Journal of Pharmaceutical Sciences 114 (2025) 103704

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Exploring industry stakeholder perspectives on a clinical testbed for evaluating the handling of protein drugs in hospitals

Jesper Arvidsson[a], Yaser Alkhatib[b], Marc Egen[b], Ulla Elofsson[c], Anna Fureby Millqvist[c,d], Carmen López-Cabezas[f], Marie Wahlgren[d], Marika Rosenberger[e], Mattias Paulsson[g,*]

[a] Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden
[b] Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65 | 88397 Biberach, Germany
[c] RISE Research Institute of Sweden, Stockholm, Sweden
[d] Department of Food Technology, Lund University, P.O. Box 124, 22100 Lund, Sweden
[e] Sanofi-Aventis Deutschland GmbH, Biologics Drug Product Development & Manufacturing, Industriepark Hoechst, K703. Brüningstr. 50, 65926 Frankfurt am Main, Germany
[f] Pharmacy Service. Hospital Clínic Barcelona, Villarroel 170, 08036 Barcelona, Spain
[g] Department of Women's and Children's Health, Uppsala University, 751 85 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 23 November 2024
Revised 18 February 2025
Accepted 19 February 2025
Available online 22 February 2025

Keywords:
Protein formulation
Monoclonal antibody
Stability
Transport
Protein aggregation
Injectables

ABSTRACT

Protein drugs, such as therapeutic antibodies, are complex and require careful handling to maintain their efficacy and quality. Stress factors in hospitals, like temperature variations and mechanical shocks during transport, may negatively impact the stability of protein drugs (e.g. various monoclonal antibodies). The pharmaceutical industry possesses extensive knowledge about their product formulations but often the transfer of knowledge from lab studies into in-hospital handling procedures is challenging. To address this gap and find a way to bridge academia, healthcare, and industry, seven semi-structured interviews were conducted with experts from pharmaceutical companies across five countries. This study aimed to explore the opinions of formulation experts regarding stress evaluation in clinical settings. Thematic analysis of the interviews revealed four key themes: The human factor in clinical sites, clinical sites as data providers, potential complexities in conducting tests within a clinical setting, and challenges associated with product-specific methods, equipment and devices. This study also suggests tools for setting up clinical test beds that can help the pharmaceutical industry improve stress evaluation and understand clinical product handling. Direct collaboration with clinical sites is crucial, as experts perceive improved evaluation methods and education to be necessary for ensuring safe medicines for patients.

Introduction

Protein drugs, such as therapeutic antibodies, are structurally complex and require careful handling and awareness to maintain their integrity and stability. Potential stress factors such as temperature, mechanical shock, shaking, vibration, and light exposure may negatively impact the efficacy and quality of protein drugs, compromise product integrity and pose patient safety concerns.[1–3] In hospitals for example, pneumatic transport systems are commonly used and their rapid acceleration and deceleration can introduce mechanical stress that may impact the stability of protein drugs (e.g. various monoclonal antibodies). However, studies show that the impact varies depending on factors such as the presence of stabilizing surfactants, headspace, and transport conditions.[4–7] This highlights the need for further real-world data to fully understand the effects of pneumatic transport systems on sensitive protein formulations and provide guidelines.[8] There is also a high degree of variation in daily handling of proteins in pharmacies worldwide.[9] Likewise, the lack of awareness and access to information among healthcare professionals and hospital porters can contribute to risks in the handling and storage of protein drugs.[10,11]

The pharmaceutical industry has extensive knowledge of its products and abundant data about how the drug product behaves during

Abbreviations: CSTD, Closed System Transfer Device; EHR, Electronic Health Record; FMEA, Failure Mode Effect Analysis; HCP, Health Care Professional; MAbs, Monoclonal antibodies; NIOSH, National Institute for Occupational Safety and Health; PDSA, Plan-Do-Study-Act; PETT scan, People, Environments, Tools, and Tasks scan; SEIPS, Systems Engineering Initiative for Patient Safety; SmPC, Summary of Product Characteristics.

* Corresponding author.
E-mail address: mattias.paulsson@kbh.uu.se (M. Paulsson).

https://doi.org/10.1016/j.xphs.2025.103704

production/storage and shipping. While the pharmaceutical industry has a solid understanding of clinical practices through collaboration during drug development, post-marketing surveillance, and regulatory requirements (e.g., filing for in-use data), there remains a gap in real-world insights into hospital-specific handling practices, such as the use of pneumatic tube systems. Also handling steps with considerable involvement of human intervention and decision making by healthcare professionals may be difficult to foresee and repeat even using e.g. site-selection questionnaires to map out site practices. Guidance from regulatory agencies request in-use stability and compatibility data to support investigational clinical studies and marketing authorization, however, no clear expectations exist to guide industry applicants on their in-use testing strategy, such as the study set-up, the range of parameters and materials to be tested.[12] For licensed drugs, access to a clinical environment can be valuable for investigating complaints or managing deviations. We believe that access to real-life handling data from clinical settings offers the pharmaceutical industry a great opportunity to conduct better in-use stability studies, understand deviations, and ultimately improve patient safety. Initiatives like the FDA's CDER Center for Real-World Evidence Innovation highlight the value of using real-world data to gain actionable insights into real-world clinical practices and streamline drug development processes. [13]

In order to create a versatile experimentation environment where academia, healthcare, and industry can meet and understand the protein drug handling challenges, it was suggested to create a clinical testbed as part of the RealHOPE project.[14] The Swedish government agency *Vinnova*, that funds innovation projects, describes a testbed as a physical or virtual environment in which companies, academia and other organisations can collaborate in the development, testing, and introduction of new products, services, processes, or organisational solutions in selected areas.[15] The primary focus being on equipment and events that cannot be independently set up within academia or the pharmaceutical industry – In short "*A space where you can try things out in a relevant setting*" and bridge the gap between laboratory conditions and real clinical practices.

The hypothesis of this study is that formulation science experts from the pharmaceutical industry would find it beneficial to have access to a clinical testbed setting to better understand in-hospital handling of protein drugs. The purpose of this study was accordingly to examine these experts' opinion on evaluating stress factors in a clinical setting and provide a correlating testbed model that can be implemented in hospital settings.

