therefore, extensive development is needed to ensure that the DPs stability has been optimized and that the product quality of the final DP is well controlled and characterized. Complex post-manufacturing stresses that the DP may experience during transportation, distribution, and clinical in-use handling and administration to patients can impact its quality and potentially affect efficacy and safety.[3] This article provides an overview of the global regulatory guidance available and its limitations to support handling and administration of the DP, it also highlights the post-manufacturing stresses that products may experience during transport and handling across the supply chain, and finally, focuses on the areas that should be developed for new investigations.[4] This manuscript has been prepared to educate the audience as a deliverable for the RealHOPE working group of the Innovative Medicines Initiative (IMI) (https://realhope.se): '*Real-life handling of protein drug products, exploration, evaluation and education*'. The review will be supplemented by future research from RealHOPE academics to industry partners to improve patient safety and increase awareness around handling and in-use in the form of publications, training materials, and best-practice guidance for healthcare professionals and patients.

Current Global Regulatory Guidance for the Handling of Post-Manufacturing DP

Adequate guidance for the post-manufacturing handling of DPs is critical to ensure product quality and patient safety. Table 1[5–17] summarizes selected harmonized regulatory guidelines for the preparation, administration and handling of DPs. Many of the regulations concerning DPs release and stability do not include in-use DPs handling processes in depth and as such, are sometimes addressed by associative or local organizations instead of regulatory agencies.[18,19] Despite the list of guidelines shown in Table 1, gaps and challenges have been identified which impact the quality of the post-manufactured DPs and may increase the complexity of the testing environment associated with post-manufacturing transport and in-use.[20–22] For example, during transport assessments, the DP manufacturer may define custom tests that mimic its intended use, following different transport standards such as ISTA, ASTM or ISO.[15,16,23] Furthermore, a complex regulatory landscape also arises during clinical in-use handling, where pharmacists/healthcare providers (HCP) must follow regulations from local sites, state pharmacy boards, as well as national licensure or pharmacopoeia recommendations. Clinical handling practices can vary widely globally because of potential gaps in regulatory considerations between national health authorities and local agencies, leaving clinical sites and hospitals in some regions to implement local practice guidance without a harmonized standard.[22] For clinical trials or market license authorization, health authorities require that the Quality-Investigational Medicinal Product Dossier (Q-IMPD) section P.3.2 supporting information are shared with healthcare providers in a site guidance document (also known as pharmacy manual) or in the Product Information/ Summary of Product Characteristic (PI/SmPC) sheet which details how the drug is prepared, handled, and administered. However, the existing guidance for in-use and compatibility assessment lacks comprehensive details and is open for interpretation. When dealing with handling and preparation, clear instructions and information on the occupational safety of the DP must be available for professionals. The PI/SmPC for marketed products are often limited, drug-specific, and cannot go into details on all aspects of the best practices of handling biologics in general to ensure their stability, including occupational safety. Finally, the aforementioned gaps can be worsened for outpatient care where therapies can be administered at home and at-times by patients themselves, a practice that has increased in popularity recently in efforts to bring down healthcare costs and increase patient convenience. Studies have shown that these environments are less regulated, often resulting in non-compliance.[21,22]

RealHOPE Work Packages Tackle Protein-Based Biologics Products Quality Concerns

RealHOPE is a European Union funded project that works to ensure patients safety by building knowledge on how to handle protein drugs better during their whole life cycle (https://realhope.se/). There are five work packages in the RealHOPE project: SHAPE, GOLD, HIGH, TEACH and PAGE. SHAPE (*Stressful HAndling of Proteins Evaluation)* evaluates drug stresses through simulations surrounding the transport and handling of DPs. GOLD (*Guidance Outlining Latest Developments)* designs experiments and develops mitigation strategies to reduce critical stress factors during clinical handling. HIGH (*Handling Improvement Guidance for Health)* provides recommendations on methods and guidelines to improve clinical handling. TEACH (*Targeted Educational Advice at Centers for Healthcare)* creates educational materials for pharmaceutical scientists, pharmacists, healthcare providers, and patients, based on lessons learned from the other work packages. PAGE (*Project ManAGEment)* supports with leadership, communication, and project management to ensure the success of the RealHOPE objectives. The data gathered during the project, including patients and HCP interviews, will be used to help bridge the gaps in knowledge and communication between the previously

Table 1
Regulatory guidelines summary about the development and handling of drug products.

