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Examination of the Protein Drug Supply Chain in a Swedish University Hospital: Focus on Handling Risks and Mitigation Measures



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ABSTRACT

Protein drugs, such as monoclonal antibodies, have proved successful in treating cancer and immune system diseases. The structural complexity of these molecules requires careful handling to ensure integrity and stability of the drug. In this study, a failure mode and effects analysis was performed based on a Gemba Walk method in a Swedish University Hospital. The Gemba Walk is focused on pharmacists observing the actual supply process steps from distributor, pharmacy cleanroom to patient administration. Relevant protein drugs are chosen based on sales statistics within the hospital and the corresponding wards were observed. Further is the Double Diamond design method used to identify major risks and deliver mitigation strategies. The study identified potential stress factors such as temperature, shock by impact, shaking, vibration and light exposure. There were also risks associated with porters' and healthcare professionals' lack of awareness and access to information. These risk factors may cause loss of efficacy and quality of the protein drug, potentially leading to patient safety concerns. In this study, a simulation is also performed to list measures that theoretically should be in place to ensure the quality of the protein drug, for example validated and protocol-based compounding in cleanroom, training and validated transports.

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Abbreviations: API, Active Pharmaceutical Ingredient; BDC, British Design Council; CSTD, Closed System Transfer Device; DUR, Drug utilization review; EFPIA, European Federation of Pharmaceutical Industries and Associations; EHR, Electronic Health Record; FMEA, Failure Mode and Effects Analysis; GDP, Good Distribution Practice; GMP, Good Manufacturing Practice; HBT, Human Based Transport; HIV, Human Immunodeficiency Virus; ICH, International Conference on Harmonization; IMP, Investigational Medicinal Products; ISO, International Organization for Standardization; mAb, Monoclonal antibody; MPA, Medical Products Agency; PDs, Protein drugs; PTS, Pneumatic Tube System; RTA, Ready-to-administer; SmPC, Summary of products characteristics; SOP, Standard Operating Procedures; TU, Transfer Unit.

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Introduction

Protein drugs (PDs) are medications that have been used for decades in different therapeutic areas to treat or reduce the symptoms of diseases like cancer and immune system diseases (e.g. diabetes, rheumatoid arthritis). Unlike a synthetic, small molecule, the Active Pharmaceutical Ingredients (API) are derived from material of biological origins and therefore they present a structurally complex molecule with unique stability considerations¹ that requires them to be handled with care at any stage of their life-cycle to ensure their stability and therefore safety and efficacy for the patient.² Chemical and/or

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physical instability could be responsible for PD products degradation depending on the properties of the specific molecule.³ Several factors can affect the stability of PDs when applied individually or in a sequence of more stressors that can cause product degradation with potential risk of side effects for the patients (e.g. loss of activity, immunogenicity reactions).⁴ Among these are product formulation (e.g. choice of excipients), which is under the control of the manufacturer, while light exposure, storage temperature, shaking (e.g. interaction with interfaces), shock (e.g. dropping of a box), material incompatibility, concentration, reconstitution (e.g. dilution, choice of reconstitution solution) are stress factors that also occur in post-production handling.

The report by Fongaro et al. gives a better understanding of the stress factors and issues involved in the post-production handling by analyzing the example mAb ipilimumab. The authors state the following: “*The hope is that this work may be useful to evaluate the issues relative to everyday hospital handling and overall raise awareness on the proper use and storage of biotechnological therapeutic drugs*”.⁵

The quality system for the development of drug products and the lifecycle management is defined by the International Conference on Harmonization (ICH) Q11 Guideline: Development and manufacture of drug substances (chemical entities and biotechnological/biological entities).⁶ Pharmaceutical manufacturers are responsible for following ICH Q5 Guideline: Quality of Biotechnological Products in order to assure the quality of the product during the development, manufacturing and storage.⁷ However, transportation, storage, preparation, administration, and use are steps only partially covered by the ICH guidelines and instead managed by healthcare professionals (in hospital settings), distributors and patients/caregivers (at home).