Experimental section

The interview study

This qualitative study was designed using semi-structured interviews (SSI) with key informants since the benefits of SSIs allow the researcher to examine unknown information from key informants.[16,17] Invitations for interviews were sent to contact persons working for the below mentioned EFPIA (European Federation of Pharmaceutical Industries and Associations) partners fitting the following criteria: Employee of an organization that is a partner of the EU IMI (Innovative Medicines Initiative 2 Joint Undertaking) RealHOPE project under grant agreement No 101007939 and had accepted to be listed as a contact person for the third work package (WP3) of the RealHOPE project. The individuals listed as contact persons were all considered formulation experts in the discussion below, as they each had a minimum of 5 years of experience working with protein drug formulation, handling, or stability testing in the pharmaceutical industry, and had been actively involved in relevant work packages focused on in-use stability. A total of 7 participants were interviewed. This number was determined based on the availability of experts who met the inclusion criteria and agreed to participate within the study timeline. While a larger sample could provide additional perspectives, the participants represented a diverse range of pharmaceutical companies and countries, providing sufficient variation for meaningful thematic analysis. Data saturation was assessed during thematic analysis using an inductive approach. Saturation was considered reached when no new themes or subthemes emerged from the data. This was monitored by reviewing the coded data and discussing potential emerging themes with a senior qualitative researcher. We acknowledge that limiting participants to specific organizations could introduce selection bias; however, these individuals were directly involved in relevant work packages, making them uniquely positioned to contribute to the study's aims.

Together with the request there was a pre-read document (Appendix 1) to give an idea of the scope and the context of the interview. The email also contained a consent form with further information about the terms regarding the study (Appendix 2). Upon agreeing to an interview, an invitation was sent by the first author of this study.

As data instrument for the SSIs, an interview guide was developed according to DeJonckheere M and Vaughn LMs paper[17] with open-ended clear questions. An initial pilot was made applying the interview-guide (see Appendix 3) with interviewee 1 (IV1). Afterwards minor changes to the wording of one guiding question and one of the possible follow-up questions was made, and it was also cross-checked with a scientist in social pharmacy at Uppsala University. The data collection took place in the period of October-November 2022 with the use of live video meetings (Zoom) that were End-to-end (E2EE) encrypted. The participants of the study were interviewed in English by the author. Audio recordings of the interviews were kept on an external hard drive, with the length of the interviews averaging 21 (17-28) minutes, including personal thoughts regarding the interview and how it went written down afterwards by the author to improve future interviews.

After the interviews were conducted, they were transcribed through intelligent verbatim according to the method described by McMullin.[18] Themes were developed through an iterative process of coding and categorization, where initial codes were inductively generated from the transcribed data, grouped into categories based on relevance, and finalized through team discussions to ensure consistency and alignment with the dataset. The thematic analysis was done in six phases highlighted in *italics* below according to the method by Braun and Clark[19] with a commitment to an inductive approach. After *familiarization* with data, *codes were generated* and sorted into a code-library. Then the process of *searching for themes* began with the goal of the themes representing patterns found in the data set as well as answering the research questions. When codes seemed to cluster around certain topics, that certain topic was tested as a theme. The next step of *reviewing potential themes* consisted of quality checking, whether the theme would better fit as a code, if there was not enough data to support the theme, if the theme could answer something related to the research questions, and if the themes were coherent enough. This would result in merging two themes into one and removing other themes, *defining and naming* the themes and finally *producing the report*.

This study used the quality criteria of credibility, transferability, confirmability, and reflexivity to establish trustworthiness [20] and we allowed the transcripts to be corrected by the participants and furthermore attempted to adapt the aspects found in consolidated criteria for reporting qualitative research (COREQ).[21] The methods of this study are novel in the field of pharmaceutics but qualitative research examining pharmaceutical industry professionals' beliefs has previously been done.[22]

Ethical approval was deemed not necessary because the study did neither include the processing of sensitive personal data nor a

method that aimed to affect a person physically or psychologically or that involved a risk of harming the interviewee. Participants were informed that the audio recording was used for the collection of data. All participants were adequately informed about the purpose of the study and were given a form for signing consent. All participants' identities were pseudonymized. Since the interviews would take place in a video conferencing media, the meetings were made to be end-to-end encrypted to prevent raw data from the interviews going to any third parties. Due to recording, there was a risk of the non-transcribed interviews being exposed to unauthorized individuals, however this risk was minimized by keeping the recordings on an external hard drive. The data was permanently deleted after transcription to further ensure participant privacy. To further ensure participant anonymity, particular attention was paid to removing any linguistic patterns, verbal tics, or small words that could inadvertently reveal the identity of individual participants. This process also included careful editing to eliminate identifiable traits related to non-native English proficiency, which could otherwise hint at participants' backgrounds. These measures were implemented to maintain strict confidentiality while preserving the integrity of the data.

To generate a word cloud, transcribed interview data were anonymized, and text sections randomized and finally uploaded to WordClouds.com. Prior to generating the word cloud, common stop words such as “and”, “the”, “not,” etc., were removed using the tool’s built-in stop word removal function. Additionally, domain-specific stop words were manually identified and excluded to ensure that the word cloud accurately represented the key themes and concepts discussed by participants. The word cloud generated from the processed text highlighted the most frequently occurring words, visually representing the prominence of specific themes within the dataset. Words appearing more frequently were displayed in larger fonts, providing a quick and intuitive understanding of the primary focus areas of the participants' responses.

Results

In order to document the perspectives of formulation scientists from the pharmaceutical industry, interviews were performed with seven scientists employed by four different pharmaceutical companies situated in five different countries (Germany, France [2 participants], Switzerland [2 participants], the United Kingdom, and the United States). Single interviews were done, with the interviewees being pseudonymized to interviewee 1-7 (IV1-IV7), to distinguish the opinions from one another when quoted. From the interviews, four themes were generated with the usage of thematic analysis, see Table 1. These themes were named: I) The human factor in clinical sites, II) Clinical sites as data providers, III) Potential complexities in conducting tests within a clinical setting and IV) Challenges associated with equipment and devices.

The first theme, ***“The human factor in clinical sites”*** summarizes experts' opinions on human factors as a significant source of protein drug stress, often referred to as human error, and their ideas on how to evaluate and address these stress factors." A substantial amount of the stresses that occurred in the clinical environment was believed to be related to human errors surrounding the handling and delivery of the drugs. This was also something that was deemed as a rather difficult stress to fully evaluate.