Guideline	Section	Scope	Guidance summary	Ref.
ICH Q8 (R2)	2.6	Compatibility	Compatibility of the drug product with reconstitution diluents including dilution of products prior to administration.	5
EMEA/CHMP/SWP/28,367/07	5.3	Reliability of small doses	Suitability of dosing solution to provide the intended dose.	6
EMA/CPMP/QWP/2934/99	N/A	In-use stability	Safety of medicinal products in multidose containers which, due to repeated opening and closing, may pose a risk to its content.	7
ICH M4Q	3.2.P.2.6	Compatibility	Compatibility testing of drug product with reconstitution diluent(s) or dosage and administration devices.	8
ICH M4Q	3.2.P.8.1	Stability summary	Common format for the summary of stability, in-use storage conditions, and shelf-life.	8
ICH Q1	B	Photostability	Light testing as an integral part of stress testing.	9
ICH Q5	C	Stability testing	Stability data considering reconstitution, dilution, storage, and stress conditions.	10
USP 787/ 788	N/A	Subvisible particles	Subvisible particles limits for therapeutic protein injections.	11,12
USP 797	N/A	Microbial contamination	Standards for preparing compounded sterile medications.	13
ISMP Guidelines	N/A	Sterility preparations	Sterile compounding and use of sterile compounding technology.	14
ASTM D4169–22	N/A	Transportation	Evaluation of DP shipping units to withstand the distribution environment.	15
ISTA 3-Series	3A-3L	Transportation	Laboratory simulation of the damage-producing motions, forces, conditions, and sequences of transport.	16
ICH Q1	F	Storage conditions	Storage conditions for stability testing in countries located in Climatic Zones III and IV.	17

ASTM: American Society for Testing and Materials; EMA: European Medicines Agency; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; USP: United States Pharmacopeia; Ref: References; ISMP: Institute for Safe Medication Practices.

cited stakeholders and aid the development of more robust DPs handling procedures to support a safe and efficient use of these medications for patients.

This paper addresses some of work package SHAPE goals: 1) generating a better understanding of post-manufacturing risk on biological DPs, 2) promoting clear guidance and communication in regard to DPs transport, preparation, and administration, and 3) ensuring that pharmacists, patients and caregivers and other HCP have access to relevant and regulated medication instructions and documents provided by the DPs manufacturers. These objectives are achieved by improving the knowledge database available to HCP and patients, updating training materials, and creating, adopting, and disseminating novel training methods (i.e. mobile applications, webinars, online media and creative manuals) where applicable. Other SHAPE goals not addressed here include development of tools and methods for simulation of real-life events during DP handling that mimic the effects on DP quality and development of new technologies for the mitigation of critical stress factors and safer handling of protein drugs at hospital pharmacies.

Post-Manufacturing Stresses: Getting Biological DP to the End Users

Once biological DPs are released from the manufacturing site, they leave a controlled cGMP/GDP environment and are subjected to transportation, storage, distribution, preparation, and administration. Numerous individuals are involved through these processes, including distributors and HCP (such as physicians, pharmacists, nurses and caregivers). Studies have shown that knowledge gaps can exist despite professional training and instructions.[22,24] Thus, biological medicines can be exposed to stressors that could influence their quality and efficacy which could potentially lead to adverse effects (e.g., immunological reactions) or loss of therapeutic potency.[25,26] Additionally, in the event of an unacceptable impact on product quality, the DP is ultimately discarded, causing wastage and negatively impacting economic and sustainability outcomes.[27] Fig. 1 summarizes the workflow of the DPs post-manufacturing supply chain, associated stresses, impact on product quality, stakeholders and participants involved behind each step. Next sections describe stakeholders involved, influence of potential stressors encountered after DPs manufacturing associated risks, and potential strategies for risk mitigation. Furthermore, Table 2 summarizes list of published studies in relation to the impact of relevant stresses encountered.[26,28–60]

While there are significant academic interests to explore DPs quality attributes and stability to improve patients care, there is low adherence to manufacturer recommendations due to potential challenges of performing meaningful and applicable research without inputs from industry partners.[61] These challenges can include the lack of validated analytical methods and instruments during drug characterization, an incomplete panel of analytical methods to get a full picture of the DPs behaviour as done in the industry and required by regulators, the unavailability of well-characterized information associated with the material tested, and a difference standard in experimental quality in a regulated, compliance drug manufacturing (cGMP) setting vs. a general hospital or laboratory. Thus, there is a need to implement patient centric changes through a collaboration between researchers, drug manufacturers and regulators so we can learn from one another and improve our processes.

Mechanical Stresses

Mechanical stresses are a broad category of physical perturbations such as agitation, stirring, and cavitation, typically involved when the DP is in motion. Potential DP degradation pathways include fragmentation, aggregation, precipitation, increases in counts and size of subvisible and visible particles, formation of higher order complexes and unfolded structures.[33,37,40,42] Certain events and potential interfacial stresses can exacerbate the negative impact on DP quality. For example, dropping (even from low heights) during normal shipping can cause rapid acceleration and deceleration of the DP, thus causing the formation of small vapor-filled cavities (or bubbles) in solution, a phenomenon known as cavitation. The subsequent implosion of these air bubbles can initiate particle formation,[37,42] as observed during a transport simulation study of Ustekinumab stored at 2–8 °C during a 48-hour, 8000 km, journey across the United States. The same study noted that mechanical transport can have cumulative effects as different types of vibrations, shocks, agitations can occur from the various modes of transportation, ranging from the rapid acceleration on a flight to the vibrations and shocks of road travel, and the drops at a loading dock.[40] This type of shipping validation study is a requirement for commercial medicine application to ensure DPs developers provide well characterized modes of transports while ensuring product quality.[62]