There are no strict procedures for the post-production handling of PDs and the lack of knowledge and variability throughout the downstream handling processes still represents a challenge.⁸ As for transportation, Good Distribution Practice (GDP) guidelines describe the minimum standards to ensure that the quality and the integrity of medications are maintained throughout the professional supply chain.⁹ Despite these, there are scenarios that cannot be completely predicted or prevented by these guidelines. Protein drug aggregation caused by stresses encountered during transportation (e.g. vibration, shock, changes of temperature) and the influence of primary packaging for PD products (syringe, vial and cartridge) was investigated and reported in a recent work⁴ that identifies the major risk factors and discusses mitigation strategies. These situations can arise during transportation with the distributor but also when the products are transported inside the hospital (e.g. from the warehouse to the hospital pharmacy and to the different wards).^{4,10}

As for the preparation step, the resolution CM/RES (2016)2 advises the health care establishment where reconstitution should take place: in a pharmacy or clinical area. This resolution applies to parenteral products, which are ready-to-administer (RTA) or must be reconstituted/diluted in the ward medication room or pharmacy cleanroom. The qualified personnel involved during the preparation should follow minimum requirements for reconstitution and use the risk assessment checklist to ensure the safety of the patient.¹¹

In pharmacy cleanrooms, medicinal products should be prepared according to the Good Manufacturing Practice (GMP) guidelines to ensure an appropriate quality system and follow the model procedure for risk assessment before the preparation, as well as the product dossier as described in the resolution CM/RES (2016)1.¹² However, the preparation procedures follow standard protocols and quite often there is a lack of information regarding the correct handling of PDs. Information related to the compatibility of certain devices used during PDs preparation (e.g. the use of Closed System Transfer Devices (CSTDs), needle free devices, filters or syringes with silicone oil) and the preparation modality (manual vs automated preparation) are not included. These uncertainties along with lack of

visual inspection of the IV bag, vigorous agitation of vials, formation of air bubbles or foam in syringes and repetitive up-and-down movements were observed and reported in a paper by Jiskoot *et al.*¹³ A recent study has analyzed particle formation in a commercial product due to mishandling during the reconstitution, the influence of silicone oil and the effect of including a syringe filter between the administration and the infusion set.¹⁴ As reported by Stucki *et al.* (2009) the aseptic conditions during reconstitution can strongly influence product quality where the highest risk of contamination was found in the ward medication room (16% of containers were contaminated), while the safest environment was in the cleanroom.¹⁵

Once the reconstituted PD product is ready to leave the pharmacy cleanroom to reach the ward, the transport and distribution can be achieved by different type of carts or by Pneumatic Tube System (PTS) (for longer distance).

Finally, once the PD has reached the administration step, nurses and patients are involved. The instructions for handling hospital administration are likely based on the information specified in the SmPC since there are no international guidelines, as mentioned before. Several risks such as light exposure, shaking (with consequent potential particle formation in the IV bag), and incompatibility with unsupported administration components may occur (either interactions with the administration set material or with other simultaneously infused drug solutions in a Y-site connection).

The objective of our study is to describe the in-hospital supply chain of commonly used PDs and to identify risks in handling and recommend mitigation strategies.

Experimental Section

Study Design

This study was designed using suggestions from the Enhancing the Quality and Transparency Of Health Research (Equator) network and more specifically the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines¹⁶ where applicable, since this study is not a traditional observational study. The methods were selected in order to map what PDs are used where in the hospital, how they are handled during transport, preparation and administration procedures in addition to outlining risks and mitigation strategies.