> “And I think, or I know from my personal experience that assessing and quantifying effects of human errors is very difficult, because you need to rely on the fact that people tell you the truth and this is not always the case...because people don’t want to lose their face, people are not aware, people remember things differently, people are not properly trained and are convinced they are doing the right thing, but they don’t.” – IV1.

> “I think real life, in front of the patient, it’s... we should always think about... avoid too many dilutions... you always have a human error factor... we can forget the real-life conditions... if procedures are too complicated, they are almost impossible to apply to patients” IV5#2

The sources of stress resulting from the human factor were attributed to insufficient training regarding the inherent sensitivity of protein therapeutics and regarding the ability to detect potential compromises in product quality. This can be traced back to inadequate training, lack of standardisation of handling among HCPs and the occasional challenges in understanding instructions.

> “And then I also think clear instructions to the end-users to understand the risks and liabilities and how to handle these drugs, pharmacy manuals, instructions for use, prescribing information, those kinds of things is another point, but I think based on learnings that we’ve had the end-users don’t always read all that information thoroughly and having things that are more... Easy to grasp and gets the main points across, whether it’s a video or web page or visuals, maybe more helpful, but we’re not generating that stuff routinely for clinical products or projects.” -IV6

> ”But as soon as you hand it over to the pharmacy or the hospital, it is completely out of control of the industry, what happens to the drug next. And what I was reported to from the clinics, the awareness among the people there is very poor, the descriptions are there but are not used frequently, so there is no one sitting with the protocol in the ward” -IV7

> “We have to ensure we have the clearest and simplest protocol to avoid any error” IV5#2

> “...So you need to find out, what is the reason for a human mistake, and I think this should be covered as well, how do you find out in the clinic? How do you tackle this? By retraining, by increasing the awareness of the danger of those measure that you take” IV1

Suggestions were made regarding mitigating the influence of the human factor. It was proposed that implementing robust error management guidelines and providing comprehensive training for healthcare personnel could be a potential way forward. However, further investigation is required to determine the most effective approach in this regard.

Table 1
Main themes generated through thematic analysis including subthemes.

The human factor in clinical sites	Clinical sites as data providers	Potential complexities in conducting tests within a clinical setting	Challenges associated with equipment and devices
The human factor as a stress factor	Knowledge of clinical procedures	Challenges regarding good laboratory practices in a clinical setting	The diverse array of closed system transfer devices
Combating the human stress factor.	Clinical stressors documentation methods	Systems already established have a clear advantage.	The inaccessibility of pneumatic tube transportation

In the second theme, ***"Clinical sites as data providers"***, the potential of clinics to offer valuable real-world data on clinical procedures, which may not be accessible to pharmaceutical companies otherwise.

> "We have, for example, standardized stress conditions which we would test according to ICH guidelines. But there is still quite some flexibility, and we also go beyond these kind of testing guidelines to really know more about our product as well. So, the more input we can get on what happens, the better." IV4

> "The world is much more than what we can actually fit in a lab... so some of the things which may be really hard to test and perceive" IV6

For both understanding real-life transport handling as well as reconstitution methods, various approaches were suggested to gather information from clinical sites about the relevant stress factors for further evaluation. One interviewee recommended employing observational methods where an individual would adopt a "fly-on-the-wall" approach (a method of observation where the observer remains as unobtrusive and unnoticed as possible), enabling them to observe from a non-healthcare provider perspective and identify stressors. Conversely, another interviewee proposed an alternative approach, suggesting the use of recordings and sensors instead of on-site human observations to generate valuable data.

> "When we are performing compatibility studies, what is more difficult to simulate is transportation. So here we are working on a model to try to define a kind of worst case. But... we may fail and see an impact of product quality if we are testing something which is not realistic [excessive stress] ... So, this is, I think, where further work and collaboration is needed between the industry and hospitals." IV2

In the third theme, ***"Potential complexities in conducting tests within a clinical setting"***, the challenges of implementing good laboratory practices in a clinical setting as well as the advantages of already established systems in the pharmaceutical industry were highlighted. When asked to talk about any potential benefits or disadvantages regarding the usage of the clinical environment (testbed) as a source of evaluation, there were expressions of doubt among the participants. The reasoning behind this was that for any kind of evaluation in a hospital, there would be a need for qualified personnel to perform the evaluations and that the clinical sites also lacked the equipment necessary to be able to give a complete picture on how the drugs would be affected by stress factors.

> "... and it makes me a little bit uncomfortable for this to be tested, for, I'm going to call it in use compatibility to be tested outside of the manufactures capability because we have qualified methods to look at purity, potency. And all these kinds of things so it's a little bit scary that those methods wouldn't be available within the hospitals and things, so I think. I would almost turn that question around and say, how would you actually demonstrate and be confident about the quality of the product if you're testing it with nonstandard, well, non-qualified methods, I guess, that we would be using within industry, and how much confidence have you got when you're doing that testing, that actually it is still good and safe for the patient." -IV5

There was also confidence expressed in the quality of the methods that the pharmaceutical companies already had at their disposal. This meant that if anything, the stresses that would be able to occur in a clinical setting should always be lesser than what is tested in the industry.

> "The other thing is that we are simulating studies which not always is exactly what is going to happen in the clinic, so our simulation studies are usually done worst-case scenario studies. So, if anything, in the clinic, the stress conditions are less, we should be ok, that is our risk mitigation step." -IV3

From the interviews, it was evident that mapping real-life stress factors in the hospital setting was valuable.

> "...doing a mapping study to understand at what level stresses are happening in the clinic, then we can ... translate that back to make appropriate stress conditions on our site" IV5#2

In the last theme, ***"Challenges associated with equipment and devices"***, interviewees were often concerned regarding the usage of certain devices, e.g. Closed System Transfer Device (CSTD) when preparing the drug or the usage of pneumatic tube transportation within the hospital. One participant discussed how there was a disapproval of using these kinds of devices for new medicines due to the lack of experience with how they would be affected and the difficulty of surrounding testing.

In addition, a concern was identified regarding the simultaneous infusion of multiple drugs in the clinic using the same line. This could mean that when the number of catheter lumens are too low to facilitate separate simultaneous drug infusions to the patient, there is a risk that different drug solutions are administered simultaneously at a Y-site connection resulting in e.g. drug inactivation or precipitation.