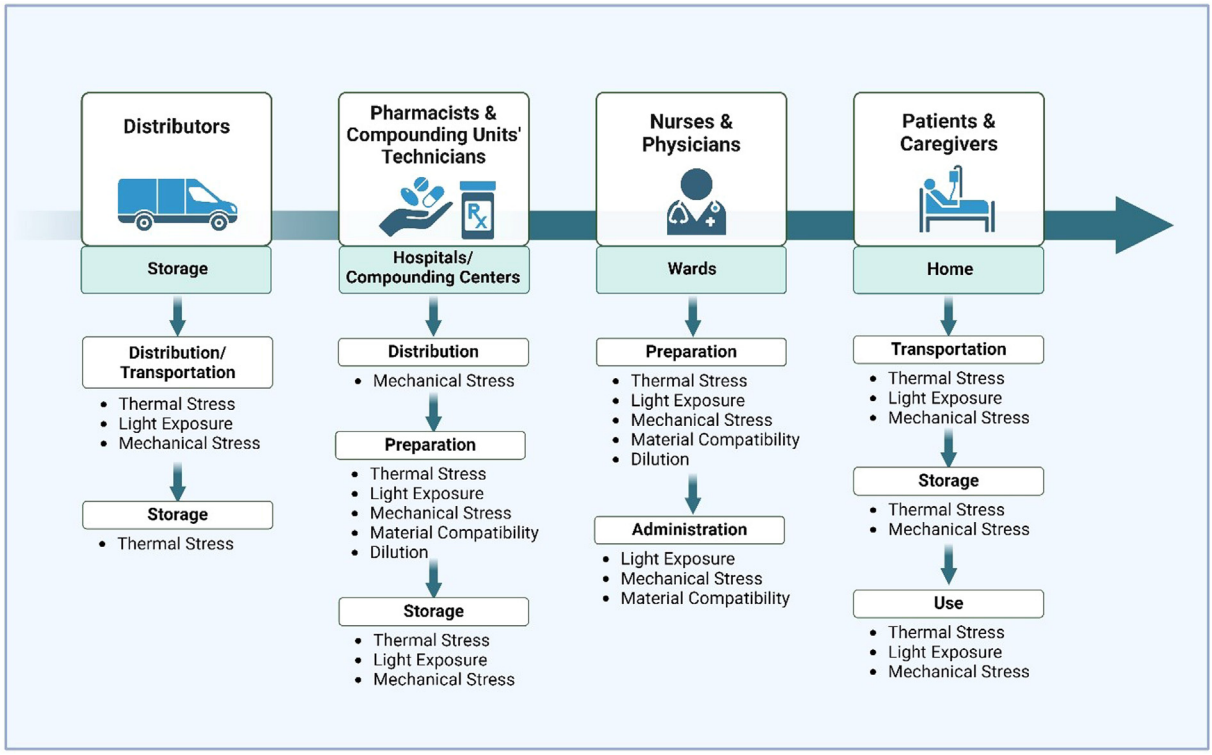

Figure 1. Process flow for post-release of DPs from a controlled environment, after cGMP manufacturing, to the end users, healthcare providers and/or patients. Potential DPs quality altering events for each process step are shown in the figure and include 1) mechanical stresses (i.e., agitation, stirring, and cavitation, 2) temperature excursions and thermal stresses, 3) ambient and extreme light exposure, 4) clinical compounding including dosing solution preparation and administration. Created with BioRender.com.

Besides long-distance journeys, short distance transport within hospitals, using for example pneumatic tube systems (PTS), may also lead to unintended product risks and impact patient safety.[63–68] Although some guidance on PTS transports is available (i.e., from the Institute for Safe Medication Practices, ISMP), there are no harmonized recommendations and these processes often follow local site practices, as stated in an earlier section. Since PDs degradation pathways depend on numerous factors, including product, formulation, and packaging, generic risk analyses are not sufficient to model these complex stresses. It is therefore recommended that representative simulated transport studies, capturing the associated mechanical stress, as measured by digital measuring devices, should drive a data-centric approach to determine product risks and mitigation strategies. Furthermore, the use of mechanical stress monitoring and documentation technologies (i.e., sensors, smart devices, distributors/HCP/patients' electronic reports) to track and monitor DPs and dosing solution transport would benefit patient safety as studies have shown that DPs undergoing non-evident mechanical stress (for example, that do not result in visible damage to the primary or secondary containers) are often administered to patients.[42] The application of these monitoring technologies should be encouraged to deduce the extent and frequency of these stresses.

Temperature Excursion and Thermal Stress

A validated shipping process and a well-established cold chain is typically required to keep the DP within the temperature specifications range throughout its post-manufacturing journey. Nevertheless, unexpected temperature excursions, both above and below the specified range, can impact DP quality.[24,28] Examples of potential degradations from thermal stress include aggregation, an increase in subvisible and visible particle and loss of potency.[22,24,28,45,69] Cold chain breaches can also occur when the DP is directly received by patients, with one study showing that compliance for proper temperature storage of medications for rheumatic diseases was only at 6.7 %.[22] Similar studies, focusing on DP in prefilled syringes (PFS), confirmed low rates of <20 % in patient compliance for proper DP storage temperature.[70,71] These studies conclude that improper temperature storage is often unintentional and can be improved by patient education, the awareness of proper maintenance, and the use of controlled-temperature technology (i.e., temperature monitoring devices).[27,72]