Hospital Drug Utilization Review

In order to determine the actual use of protein drugs in the hospital including the logistical flow, a retrospective Drug Utilization Review (DUR) was conducted based on sales statistics within the hospital and ward delivery addresses (inpatient use) or ordering physician specialty (for outpatient prescriptions). The terms “*inpatient*” and “*outpatient*” have different meanings in different countries and could often be difficult to define. In this study the distinction was made based on who the payee is; for inpatients medication costs is invoiced to the hospital pharmacy and covered by the hospital and for outpatients the medication cost is paid to a retail pharmacy by the patients themselves with support from the pharmaceutical benefits agency. The sales statistics were extracted using the Concise Database hosted by the Swedish eHealth Agency.¹⁷ Active substances were classified using the Anatomical Therapeutic Chemical (ATC) classification system¹⁸ and this classification was used for further analysis. In this study, wards defined as “*daycare wards*” handles inpatients where the medical treatment requires hospitalization for less than 24 h, typically less than 4–6 h.

In order to assess to what degree cleanroom compounding services were used, reports were extracted from the billing module of the Cytodose computerized physician order entry software (CSAM, Oslo,

This tool was provided as a software template by one of the authors associated with the European Federation of Pharmaceutical Industries and Associations (EFPIA). The aim of using this tool is to improve the knowledge about the risks of failures and take actions to eliminate or reduce them. The failures are prioritized depending on the severity, the likelihood of occurrence, and the possibility to detect the failure.

The development of FMEA is based on the process map of the Gemba Walk. Following the four main steps, the different process tasks and subtasks involved in the supply chain are assessed. Errors that can be made during every task were noted and the impact in worst case scenarios described. Of all the impact factors, we selected the ones that were related to patient safety and we scored them depending on the severity, likelihood of occurrence and failure detection.

Severity score of 1 denotes minor risk to the patient, score of 3 moderate risk and score of 5 a high risk to the patient. Occurrence score of 1 denotes low probability of happening, score of 3 occasional failure and score of 5 denotes high probability of the risk happening or repeated failure. Detection score of 1 means that the failure will be certainly detected, score of 3 moderate probability to catch the failure and score of 5 means low probability to detect the failure. The aim is to give a risk priority number (RPN) to the risk factors found in each step by multiplying Severity, Occurrence and Detection based on equal weight according to the chosen standardized method. The scores were set by two pharmacists employed by the hospital, as well as working in the RealHOPE IMI project (www.realhope.se). The scores were then scrutinized and further discussed with a third scientist and coauthor employed by a pharmaceutical company participating in RealHOPE. For RPN score over 45, factors were considered to be high-risk. This figure was based on proven experience and standard procedures from the EFPIA author's setting.

Double Diamond

The *Double Diamond* tool was developed by the British Design Council (BDC) in 2005. This tool is an easy and visual way to represent processes.³⁰ This method consists of two diamonds that link the divergent and convergent thinking of a design process. The divergent parts involve exploring and amplifying the knowledge of the process. The convergent parts consist of taking the ideas of the divergent part and refining them to get to the aim.

The Double Diamond is built in four steps named; Discover, Define, Develop and Deliver. The aim of this design is to identify the challenge starting to the left of the first diamond and moving through the common point of the two diamonds to identify the real problem.

The second diamond aims to find the best solution to improve the initial problem.^{31–33}

In our research we have applied this tool to represent our findings followed by the improvements to be implemented. The risk mitigation strategies were discussed by virtual meetings with different partners from the EFPIA with the aim of combining the knowledge of hospital/clinical pharmacy and industry to bring new perspectives regarding the safety and efficacy of PDs.