> "So, some of the things which may be really hard to test and perceive. For example, if the same catheter or IV-line is used for multiple medicines, so you have these indwelling catheters, for example, for oncology patients, we receive a lot of different treatments, basically through the same tube, and I think it's quite obvious that some of it will be residue there even though you maybe flush it with whatever diluent you have at hand. So of course we also don't want, we don't suggest to use these devices for new medicines because we don't have the experience with it." -IV4

There was concern expressed among the participants of the fact that some hospitals seemingly used pneumatic tubes for the transportation of drugs without having evaluated the effect on the drugs. This was further reinforced as something the participants thought was problematic by the fact that pharmaceutical companies were described as lacking pneumatic tube systems to support sufficient evaluation and mimicking the stress that occurred was something that they struggled with.

> "The pneumatic tube transportation I think would be my, one of the biggest concerns ...because of the speeds that they travel in, the potential for cavitation... We don't have access to a pneumatic tube system" -IV5

Another aspect that made it difficult to evaluate the effect of pneumatic tube transportation by pharmaceutical companies was mentioned as something that had a lot of variability between hospitals such as the speed of transportation. This as well as the amount of turns that could occur during the transportation process, made it hard to replicate the stress.

> "I think there are several challenges around the transportation of the drugs such as pneumatic tube systems. I don't know if many pharmaceutical companies have access to that. In general, things with a lot of variety or variability, such as transportation of a drug is hard to... I mean there are some testing procedures but... It's hard to get real world data on it." -IV4

The other piece of equipment that gained a lot of attention by the participants were CSTDs together with the pneumatic tube transportation. Many concerns were raised over the usage of CSTDs without having properly evaluated the effect of the specific device on the drugs as the usage could potentially impact the quality.

> “But in terms of some of the ways that clinical sites handle things and what we’ve seen, there’s been a lot of discussion on the closed system transfer devices and trying to educate sites that to not use those if it’s not really needed so if there’s not an occupational hazard to not use these devices that may cause product quality impact”-IV6

Unlike the testing of pneumatic tube systems compatibility testing of specific devices was more feasible as the pharmaceutical companies could easier conduct compatibility studies to evaluate if any stresses occurred, however, as there are multiple devices of CSTD only the compatibility of specific devices at a time can be assessed.

> “So, then the manufacturer should be contacted. If the clinic wants to use CSTDs, manufacturers should be contacted and, sometimes they perform some compatibility studies with CSTD so they can also recommend which devices are compatible.” -IV2

A unique comment not being part of the themes is the below comment talking about clinical testbeds proving data for setting up new common guidelines for industry:

> “. . .funneled back into testing guidelines for drug developers.” IV6

In addition to the qualitative analysis of the interviews, the results are visually summarized in Fig. 1 using a word cloud to highlight common themes.

Discussion

This study aimed to examine the opinions of pharma industry experts regarding the evaluation of stress factors in clinical settings. The results presented a focus on four themes including the human factor in clinical sites, clinical sites as data providers, the potential complexities in conducting tests within a clinical setting, and challenges associated with equipment and devices, which will be discussed below from a formulation science perspective.

Human factor in clinical sites: Interviewed experts identified the human factor as a challenging stress factor to evaluate and quantify based on their experiences and perspectives. They expressed concerns that healthcare providers (HCPs) may lack sufficient information when faced with too many procedures, leading to potential mishandling of protein therapeutics during preparation and transportation. This risk arises from the sensitive nature of protein drugs being overlooked, as HCPs may fall into routines suited for traditional small molecule drugs. It should be noted that in some fields of healthcare, polypharmacy is common with e.g. 25% of patients prescribed more than 16 unique medications, many to be given the parenteral route.[23] With lengthy SmPCs and complex preparation processes, there is a high risk of deviations from the correct preparation process in a busy ward environment.[24] This complexity and the accompanying knowledge gap were thus considered hurdles in reducing the impact of stress factors in the clinical setting. Strategies to combat the impact of human stress factors included education and proper training and making drug labels more accessible to healthcare professionals. However, the variability in post-production handling practices in clinics for therapeutic proteins posed a challenge in finding a single comprehensive strategy.

Challenges associated with equipment and devices: When discussing the usage of pneumatic tube transfer, participants expressed a

Fig. 1. A word cloud of frequently occurring words from interview transcripts. Figure was made using WordClouds.com

keen interest in obtaining real-world data on their potential effects on protein therapeutics. However, the inaccessibility of pneumatic tube systems at pharmaceutical companies hindered this process. Some hospitals do not have restrictions on using pneumatic tubes for drug transportation according to the experts, but studies raised concerns about their impact on therapeutic proteins. Access to clinical sites' pneumatic tubes could provide valuable information for developing specific transportation recommendations and strategies to reduce stress during transportation. PTS transportation has been shown to result in large increases in protein particles depending on the protein itself, the formulation, the bag material, headspace and the IV solution.[5,7] For a small number of routinely used mAbs, PTS has been shown to be safe. [6]

Additionally, participants recommended conducting compatibility studies for hospital equipment, such as Closed System Transfer Devices (CSTDs), before usage, to ensure proper handling of medications. The CSTDs are generally recommended when preparing hazardous drugs in an environment devoid of safety cabinets [25] but the devices are provided by various suppliers and intended to be used in different ways, adding complexity to the examinations. For example, CSTDs may compromise final product quality, as silicone oil may be released from these devices and contaminate the administered product.[26] Furthermore, studies have shown that the impact of CSTDs on monoclonal antibody stability can vary significantly depending on the specific device and formulation, with some devices contributing to protein aggregation or particle formation.[27–29] Ongoing research is necessary to establish standardized guidelines for CSTD compatibility with different biologics to ensure optimal product safety and efficacy in clinical settings. Thorough communication between industry and clinical sites is essential to ensure alignment on CSTD use and risk mitigation strategies.[30]

The complexities in conducting tests within a clinical setting and *clinical sites as data providers*: In certain circumstances it is advisable to perform certain tests directly at the hospital site because samples should be analyzed directly and cannot be shipped to other locations. Participants expressed however uncertainty about evaluating protein therapeutics in clinical settings, given the resource-intensive nature of current industry practices, e.g. Good Laboratory Practice. However, they showed a positive attitude towards collaborating with clinical sites to improve test methods, presenting opportunities for clinical evaluation. One proposed approach was to have a 'fly-on-the-wall' to collect data on frequently occurring stress factors, but the ownership of this data raised issues of confidentiality and openness. While a study provides insights based on observations at a single site, it is important to acknowledge that the clinical handling practices may vary across different sites, and therefore, the findings cannot be generalized to all locations.