Light Exposure and Photodegradation

Light exposure can induce photodegradation of the DP or of the dosing solution by direct and indirect mechanisms. The former includes direct interactions with the active pharmaceutical ingredients. The latter includes interactions with photosensitive components such as buffer salts, surfactants, and other excipients.[52,73,74] Photo-induced degradation can impact both physical and chemical quality attributes and lead to aggregation, fragmentation, oxidation, deamidation, and loss of potency.[49,74] Furthermore, changes in visual appearance including discoloration have been observed.[75] More insights about DP photodegradation mechanisms can be found in the published literature.[74,76] The exposure to different sources and light intensities has been shown to correlate with the extent of photodegradation, with exposure to natural light (i.e., sunlight) being usually more harmful than indoor light exposure.[50] To avoid photo-induced degradation, changes to the DP formulation can be made to include potentially photo-protective excipients.[74] In addition, alterations to packaging can be used to protect from light exposure including the use of both primary and secondary packaging made of dark amber glass and cardboard boxes, respectively. However, during end-user handling (such as with patients or HCPs), the DP is taken out from its protective packaging and could inadvertently be exposed to ambient

Table 2
Summary of published studies investigating the impact of stress factors on DP stability.

Reference	Molecule name (manufacturer) [Concentration]	Stressors description	Stability outcomes description	Main stressors investigated
Henkel et al. (2020)[28]	Lyophilized Tenecteplase	Vials containing 50 mg lyophilized drug are stored at 4.0 °C, 35.5 °C, or 44.9 °C for 8 h prior to reconstitution	Exposure to elevated temperature negatively affect lyophilized tenecteplase stability and pharmacological efficacy.	Temperature
Chandler et al. (2008)[29]	Regular Insulin and NPH Insulin (Novolin R, Novo Nordisk, Princeton, NJ) [70 % isophane/30 % regular insulin]	Stored in insulated transport containers from 22 °C to 45 °C (summer) and from −10 °C to 18 °C (winter) transit conditions for 24 h to 120 h.	All insulin types studied met the USP specifications and retained product stability.	Temperature
Davis et al. (2020)[30]	Ebolavirus vaccine ERVEBO	Thawed from −80 °C to room temperature and placed on a horizontal orbital plate shaker at 200 rpm, 2–8 °C, for 1, 3 and 7 days.	No impact on drug product potency.	Mechanical stress
Sharrow et al. (2012)[31]	Insulin Lispro	Delivery of different insulin doses from continuous subcutaneous insulin infusion devices at 37 °C and 100 rpm over 14 days.	No insulin precipitation, no device occlusion. The drug met the USP criteria for potency.	Temperature Mechanical stress
Senesh et al. (2010)[32]	Humalog® (insulin lispro, Eli Lilly) Novolog®/Novorapid® (insulin aspart, Novo Nordisk) Apidra® (insulin glulisine, Sanofi-aventis).	Tested inside Solo™ MicroPump (Medingo Ltd) at 37 °C, 40 % relative humidity, 35 rpm at different pump delivery rate for 6 days.	Insulin analogs lispro, aspart, and glulisine maintained physical, chemical, and biological properties.	Temperature Mechanical stress
Fradkin et al. (2009)[26]	rhGH Nordiflex1 (Novo Nordisk1, Bagsvaerd, Denmark) [1 mg/ml] rhGH Saizen1 (Serono, Rockland, MA) [1 mg/ml]	A. After reconstitution, vials were shaken at 1000 rpm for 72 h at room temperature. B. After reconstitution, vials underwent 20 freeze-thaw cycles.	Stressor dependent levels of aggregation in both products. Only one of the two aggregated drugs results to be immunogenic in mice.	Temperature Mechanical stress
Kiese et al. (2008)[33]	mAb (IgG1) [10 mg/ml]	200 rpm at 5 °C or 25 °C with different headspace and different polysorbate 20 concentrations up to 168 h.	Formation of visible particles and soluble aggregates promoted by headspace and absence of surfactant.	Temperature Mechanical stress
Senstius et al. (2007)[34]	Insulin Aspart	Worst case real-life scenario simulation. Insulin shaken at 30 oscillations/min and 37 °C for 7 days while stored in a Medtronic (Northridge, CA) MiniMed® 508 pump.	No impact on stability and potency	Temperature Mechanical stress
Senstius et al. (2007)[35]	Insulin Aspart Insulin Glulisine	Insulin shaken at 30 oscillations/min and 37 °C for 10 days while stored in a Medtronic MiniMed® 508 pump, with different injection flow-rate.	Both Insulin Aspart and Glulisine retained a high proportion of native insulin. Some differences in stability between the two insulin type.	Temperature Mechanical stress
De Felippis et al. (2006)[36]	Insulin Lispro	Insulin shaken at 100 rpm and 37 °C for 7 days while stored in different continuous subcutaneous insulin infusion devices.	Increase in high molecular weight species but potency and aggregates met specifications limits.	Temperature Mechanical stress
Torisu et al. (2017)[37]	humanized immunoglobulin G1 (IgG1) [0.9 mg/ml]	Shaking and mechanical shock.	Aggregation rate under combination stress was much faster than under shaking stress alone.	Mechanical stress
Guo et al. (2016)[38]	Vaccine suspension in syringes [0.5 ml of suspension in 1 ml syringes]	A. Simulated shipping study with vibration table employing the International Safe Transit Association 3A profile. B. Actual Shipping: from the manufacturing site to the testing site.	Product quality and physical properties not affected.	Mechanical stress
Jiao et al. (2020)[39]	mAb in syringes coated with silicon oil [140 mg/ml]	102 drops in the range 30 cm − 90 cm (ISTA 3A shock procedure)	Particle counts for mAb1+PS80 exceeded the USP ⟨788⟩ limit for $\geq 10\ \mu$m subvisible particles.	Mechanical stress
Siska et al. (2020)[40]	Ustekinumab [90 mg/ml]	Real-world observation of priority overnight shipping. Samples were maintained at 2–8 °C. Up to 40 shock events from 8 G to 36 G.	Different particles formation depending on the presence of polysorbate 80 in the preparation.	Mechanical stress
Wu et al. (2020)[41]	mAb [1 mg/ml]	1 or 2 drops from heights between 0.5 m and 1 m	Generation of subvisible protein particles ($\geq 2\ \mu$m)	Mechanical stress
Randolph et al. (2015)[42]	antistreptavidin IgG1 (Amgen, Inc.) [1 mg/mL or 35 mg/mL] rhGH [1.75 mg/mL]	1 drop in the range between 25 cm and 1 m	No monomer loss or soluble aggregates formation. No significant chemical degradation. Increase in subvisible particles number. Formation of surface adsorbed aggregates.	Mechanical stress