Results and Discussion

Hospital Drug Utilization Review

The results of the general DUR conducted based on sales statistics within the hospital and ward delivery addresses can be seen in [Table 1](#). All of the top 10 most commonly prescribed protein drugs are found in the antineoplastic and immunosuppressive ATC groups L01 or L04, for example infliximab, rituximab and bevacizumab. It is evident that the use of generic products is common for these top three substances where biosimilars are readily available to provide cost benefits. It should be noted that insulin (ATC A10A) is available in several dosage forms (e.g. rapid-acting), with a large range of formulations and containers and therefore no single product is within the top 10 list despite insulin being a protein drug commonly used in the hospital. This is in contrast to daratumumab which is specifically used in only one ward, the Haematology ward. Based on these data it can be noted that inpatient daycare wards account for a large proportion of the administrations, probably due to Sweden having the lowest number of hospital beds per capita in the European Union.³⁴

When examining the need for extemporaneous compounding it can be noted that there is a limited availability of prefilled syringes or ready-to-administer containers and that many products are not compounded by the pharmacy (i.e., infliximab). Since many of the monoclonal antibodies (mAbs) do not meet the National Institute for Occupational Health and Safety (NIOSH) definition of hazardous drugs,³⁵ nurses are allowed to order the material directly to the ward and prepare the products in situ immediately before administration. Nurses will perform steps such as reconstitution of lyophilized medications (e.g. infliximab), or dilution of concentrates (e.g. bevacizumab) following the SmPC instructions and other quality criteria recommended by the European Directorate for the Quality of Medicines & Health Care (EDQM), Council of Europe. Some of the recommendations are: qualified and competent personnel, procedures for handling, hygiene, clothing requirements, list of approved medicinal products, policy of checking, among others.¹¹

Table 1
Inpatient sales statistics for 2021, Uppsala Region. The use of branded vs generic product, product presentation as well as the pharmacy cleanroom compounding (compnd.) and the most common wards for administration are shown for the top 10 active pharmaceutical ingredients (API).

API	Brand/Generic	Prefilled syringes	Lyophilised	Cleanroom compnd	Common departments/users
Bevacizumab	33%	0%	0%	99%	Onc. daycare, Pulm. daycare and Ped. Onc.
Daratumumab	100%	0%	0%	0%	Haem. daycare
Filgrastim	23%	77%	0%	0%	Onc. and Haem. daycare
Immunoglobulin	100%	0%	100%	1%	Haem. and surgery wards
Infliximab	5%	0%	100%	5%	Gastro. daycare, Care close-to-home unit
Pegfilgrastim	2%	100%	0%	0%	Onc. and Haem. daycare
Pembrolizumab	100%	0%	0%	100%	Onc. daycare, Pulm. daycare and Ped. Onc.
Rituximab	14%	2%	0%	77%	Onc. daycare, Skin/Rheuma. daycare
Tocilizumab	100%	0%	0%	0%	Skin/Rheuma. daycare, Specialised Paed., ICU
Trastuzumab	1,7%	1,7%	98%	98%	Onc.department

API = Active Pharmaceutical Ingredient, Gastro = Gastroenterological, Onc = Oncological, Rheuma= Rheumatological, Haem = Hematology, Pulm = Pulmonary, Paed = Paediatric, ICU = General Intensive Care Unit.

Table 2

Outpatient sales statistics for 2021, Region Uppsala. The use of branded vs generic product, product presentation and the most common prescriber specialization are shown for the top 12 active pharmaceutical ingredients (API).

API	Brand/Generic	Prefilled syringes	Lyophilised	Common specialization prescribing/users
Abatacept	100%	100%	0%	Rheuma. and others
Adalimumab	58%	100%	0%	Rheuma. and specialised paed.
Anakinra	100%	100%	0%	Rheuma. and others
Certolizumab pegol	100%	100%	0%	Rheuma.
Etanercept	55%	99%	1%	Rheuma. and general practitioner
Filgrastim	2%	97%	3%	Paed. Onc./Haem.
Golimumab	100%	100%	0%	Rheuma. and others
Peginterferon beta-1a	100%	100%	0%	Neuro.
Sekukinumab	100%	100%	0%	Rheuma. and skin/venereal diseases
Somatropin	–	70%	30%	Specialised paed., Endocrin.
Tocilizumab	100%	100%	0%	Rheuma. and others
Ustekinumab	100%	100%	0%	Gastro. and skin/venereal diseases

API = Active Pharmaceutical Ingredient, Endocrin = Endocrinology, Rheuma = Rheumatological, Haem = hematology, Paed = Paediatric, Neuro = Neurology, Gastro = Gastroenterology.