Another possibility addressed in the interviews is to help pharma industry by mapping real-life stress factors in the hospital setting, using qualitative tools, such as the SEIPs model. It consists of different tools of which three tools were found especially useful in this setting: i) The Journey map tool to explain the work processes in a hospital and, ii) the PETT scan tool (PETT being an acronym for People, Environment, Tools, and Tasks) and iii) the Tasks and tools matrices to identify gaps.[31] The model was used to show examples based on input from previously published material.[11,32] Examples showing a typical hospital protein drug *Journey map* can be seen in Fig. 2 or the *Task and tools matrix*, created to illustrate a gap analysis (Table 2) based on experience from the last author's hospital setting.

Other authors have mentioned a gap in guidance from regulators regarding expected in-use stability data due to the wide range of in-use conditions and administration components globally. To address this, a working group has reviewed and consolidated industry approaches for assessing the physicochemical stability of traditional protein-based biological products during both clinical development and commercial use.[12] In today's healthcare, challenges are

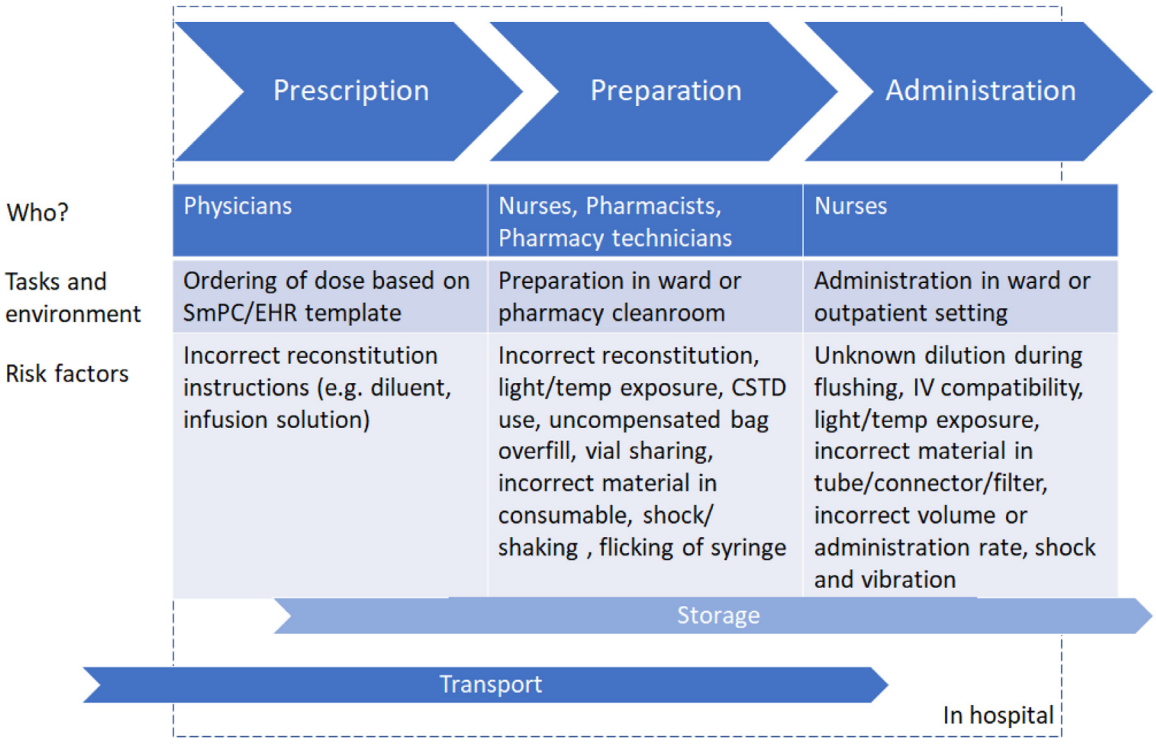

Fig. 2. Journey map for a typical protein drug at the studied hospital as an example based on the of drug chain of medicines in a hospital adapted from Holden, *et al.*[31] SmPC -Summary of Product Characteristics, EHR – Electronic Health Record, CSTD - Closed System Transfer Device, IV – intravenous. The dotted line represents the hospital area. Some administration may take place at other healthcare sites or in the home.

Table 2
Tasks, Tools and Tasks x Tools matrices base on an example of within-hospital logistics of ready-to-administer protein drugs in the studied hospital. SOP = Standard Operating Procedure, PTS = Pneumatic Transport System.

Tasks matrix

Task	Who performs	Goal of task	Frequency	How performed	Lab scale reproducible	Notes
Packaging of ready-to-administer drug container	Pharmacy technician	To safeguard the individual containers from damage, light exposure etcetera	Frequently throughout the day	According to SOP, with temperature control when applicable	Easy	How are shock-sensitive drugs protected?
Transport within ward	Nurses, nursing assistants	To have access to drug for administration at the right time	Frequently throughout the day	Walking and holding container in hand or in bag	Easy	No temperature control, but a short duration
Transport from central pharmacy cleanroom	Pharmacy technician or porters	To have access to drug for administration at the right time	Frequently throughout the day	PTS not in use at the moment for protein drugs	Difficult	Equipment may be used in the future

Tools matrix

	Users	Purpose	Degree of variation	Sensors that can document
Packaging material	Pharmacy technician	To safeguard the containers	Large	Temperature, light
Cart	Porters	To transport goods effectively	Large, risk of drop	Temperature, light
Pneumatic transport PTS	Pharmacy technician	To transport goods effectively	Small	Temperature, gyroscope

Tasks x Tools matrix

	Packaging	Transport within ward	Transport from central pharmacy cleanroom
Packaging material	Yes	Yes	Yes
Cart		Yes	Yes
Pneumatic transport PTS			(Yes, in the future)

significant, and there may be a need to quickly adjust routines to meet the demands of workload, technical development or economic requirements. In such situations, we believe that meeting platforms between industry and healthcare become even more crucial.