(*continued on next page*)

Table 2 (*Continued*)

Reference	Molecule name (manufacturer) [Concentration]	Stressors description	Stability outcomes description	Main stressors investigated
Crampton et al. (2020)[43]	ABP980 (Trastuzumab biosimilar) [0.3 mg/mL and 3.8 mg/mL]	Stored in polyolefin IV bags (diluted in 0.9 % saline), protected from light for 35 days at 2 °C-8 °C or 30 °C plus 2 days at 30 °C. Prior to storage, 2 h of transportation simulation and 4 drops (2 before shaking + 2 after shaking) from 46 cm.	Sensitive to chemical degradation at 30 °C storage. Increase in ≥ 10 μm subvisible particles in low-dose dilution	Temperature Mechanical stress In-use handling
Kim et al. (2019)[44]	CT-P10 (Truxima®, CELLTRION, Incheon, Republic of Korea) [1 mg/ml and 4 mg/ml]	IV bags containing DP were prepared and stored under dark 2 −8 °C conditions for up to 6 weeks. Infusion bags were then incubated in the dark at 25 °C at 60 ± 5 % relative humidity for 24 h	Drug product retain stability, binding affinity, and potency.	Temperature In-use handling
Lamanna et al. (2019)[45]	Rituximab biosimilar (Rixathon/Riximyo) [1 mg/ml]	DPs in the final month of their 36-month shelf-life were used and were exposed to 14 days of room temperature and light. Samples were diluted in saline solution and stored in IV bags for 14 or 30 days at 5 °C followed by 24 h at room temperature to simulate product handling.	Concentration, physicochemical and biological properties remain unchanged. Product remains stable.	Temperature Light In-use condition
Kumru et al. (2012)[46]	mAb [1 mg/ml, 3.5 mg/ml, 6.5 mg/ml]	DP injected in IV bags containing 0.9 % saline and incubated horizontally at 100 rpm and 30 °C for up to 6 h. Presence of different PS20 amount in the IV bag.	Significant loss of monomer, formation of aggregates and subvisible particles. Trend decreased with added PS20.	Temperature Mechanical stress
Ikesue et al. (2010)[47]	Cetuximab [2 mg/ml] Panitumumab [20 mg/ml; 2.5 mg/ml]	DPs in glass vials and diluted inside bags with 0.9 % saline and stored at 4 °C for 7 and 14 days.	No change in concentration, color or turbidity were observed.	In-use handling
Piro et al. (2009)[48]	Different pediatric drugs for continuous infusion	Stored in syringes or chambers for infusion at 22.5 °C for 72 h	None of the syringes or chamber samples demonstrated contamination, bacterial growth or discoloration after 72 h.	Temperature In-use handling
Fongaro et al. (2022)[49]	Ipilimumab (Yervoy, Bristol-Myers Squibb) [5 mg/ml; 1 mg/ml]	A. Incubated at 37 °C and 750 rpm up to 45 days. B. Concentrated and diluted (0,9 % saline, 5 % glucose) PDs irradiated with 720 kJ/m^2 (200 W hours/m^2) in the UV region (320–400 nm). 10,460 kJ/m^2 was applied to maximize the light stress. Temperature kept at 22 °C. C. Diluted DP (1 mg/ml and 0,1 mg/ml) in 0.9 % saline or 5 % glucose solutions stored for 30 days.	A. No change in stability B. Light induced aggregation and chemical modifications (oxidation and deamidation) of DP when irradiated with 720 kJ/m^2 or 10,460 kJ/m^2. Diluted DP is more susceptible to light induced instability. C. Presence of aggregation and chemical modifications, increasing with dilution.	Light Exposure In-use handling Mechanical stress Temperature
Kaiser et al. (2021)[50]	mAb-A [90 mg/ml] mAb-B [90 mg/ml] mAb-C [90 mg/ml]	Glass syringes exposed to visible light at 700, 2200, or 8000 lux for up to 528 h at 25 °C and 60 % relative humidity.	Increase of 0,65 % in HMW species upon light dosage of 400,000 lux h. Chemical modification of Methionine and Tryptophan.	Light
Seckute et al. (2020)[51]	ABP215 (Bevacizumab biosimilar) [1.4 mg/ml and 16.5 mg/ml]	Diluted into IV bags with 0.9 % saline and stored at 2 °C–8 °C for 35 days, followed by storage at 30 °C for 2 days and IV infusion simulation on day 37. DP was exposed to ambient light during preparation, sampling and infusion operations.	DP remains physically and chemically stable	Temperature in-use handling
Shah et al. (2018)[52]	mAb8 (IgG1) [10 mg/ml]	DP exposed to light as per ICH guidelines (1.2 million lux hours of visible light, 200 W-h/m2 of UVA light), in clear glass vials, at 25 °C with different formulations	Formation of aggregates, fragments, and loss of monomer. Increase in hydrodynamic radius. Decrease in ADCC activity and biologic efficacy.	Light Temperature
Schargus et al. (2021)[53]	Bevacizumab [25 mg/ml] Aflibercept [40 mg/ml] Brolucizumab [120 mg/ml]	Tested in original glass vials or repackaged in Luer-Lock syringes by compounding pharmacy. The samples were stored at 4 °C up to 5 days.	Repackaged bevacizumab shows similar attributes to the other original products. Subvisible particles exceed USP<789> guidance. Nanoparticles levels are the highest in brolucizumab and seems to correlate to protein concentration.	In-use handling
Crul et al. (2019)[54]	Bevacizumab	DP repackaged from glass vials to Luer-Lock polycarbonate syringes from compounding centers and stored at 2–8 °C for 28–37 days.	Particles present in the original glass vials (meet EU criteria). Repackaging increases the number of particles. No further increase during storage (meet EU criteria).	In-use handling
Maruno et al. (2018)[55]	Adalimumab [0,1 mg/ml and 10 mg/ml] Etanercept [1 mg/ml] Infliximab [1 mg/ml]	Stored in glass syringes (with and without silicone oil coating) and cycloolefin polymer syringes at 4 °C for 1 week, protected from light.	Formation of aggregates upon ejection from syringes. Glass syringes with silicone oil have the highest concentration of protein adsorbed to surfaces.	In-use handling
Schargus et al. (2018)[56]	Bevacizumab [25 mg/ml] Aflibercept [40 mg/ml] Ranibizumab [10 mg/ml]	Tested in original glass vials or repackaged by central pharmacy.	All samples present particles formation. Bevacizumab shows higher number of particles. Ranibizumab retains higher quality	In-use handling