Another way of providing advanced healthcare in a country with few hospital beds is to administer parenteral drugs at home, either by the patient themselves, caregivers/next of kin or visiting healthcare professionals. The medication supply for these cases starts with a prescription that is dispensed by a retail pharmacy and administered in a doctor's office, daycare wards or health centres or at home by the patient. These prescriptions are called 'outpatient prescriptions' in Sweden. Comparing the inpatient data with outpatient data (Table 2) it is expected to see a high use of prefilled syringes. Almost none of the substances are compounded for outpatients by the pharmacy, with some exceptions (e.g. paediatrics, data not shown). Most substances are in ATC group L04 (immunosuppressive) similar to the inpatient use, but also L03 (immunostimulants) and H01 (hormone analogues) are seen. The typical diabetic patient often has a lot of knowledge around the preparation of drug before administration due to the extensive and successful patient education programs.³⁶ However, for other conditions this may not be the case. Several studies have reported the everyday issues with stability of PDs at home.^{37,38}

To conclude, the DUR presents a great portion of mAbs but also rabbit anti-human thymocyte immunoglobulin, fusion proteins, growth hormone, interleukin antagonist proteins and interferon beta proteins.

Protein Drug Supply chain

Based on the findings from the DUR, it was decided to follow the actual flow of PDs from wholesaler delivery through to the patient administration in the hospital. Using the Gemba Walk method the results can be divided into four sections (distributor, hospital internal transport, cleanroom compounding and patient administration) as presented in Fig. 2. Findings include control steps, consignment, temperature control, visual inspection, etc. for both licensed product and investigational products. Detailed descriptions of the observations during the Gemba Walk are described in Table 3 support by photos as supplementary material and the identified risks presented with FMEA in the section *Identified risks and mitigation strategies* below.

In the hospital, drug products are ordered non-patient specific, by the pharmacy supply staff or sometimes by nurses to be delivered to the ward medication room, pharmacy cleanroom or for central stock (exceptional). The order is placed using an e-trade software (Agresso, Unit4 AB Solna, Sweden) to purchase from the procured distributor called ApoEx (see distributor section below) shipped to the hospital consignee, distributed throughout the hospital, some products being compounded in the pharmacy cleanroom, transported and administered to the patient. The legal framework covering placed order to