Based on the insights gained from the expert interviews, we observed that a clinical test bed would be valuable for the pharmaceutical industry but challenging due to many reasons. A prerequisite, of course, is that a confidentiality agreement is signed between the hospital and the industry partner. In addition, we recommend on-site presence in the *Gemba* (Japanese for the physical place where work is performed). The observer effect (the consequence of research participation on behaviour - people tend to change their behaviour if they know they are being observed) can be reduced by performing the study in a setting that is used to extra persons (e.g. students) being around and with a long observation time.[33] Most hospitals already have long experience from clinical trial onsite audits (to assess compliance with regulatory requirements, Good Clinical Practice guidelines, and the study protocol). We have previously published examination tools based on Gemba walk and FMEA failure mode effect analysis.[32] For example temperature, shock, or light sensitive probes can be used to examine handling situations in the hospital. After acquiring sufficient knowledge about the handling, laboratory scale simulations, or real-life handling tests on-site and analysis can take place. If the SEIPS model tools are used by the hospital and industry expert together in a transparent and quality-focused manner, it will also be clear what instructions are needed, how they should be written and what education should be provided. A plan-do-study-act (PDSA) cycle[34] could be very useful help to follow from early development to post-approval.

The correct handling of medicines in the ward could be ascertained by appointing a hospital pharmacist as a designated person in every hospital, who will advocate for safe reconstitution practices, through setting up procedures and training personnel[35], or promote the creation of centralised reconstitution in hospitals[36] including robotic preparation resulting in more consistent and reproducible preparations.[37] In addition, drug development should be involving patients so that e.g. drug products design is tailored to the respective patient population, also known as patient centric drug product design.[38] Likewise, home-based chemotherapy is nowadays seen as a safe and patient-centred alternative to hospital- and outpatient-based service[39] if proper resources, education, and support are available.[40] When hazardous chemotherapy is given in the home it can either be delivered in a ready-to-administer container (reconstituted in a pharmacy cleanroom) or reconstituted with CSTD in the patient home. The model of a clinical testbed can also be useful in the future for academia or other industries such as the medical devices industry, providing significant benefits in the development, validation, and optimization of products.

Practical tools are presented in this study that cover evaluation of hospital-site-bound equipment such as pneumatic transport systems or preparation robots as well as the non-physical aspects of human infrastructure and use of medical device such as CSTDs. One testbed site is not enough since there are large difference between hospitals[9] instead we provide this generic testbed method. We also believe that a testbed can increase the collaboration between HCP and pharma industry how e.g. a “pharmacy manual” should be designed for a clinical trial. As a result of a reflective analysis of the interviews, key components are presented in Table 3 to help bridge the gap between the lab setting and the clinical application. It is likely that the testbed is only relevant for sensitive protein drugs that are e.g. used in a manner that includes transport from a centralized preparation unit in a reconstituted state to the site of patient administration or where PTS needs to be tested, i.e. equipment that is not feasible to have in industry. Cell and Gene therapy (CGT) products, particularly made-to-order patient-specific drug products and kits, fall outside the scope of

Table 3
Key components in the design and implementation of the testbed offered by e.g. a hospital pharmacy to support a wide spectrum of needs.

Component	Description
Intellectual property and confidentiality	When a hospital pharmacy is selling a testbed service it is crucial to establish clear and legally binding agreements to protect both parties
Controlled and Structured Environment	The testbed provides a controlled and structured setting that ensures reproducibility and reliability in clinically relevant experiments although likely not according to GLP within the hospital.
Interdisciplinary Collaboration	The testbed encourages interdisciplinary collaboration by bringing together researchers from different fields, including academia, pharmaceutical industry, and healthcare professionals. This collaborative approach allows for a holistic understanding of the challenges and opportunities in handling protein drugs. However, conducting a clinical testbed in a hospital faces challenges such as visitors' reluctance to disturb the process, a potential lack of healthcare resources, and potential conflicts of interest
Evaluation of Stresses	The testbed encompasses evaluations of various stresses that protein drugs may encounter during their lifecycle. This includes stress during transport (utilizing pneumatic transport systems or traditional trolley transport), reconstitution including using robots or CSTDs, incorrect storage temperature, and simulated drug administration.
Early Product Development	The testbed serves as a valuable resource in the early stages of product development. Researchers can use the platform to gain insights into the optimal handling of protein drugs before finalizing formulations and handling instructions. In-use stability and compatibility data to support investigational clinical studies and marketing authorization
Complaints handlings or deviation examinations	The clinical testbed allows researchers to replicate the exact conditions under which the product was handled in the clinic. This includes mimicking storage conditions, preparation procedures including equipment such as CSTDs, administration techniques, hang-times and environmental factors
Pharmacy Manual Validation	One aspect of the testbed involves the validation of pharmacy manuals. This includes assessing the readability and comprehensibility of the information presented in the pharmacy manual, ensuring that it can be easily understood by the average pharmacy reader. This work can continue when templates in the prescription software is used to produce information for decision support at point of care.
Simulated Administration	The testbed allows for simulated drug administration, mapping stresses in IV-line pumping, evaluating dead volume in transfer sets/IV-lines, and assessing interactions with tube materials and filters. This simulation provides valuable data on the performance of protein drugs in real-world scenarios including filling in novel containers such as cassettes or storage in patient-carried backpacks
Communication and Collaboration Channels	The testbed facilitates communication and collaboration by offering contact channels for various aspects, such as temperature monitoring, smart labels, academia partner analysis methods, and more.

this study and require further specialized evaluation to optimize CGT formulations.

Study Strengths and Limitations:

The interview study benefited from convenience sampling, resulting in all participants being pharmaceutical experts with extensive experience in working with therapeutic proteins globally. The use of qualitative research through semi-structured interviews allowed for in-depth discussions and valuable insights from the participants. The study applied strategies to enhance trustworthiness and authenticity, including credibility, transferability, confirmability, and reflexivity. A notable limitation of this study is the absence of direct observations or interviews with healthcare personnel handling protein drugs in clinical settings. While this would offer a more comprehensive understanding of the human factor, it poses logistical and ethical challenges, such as securing consent and ensuring patient safety. Future research could address this by incorporating direct observations or mixed-method approaches to validate and expand on the perspectives of the 7 interviewed experts. Expanding the sample size and including other stakeholder groups, such as healthcare professionals, would further enhance the understanding of this complex topic.

The term testbed is not easy to grasp, and it needs additional context and explanation. The language barrier during the interviews, conducted entirely in English, may have affected respondents' answers, and led to some misunderstandings. Conducting interviews via video meetings might have hindered full attentiveness due to potential limitations in perceiving body language and verbal cues. The sample size was relatively small, with seven participants out of twenty-two contacted. Although saturation was achieved, a larger sample size could have provided additional perspectives.