(*continued on next page*)

Table 2 (*Continued*)

Reference	Molecule name (manufacturer) [Concentration]	Stressors description	Stability outcomes description	Main stressors investigated
Waxman et al. (2017)[57]	A. 4 different DP in late-stage development B. Abatacept [1 mg/ml] Human IgG1 [1 mg/ml]	DPs in glass siliconized syringes or cycloolefin polymer syringes without silicone oil. A. Stored at 2–8 °C or 25 °C for 14 months protected from light. B. End-over-end rotation (7–10 rpm) for 48 h.	A. stable at 2–8 °C while degraded at 25 °C. No significant differences between glass and plastic syringes for 3 out of 4 proteins. 1 protein is less stable in siliconized glass syringes upon storage at 25 °C. B. Maintains stability. No significant differences between proteins stored in different primary containers	In-use conditions Temperature Mechanical stress
Gerhardt et al. (2014)[58]	Humanized IgG1 mAb [1 mg/ml]	DP in glass siliconized syringes, with air bubble and no surfactants. During incubation the syringes are rotated end-over-end at 1.5 rpm at room temperature for 2 weeks.	Formation of particles ≥ 2 μm in all samples. Air bubble, silicone oil and agitation alone promote particles formation. When applied together synergic effect in particles formation	In-use conditions Mechanical stress
Palmer et al. (2013)[59]	Bevacizumab	DP repackaged by compounding pharmacies and stored for 14 days at 4 °C.	Great variability between samples after repackaging. Repackaging causes particles formation, which further increase upon incubation. Formation of silicone oil derived particles.	In-use conditions
Liu et al. (2011)[60]	Bevacizumab (Avastin; Genentech Technology, Inc., South San Francisco, CA)	A. DP repackaged by 4 different compounding pharmacies in insulin plastic and tuberculin siliconized syringes at 2–8 °C. B. DP stored inside insulin plastic siliconized syringes at 4 °C, protected from light up to 12 weeks. C. DP in insulin and tuberculin siliconized syringes subjected up to 10 freeze-thaw cycles (−20 °C freezing). D. DP in insulin and tuberculin siliconized subjected to 20 drops from 1.2 m height.	A. Great variability between samples. Formation of HMW particles and substantial monomer loss in some samples upon repackaging. B. No further increase in particles during storage after repackaging. C. Freeze-thaw cause increase in total particle count, about 10 % monomer loss and slight increase in HMW species. D. Mechanical shock generates particles.	Temperature In-use condition Mechanical stress

light. It could also be placed in transparent syringes or IV bags, increasing the exposure to light and so the likelihood of photodegradation.[50,51,77–79] Specific means of mitigation for the prepared DP of very photo-sensitive molecules could be to use colored, but transparent, covers for e.g. IV bags and infusion lines, but this would then be described in the site instruction or in the product label if required.