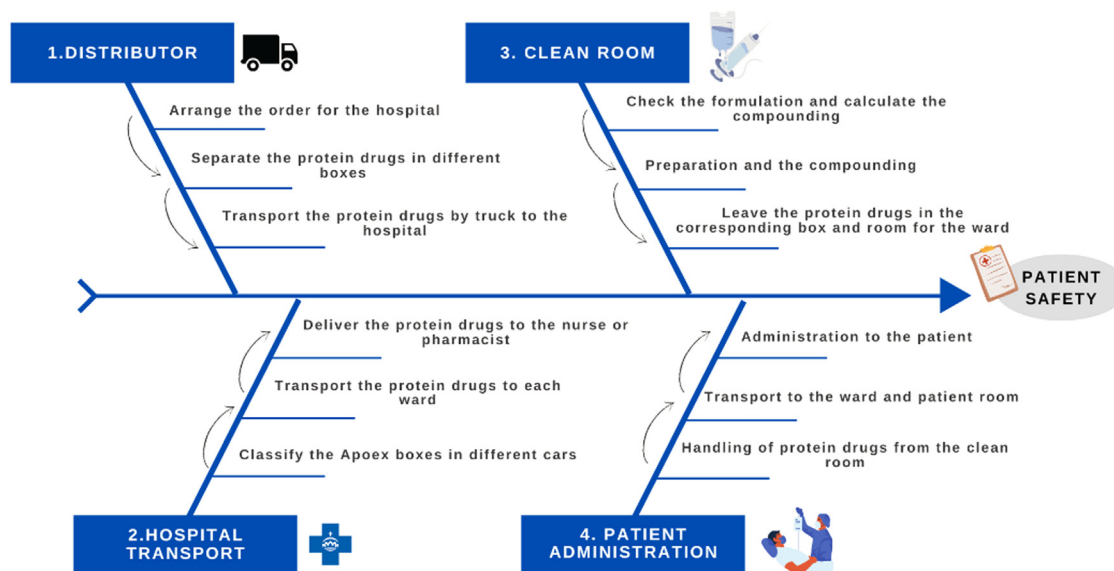


Figure 2. Conceptual framework of drug supply chain based on the Gemba walk method.

Table 3
Observations from the Gemba walk performed at Uppsala university hospital.

STAGE	FINDINGS
1. Distributor	<ul style="list-style-type: none"> - The distributor is situated in an old factory building in an industrial area. - Good timing control during all the process since the distributor know the time that the first orders arrive and at what time the truck has to leave for the hospital. - The senior staff teach new hires how to handle and load the different medications into the boxes but there is no specific protocol. - 100% bar code verification in the manual picking process - 20% of all the drugs (usually all controlled substances and special drugs) are subsequently manually checked by pharmacists. - The distributor appears to have good control of the temperature (room and refrigerator) - Great control of documentation during all the process - The majority of staff do not know what kind of drugs they are handling, most of the workers aren't pharmacist so they don't know anything about protein drugs.
2. Hospital transport	<ul style="list-style-type: none"> - If someone drops a box containing drugs, there is no report on that or a superior controlling - The ordered medications arrive to the hospital's goods reception area and are unloaded from the distributor's truck between 12.30–13.00 by hospital porters. - The medication delivery boxes are deposited from the truck carts to hospital carts in the goods reception area depending on the hospital delivery address (different houses) - This repacking process takes between 10 and 20 min. - Depending on the house, the indoor car route could take between 40 min and 2 h. - Before the truck arrives, responsible coordinator at the reception area receives an email with a packing list with the medications that they will deliver - Observed difficulties: tiny routes and some curves where the car has to slow down the speed. - The car can go between 6 and 11 km/hours maximum - The porters have limited knowledge of the contents they are handling. They just know the difference between refrigerator goods (blue boxes), normal medications (orange) and fragile material (could be glass in cartoon boxes). - Porters lock carts that are left unattended in the basement. - If one of the trailer carts falls, all of them will fall. (It has happened more than one time, usually when the porters are in training). - In the ward the porters need to find a nurse or a clinical pharmacist to hand over the boxes and to get the regulation paper signed. The boxes are further handled in the ward medication room where the contents are unpacked and checked.
3. Cleanroom	<ul style="list-style-type: none"> - During manual preparation, it was found that in order to remove air bubbles, syringes are hit with a pair of tweezers, potentially causing shock to the PDs. - Addition of certain substances, e.g., albumin, generate foam inside the bag - Light protection of infusion bags is achieved using an overpouch - For transport from the cleanroom the container is placed in a clear, resealable bag. - There are different controls in place depending on the specifications of the protein drug. - Double or triple check of the preparation by compounding pharmacists in finished product control step. - Appropriate system with pass-through boxes for the delivery from the cleanroom to nurses (restricted zones depending on ward and temperature).
4. Patient administration	<ul style="list-style-type: none"> - Detailed interview with the patient before administration - Medications stored in refrigerator are kept in room temperature before the administration around 40min-2 h depending on size of container and other recommendations - Nurses may be unaware of special precautions handling protein drugs unless it is stated in the EHR template (e. g., inline filters) and only occasionally reads the SmPC where instructions on careful reconstitution is available. - Shaking when using transportation carts to the patient room from the pharmacy of ward medication room takes place - All orders are verified in the EHR before administering the dose (dosage, patient, drug. .etc.) - Photoprotective light bag are used - No or infrequent visual control of particles by nurse
5. The special handling of investigational products (Clinical trial unit)	<ul style="list-style-type: none"> - There is currently 100 studies with active agreements and 50 of them include monoclonal antibodies. However not all of them have patients actively in treatment. - Drugs are kept in quarantine in a separate refrigerator until they are released from the internal control. - Every study has its own internal protocol including the specific control requirements. - 90% of the industry supplied material have temperature dataloggers when arriving - For intra-hospital transport, some material goes in validated boxes and few without any control (for example non-PDs like bortezomib). - The validated boxes are of the Aircontainer brand validated (2–8 °C) in 36 h in Swedish indoor/outdoor climate. - There is no control or validated box for indoor room temperature transports. - There is no other control measurement to prevent vibration or shaking, despite the TempTale to control the temperature. - Transports of IMP from clinical trial unit to pharmacy cleanroom are done by packing individual patient dose kits containing all necessary material including light protection bags and further placed in a resealable bag. - The refrigerator is mapped at three different measuring points both empty (24 h) and full (72 h) before being used for IMP. - The loggers to monitor the temperature are from Libero (ELPRO-BUCHS AG, Buchs, Switzerland). - Manual check of temperature deviations once a day and every first day of the month the temperature report is printed and signed.