The pre-read of clinical procedures might have influenced participants' ideas and should be acknowledged as a limitation.

One strength of this study is that it provides a collaboration solution for a need that is described by others in protein drug literature.[41] It offers tools that can be used in the form of contacting specialized hospital offering a testbed or performing examination resembling onsite clinical trial audits. Overall, the study provides valuable insights into stress factors evaluation in the clinical setting, while also acknowledging its limitations.

Conclusions

In conclusion, this study provides insight into the evaluation of stress factors in clinical settings, concerning protein drugs. The findings reveal that the interviewed experts perceive the human factor as a significant challenge in quantifying and mitigating stress, suggesting that educational initiatives and enhanced training for healthcare professionals and supporting staff, such as porters, could be beneficial. Concerns about the impact of accessories (consumables, including CSTDs) and equipment, such as pneumatic tube transport, on therapeutic proteins highlight the need for real-world data and compatibility studies for hospital equipment. Collaborating with clinical sites presents an opportunity to improve evaluation methods, though issues of data ownership and confidentiality must be addressed. The study's strengths lie in its expert participant sampling and qualitative approach, though language barriers and sample size are limitations. Recommendations for evaluation tools and a plan-do-study-act cycle offer practical insights for pharmaceutical industry experts in this domain. Further research in home healthcare settings and exploring product handling through testbeds could enrich the field. Overall, this study confirms the hypotheses that it is valuable to have access to a clinical testbed. We recommend that stakeholders prioritize collaborative initiatives to establish pilot clinical testbeds. The study contributes valuable perspectives while acknowledging its limitations and providing potential directions for future research.

Declaration of competing interest

None stated.

Declaration

None of the authors from the pharmaceutical industry were involved in conducting or participating in the interviews. The opinions and statements cited from these interviews are independent and do not necessarily represent the views of the companies the authors are affiliated with.

Funding

This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (RealHOPE grant n° 101007939). [14]

Data availability statement

The data supporting the findings of this study consist of anonymized interview transcripts, which are not publicly available due to privacy and confidentiality agreements with participants. However, key excerpts relevant to the analysis can be made available upon reasonable request to the corresponding author.

Acknowledgement

The experts working for companies being EFPIA partners in RealHOPE are gratefully acknowledged for letting us interview them.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the last author used ChatGPT-4o (OpenAI) for linguistic improvements. After using this tool/service, all authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2025.103704.