The Complexity of Clinical Handling and Administration

The recently revised USP chapters <797> and ⟨800⟩ provide updated guidance in pharmaceutical compounding and hazardous DP handling. These complement the existing chapters USP ⟨795⟩ and ⟨825⟩.[13,80–82] The importance of adequate clinical handling guidelines to patient safety cannot be understated as it is the "last mile" prior to administration in patients. Although a DP is manufactured compliantly following cGMP guidelines, potential compounding and administration errors can compromise DP efficacy and patient safety.[56,60,68,83,84]

To enable safe, accurate, and precise dosage preparations, DP sponsors perform clinical in-use simulation studies representative of the clinical process, including experiments to understand and potentially mitigate the impact of the aforementioned stresses such as transport, light, and temperature excursions. In addition, detailed steps on DP preparation, including reconstitution and dilution, are carefully described in the drug marketing submission and on the DP label. However, unintended stresses can be introduced during the clinical handling processes.

When the DP arrives at its clinical destination, safe and controlled unpacking and storage is needed prior to dose preparation and distribution, otherwise risks of exposing the DP to temperature excursion and undesired light can occur. Once outside the secondary package (i.e., cardboard box), the DP is aseptically handled by local hospital site rules as well as national and state laws. The subsequent drug compounding step should be handled by educated and trained professionals in controlled settings, but some at home manipulation may be necessary. For certain steps that require specific attention (e.g., DP reconstitution), regulatory guidance to minimize poor practices are available (as described in Table 1).[10,85] The challenges associated with DP dilutions, handling and storage, and the associated product impacts are reported in many works.[43–52,75,78,86–91]

Once the DP is removed from the primary and secondary packaging, potential photo-induced stress can be introduced, as described previously. Although guidelines on the evaluation of photo stress on DP for manufacturing exist, many of these guidelines (including ICH) are limited in scope as they do not provide the necessary nuances on ambient level of lighting and specific product susceptibility (e.g., ADC) at the clinic but instead focus on the risks of extreme product degradation.[9] Clearer guidance on product risks during clinical in-use is necessary to align expectations between regulators, DP manufacturers/sponsors, HCPs, and professionals. Due to the lack of a clear definition for photo-sensitivity, many DPs are labelled as photo-sensitive, despite the mild ambient lighting condition at a typical pharmacy and in the clinical setting. In addition, the definition of stability for clinicians versus DP developers are different, thus raising issues of unnecessary complexity due to different terminologies such as reconstitution time, puncture technique, and storage, infusion, and beyond-use times. These differences could be reduced through an alignment between DP manufacturers, regulators, and pharmacy and health care providers.

In addition, the quality of the DP and the dosing solutions must meet compatibility acceptance criteria with clinical components such as spikes, IV bags, IV lines, CSTDs, and syringes, as well as with clinical diluents (e.g., 0.9 % sodium chloride, 5 % dextrose or lactated ringer). The dosing solution is particularly susceptible to degradation due to