delivery is regulated by the Medical Products Agency's regulation (MPA) LVFS 2012:8.³⁹

Distributor

The distributor has a regulatory authorization as a hospital pharmacy and an agreement with the Region Uppsala to be the hospital pharmacy even though it is situated in Bromma, 70 km from the Uppsala University Hospital. At ApoEx, orders are processed using order management procedures to meet the specified requirements and further packed depending on the storage temperature for each product (e.g. products that need cold chain logistics are packed in insulated blue boxes with cold packs and products held at ambient temperature are packed in orange boxes). The standard ApoEx boxes used are KMB-DH 422 model with a volume capacity of 18 liters. The boxes offer light protection and have a cushioning polyurethane foam insert among other additional advantages.⁴⁰ For the cold transport ClimSel System is used to protect specific products from temperature variations. This system provides solutions for controlled temperature transport of small and large volumes with a duration of 24 h up to 96 h.⁴¹ The packaging process relies on bar code-control with random manual checks being performed. For controlled substances, 100% additional manual control are performed by pharmacists.

At the final stage of the procedure, the boxes are packed into a temperature control truck and transported by a subcontractor to Uppsala University Hospital. Also, this process is within the MPA regulation and surveillance, however the complexity of the process and the different stakeholders involved make it difficult to control the different risk factors where the biologicals can be affected.

Monitoring of the temperature during the transportation takes place but there is no specific control or monitoring regarding risk factors as vibration and shaking that may occur during the transportation due to truck acceleration/braking, road/truck conditions and uncontrolled movements. This is also in accordance with literature where studies primarily focus on temperature during simulated transportation studies.⁴²

Hospital Transport

The standard order arrives in the hospital goods reception unit (see Fig. 1) Monday–Friday between 12.30–13.00 h. The hospital porters receive a packing slip, they check the delivered items and sign to acknowledge receipt.

The unpacking process in the goods reception area can take between 15 and 20 min, during this time the porters classify the boxes from ApoEx in different carts depending on the location of the receiving ward. All medications stay in the ApoEx boxes (blue or orange as described above).

The intrahospital delivery is operated through underground corridor passageways by porter-operated electric minicars and the route time for this HBT can be between 40 min and 2 h depending on the delivery location. Porters can only deliver to authorized staff (nurses, pharmacy staff) and this is checked by signing of a goods receipt confirmation slip. The responsible person in the ward, unpacks the medicines from the ApoEx box. The medications are distributed to different shelves in the ward medication room, pharmacy cleanroom or, if appropriate, stored in dedicated medication refrigerators. Only a small fraction (<1%) of the delivery is for immediate use, so the majority of the medications may be stored in ward medication rooms for weeks/months where temperature monitoring of the room and refrigerator is performed daily with most rooms having an alarm system for refrigerator out-of-specification temperatures.