References

1. Jiskoot W, Nejadnik MR, Sediq AS. Potential issues with the handling of biologicals in a hospital. *J Pharm Sci*. 2017;106(6):1688–1689. https://doi.org/10.1016/j.xphs.2017.02.029.
2. Crommelin DJA. Differences between biopharmaceuticals and low-molecular-weight pharmaceuticals - immunogenicity of biopharmaceuticals: Why proteins should be treated with respect. *Eur J Hospital Pharmacy-Sci*. 2003;1(112):86–88.
3. Cappelletto E, Kwok SC, Sorret L, et al. Impact of post manufacturing handling of protein-based biologic drugs on product quality and user centricity. *J Pharm Sci*. 2024: S0022354924001953. https://doi.org/10.1016/j.xphs.2024.05.027. Published online May.
4. Desai KG, Colandene JD, Crotts G, et al. Transportation of mAb dosing solution in intravenous bag: impact of manual, vehicle, and pneumatic tube system transportation methods on product quality. *Mol Pharmaceutics*. 2023;20(12):6474–6491. https://doi.org/10.1021/acs.molpharmaceut.3c00859.
5. Kjellström A, Cederwall I, Martínez CS, et al. Pneumatic tube transport of trastuzumab in IV bags-effect of headspace and surfactant on subvisible particle formation. *J Pharm Sci*. 2025:8S0022-3549(24)00604-X. https://doi.org/10.1016/j.xphs.2024.12.003.
6. Coliat P, Erb S, Diemer H, et al. Influence of pneumatic transportation on the stability of monoclonal antibodies. *Sci Rep*. 2023;13(1):21875. https://doi.org/10.1038/s41598-023-49235-6.
7. Linkuvienė V, Ross EL, Crawford L, et al. Effects of transportation of IV bags containing protein formulations via hospital pneumatic tube system: particle characterization by multiple methods. *J Pharm Sci*. 2022;111(4):1024–1039. https://doi.org/10.1016/j.xphs.2022.01.016.
8. Wang P, Nguyen L. Update to delivering medications via a pneumatic tube system. *Am J Health-Syst Pharmacy*. 2017;74(19):1521–1522. https://doi.org/10.2146/ajhp150107.
9. Fayek R, Soleyman M, Jiskoot W, Crul M. Evaluation of post-production handling practices of monoclonal antibodies throughout the world. *Eur J Oncol Pharmacy*. 2021;4(3):e031. https://doi.org/10.1097/OP9.0000000000000031.
10. Martínez CS, Amery L, De Paoli G, et al. Examination of the protein drug supply chain in a swedish university hospital: focus on handling risks and mitigation measures. *J Pharm Sci*. 2023;112(11):2799–2810. https://doi.org/10.1016/j.xphs.2023.05.003.
11. Sabaté-Martínez C, Paulsson M, González-Suárez S, et al. How are we handling protein drugs in hospitals? A human factors and systems engineering approach to compare two hospitals and suggest a best practice. *Int J Qual Health Care*. 2024;36(1):mzae020. https://doi.org/10.1093/intqhc/mzae020.
12. Blümel M, Liu J, de Jong I, et al. Current industry best practice on in-use stability and compatibility studies for biological products. *J Pharm Sci*. 2023;112(9):2332–2346. https://doi.org/10.1016/j.xphs.2023.05.002.
13. Research C for DE and. CDER Center for Real-World Evidence Innovation (CCRI). FDA. December 13, 2024. Accessed January 27, 2025. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-center-real-world-evidence-innovation-ccri.
14. RealHOPE |. Accessed July 24, 2023. https://realhope.se/.
15. Test beds in Sweden | Vinnova. Accessed July 17, 2023. https://www.vinnova.se/en/m/testbed-sweden/testbeds-in-sweden/.
16. Elseviers M, Poluzzi E, Wettermark B, et al. *Drug Utilization Research: Methods and Applications*. John Wiley & Sons; 2016. Incorporated. Accessed July 17, 2023; http://ebookcentral.proquest.com/lib/uu/detail.action?docID=4462519.
17. DeJonckheere M, Vaughn LM. Semistructured interviewing in primary care research: a balance of relationship and rigour. *Fam Med Com Health*. 2019;7(2):e000057. https://doi.org/10.1136/fmch-2018-000057.
18. McMullin C. Transcription and qualitative methods: implications for third sector research. *Voluntas*. 2023;34(1):140–153. https://doi.org/10.1007/s11266-021-00400-3.
19. Braun V, Clarke V. Thematic analysis. In: Cooper H, Camic PM, Long DL, Panter AT, Rindskopf D, Sher KJ, eds. *APA Handbook of Research Methods in Psychology, Vol 2: Research Designs: Quantitative, Qualitative, Neuropsychological, and Biological*. American Psychological Association; 2012:57–71. https://doi.org/10.1037/13620-004.
20. Korstjens I, Moser A. Series: practical guidance to qualitative research. Part 4: trustworthiness and publishing. *Eur J Gen Pract*. 2018;24(1):120–124. https://doi.org/10.1080/13814788.2017.1375092.
21. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349–357. https://doi.org/10.1093/intqhc/mzm042.
22. Parsons S, Starling B, Mullan-Jensen C, Tham SG, Warner K, Wever K. What do pharmaceutical industry professionals in Europe believe about involving patients and the public in research and development of medicines? A qualitative interview study. *BMJ Open*. 2016;6(1):e008928. https://doi.org/10.1136/bmjopen-2015-008928.
23. Heneghan JA, Trujillo Rivera EA, Zeng-Treitler Q, et al. Medications for children receiving intensive care: a national sample. *Pediatric Crit Care Med*. 2020;21(9):e679–e685. https://doi.org/10.1097/PCC.0000000000002391.
24. Alexander M, King J, Lingaratnam S, et al. A survey of manufacturing and handling practices for monoclonal antibodies by pharmacy, nursing and medical personnel. *J Oncol Pharm Pract*. 2016;22(2):219–227. https://doi.org/10.1177/1078155214559113.
25. Hodson L, Ovesen J, Couch J, et al. *Managing hazardous drug exposures: information for healthcare settings*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2023. doi:10.26616/NIOSHPUB2023130.
26. Wozniewski M, Besheer A, Sediq AS, Huwyler J, Mahler HC, Levet V. Characterization of silicone from closed system transfer devices and its migration into pharmaceutical drug products. *J Pharm Sci*. 2023:S0022354923004859. https://doi.org/10.1016/j.xphs.2023.11.012. Published online November.
27. Grzincic EM, Parikh T, Hong C, Rabiah NI, Yi L, Gupta S. Impact of Closed System Transfer Device (CSTD) handling procedure for low-transfer-volume dose preparation of biologic drug products. *J Pharm Sci*. 2024;113(6):1523–1535. https://doi.org/10.1016/j.xphs.2023.12.016.
28. Patke S, Gaillat EN, Calero-Rubio C, et al. A systematic approach to evaluating closed system drug-transfer devices during drug product development. *J Pharm Sci*. 2022;111(5):1325–1334. https://doi.org/10.1016/j.xphs.2021.12.020.
29. Seeler JF, Ma Y, Swami V, et al. A systematic study of CSTD-generated stress on different biomolecular modalities. *J Pharm Sci*. 2025;114(2):1051–1060. https://doi.org/10.1016/j.xphs.2024.11.015.
30. de Jong I, Tan DCT, Lehermayr C, et al. Current industry practices on closed system drug-transfer devices for parenteral drug products. *J Pharm Sci*. 2025S0022354925000401. https://doi.org/10.1016/j.xphs.2025.01.019. Published online January.
31. Holden RJ, Carayon P. SEIPS 101 and seven simple SEIPS tools. *BMJ Qual Saf*. 2021;30(11):901–910. https://doi.org/10.1136/bmjqs-2020-012538.
32. Examination of the protein drug supply chain in a swedish university hospital: focus on handling risks and mitigation measures. *J Pharm Sci*. 2023. Accessed May 9; https://jpharmsci.org/article/S0022-3549%2823%2900191-0/fulltext.
33. Svensberg K, Kalleberg BG, Mathiesen L, Andersson Y, Rognan SE, Sporrong SK. The observer effect in a hospital setting - experiences from the observed and the observers. *Res Social Admin Pharmacy*. 2021;17(12):2136–2144. https://doi.org/10.1016/j.sapharm.2021.07.011.
34. Taylor MJ, McNicholas C, Nicolay C, Darzi A, Bell D, Reed JE. Systematic review of the application of the plan-do-study-act method to improve quality in

healthcare. *BMJ Qual Saf*. 2014;23(4):290–298. https://doi.org/10.1136/bmjqs-2013-001862.
35. The Committee of Ministers of the Council of Europe. Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use. February 15, 2017. https://www.edqm.eu/en/d/162941.
36. van der Schors T, Amann S, Makridaki D, Kohl S. Pharmacy preparations and compounding. *Eur J Hosp Pharm*. 2021;28(4):190–192. https://doi.org/10.1136/ejhpharm-2020-002559.
37. Geersing TH, Dogan D, Nejadnik MR, Romeijn S, Knibbe CAJ, Crul M. Aggregate formation and antibody stability in infusion bags: the impact of manual and robotic compounding of monoclonal antibodies. *J Pharm Sci*. 2024;113(4):1029–1037. https://doi.org/10.1016/j.xphs.2023.10.015.
38. Stegemann S, Klingmann V, Reidemeister S, Breitkreutz J. Patient-centric drug product development: acceptability across patient populations – science and evidence. *Eur J Pharmaceutics Biopharmaceutics*. 2023;188:1–5. https://doi.org/10.1016/j.ejpb.2023.04.017.
39. Evans JM, Qiu M, MacKinnon M, Green E, Peterson K, Kaizer L. A multi-method review of home-based chemotherapy. *Eur J Cancer Care*. 2016;25(5):883–902. https://doi.org/10.1111/ecc.12408.
40. Tranberg A, Sporrong SK, Paulsson M. Parenteral cancer therapy in the patient's home: expectations from policlinical oncology nurses – an interview study.
41. Wozniewski M, Besheer A, Huwyler J, Mahler HC, Levet V, Sediq AS. A survey on handling and administration of therapeutic protein products in German and Swiss hospitals. *J Pharm Sci*. 2023:S002235492300374X. https://doi.org/10.1016/j.xphs.2023.09.010. Published online September.