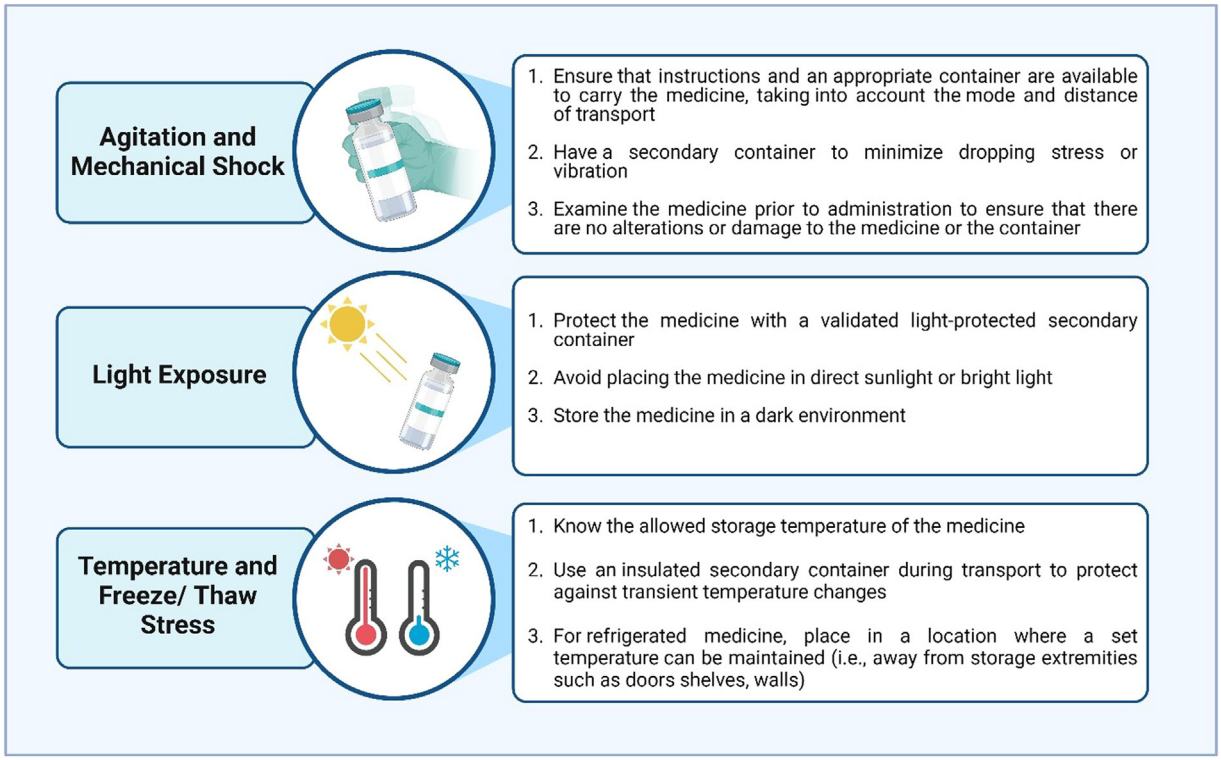

Figure 2. Example of a user-focused infographic for proper storage and handling of biological medications to protect against damages due to common stresses. Created with BioRender.com.

the dilution of protective excipients otherwise typically present in the DP formulation. Furthermore, the potential drug interactions with surfaces after dilution with clinical diluents can lead to challenges such as underdosing, aggregation and particle formation. Examples of surface-induced adsorption or degradation include exposure to air-liquid interfaces and hydrophobic surfaces such as common plastic IV bags, filters, lines, and leached silicone oil.[39,55,60,92] Adsorbed denatured proteins can also potentially dislodge, providing seeding events for future degradation.[58,93] Finally, many of the modern biologic modalities are delivered using patient centric devices such as prefilled syringes, auto-injectors and on-body devices. Due to the nature of the moving parts in these devices, the presence of silicone oil and tungsten can impact DP quality, and subvisible and visible particle counts.[39,92,94] Although silicone oil at the levels present in these devices is unlikely to introduce toxicological and immunological risks,[95] the complexity of DP delivery devices requires clear instructions for pharmacists to prepare, for the nurses to administer, and for the patients to monitor.[96]

To protect against the undesired events described during clinical handling, formulations are carefully designed to include stabilizing excipients such as sugars, buffers, salts and surfactants. Although excipients such as surfactants can offer protection, these chemicals have to be carefully controlled (e.g., quality level, content at above critical micelle concentration) because they can also degrade and impact product stability.[93,97] Examples of excipient degradation can include oxidation that can lead to reactive species generation and degradation.[91,98] In a clinical or home setting, there is also the possibility to experience combined or cumulative stresses. For example, dosing solutions can be exposed to elevated temperature and mechanical stress during transport. Case studies have shown that degradation causes an increase in the subvisible count which can be amplified by combined stresses.[46,47,86,87] It is therefore critical for drug developers to understand the regional nuances of pharmacy compounding and handling so they can develop a robust and stable process for DP compounding and administration to ensure patient safety.

Events Prior to Administration by Caregivers and/or Patients

Patients, caregivers, and HCPs play a critical role towards ensuring that the DP administration process complies with the manufacturing instructions. Advances in hospital technology result in multiple routes for the DP to be transported across short distance (e.g. robots, pneumatic tubes, manual transport, road transport, etc.).[64–66,99] Special containers and handling instructions should be provided to ensure that the DP is protected. Several studies have highlighted the lack of detailed information for patients to maintain DP quality.[37,40,100,101] Thus, training materials, to ensure proper DP handling to maintain stability, should include input from HCPs to ensure that they understand how to properly educate patients and caregivers.[64,102] Recent publications highlight that patients are more likely to get their DP instructions from nurses and pharmacists.[80] Therefore, an area of focus for RealHOPE is to generate material targeting this professional group to have the greatest impact on the patients.[22,100] Fig. 2 depicts an example of a user-focused infographics that could be used in the clinics as an education tool.

Conclusion

The objectives of this review were to raise regulatory and technical awareness about post-manufacturing stresses on protein-based biologics and the potential detrimental impact on the product quality of the drug product and dosing solutions. The goal was to provide an overview of the post-manufacturing framework and to create informative and educational material for all users of biologic medicine to avoid potential unintended stresses and misuse.

Unlike synthetics, this class of molecule presents unique product quality attributes that require special considerations, and newer modalities within biologics with complex stability pathways, such as lipid nanoparticles, nucleic acids, antibody drug conjugates, and cell and gene therapy technologies, are being evaluated in the clinic. In addition, advances in post-manufacturing technologies engender the

introduction of new processes (e.g., robots, drones) that remain to be fully assessed in terms of compatibility and safety. To tackle these challenges, RealHOPE project is encouraging communication and collaboration among scientists, healthcare providers, device manufacturers, and regulators to develop patient centric processes and help further bridge the aforementioned gaps to build a true path for safer handling of protein-based biologics.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclaimer

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