The recommendations and regulations by MPA are applied in the hospital to ensure that the quality of pharmaceuticals is maintained. In practice, some of the staff involved in this part of the chain are not pharmacists and their knowledge about handling is only related to

the color of the box. There are several risks involved during the distribution inside the hospital since it is difficult to control the vibration, shaking and potential drops in the underground route. When a high number of orders are being processed, particularly with large numbers of delivery points, or if staff are inexperienced, delivery delays may occur. No temperature measurements during the intrahospital transport are performed since the underground corridors have room temperature all year round and the PDs are packed in the ApoEx cool boxes during the whole process.

Cleanroom Reconstitution

In the pharmacy cleanroom (hospital entrance 100, see Fig. 1), the activities are performed in accordance with Standard Operating Procedures (SOPs) to comply with GMP and other regulations. Compounding is performed in Grade A microbiological safety cabinets (Class II) situated in Grade B cleanrooms. As described in Table 1, most of the PDs reconstituted in the pharmacy cleanroom are used for oncology or hematology treatments. When examining the rationale for reconstituting a medication in the pharmacy cleanroom versus in a ward medication room, explanations pertaining to occupational health is given by the pharmacists. The risk of hazardous drugs exposure is true for the traditional ATC L01A/B/C/D chemotherapy but generally not for other PDs according to the NIOSH list.³⁵ It is likely that the more recent oncological treatment protocols with PDs are reconstituted in cleanrooms for financial (vial sharing), or quality (e.g. aseptic conditions, traceability) reasons, or to rationalize the work for the nurse. Also, the rationale for reconstituting/diluting a medication in the pharmacy should be based on a risk assessment.¹¹

The compounding pharmacy receives individual patient orders from the electronic health record software (EHR) Cytodose and the pharmacists check the orders and calculate the specific dose (where applicable) before compounding the preparation manually or using a compounding robot (Kiro Oncology, Grifols, Arrasate-Mondragón, Spain). For manual preparation, information about special precautions for reconstitution, e.g. recommendations to “swirl the vial gently during reconstitution” is available from the instruction template of the EHR. Robotic preparation is based on gravimetric control using PD density to reconstitute or extract the ordered PD volume. Different reconstitution programs for e.g. viscous products or lyophilizates that take a long time to dissolve, are available. Robotic compounding of mAbs has been described in the literature as a feasible method if the robot is programmed according to the SmPC, to achieve reproducible high-quality compounding for sensitive formulations.⁴³ Further research should be undertaken to validate accurate programs for PDs preparation for specific robot models. In Uppsala, only three of the top 10 PDs (Table 1) were reconstituted by the robotic compounding system during the study period: rituximab, bevacizumab and trastuzumab. However, also cetuximab, nivolumab, panitumumab and pertuzumab are occasionally compounded using the robot.

It was found that partially used vials are stored in the cleanroom and re-used according to stability data from manufacturer or bibliographic data.

The location of the cleanroom allows for many nurses in oncology and hematology to collect the finished preparation from the locked delivery pass-through boxes of the cleanroom. In the pediatric oncology ward, which is situated in another building (the Children's hospital), the preparations are either picked up by ward administrative staff or by hospital porters using indoor scooters or electric minicars that are driven in the underground corridors.

Patient Administration

The last step of the Gemba Walk involves nurses and patients. Before meeting with the patients, the nurse follows different steps: investigates the patient's EHR to verify the planned treatment, then

walks to the ward medication room to fetch ready-to-administer PDs or reconstitute PDs. For PDs compounded by the pharmacy the nurse can either fetch them directly from the pass-through boxes (as described above) or bring them from the medication room if they have previously been delivered and temporarily stored there.

For PDs reconstituted by nurses in ward medication rooms it was found that CSTDs are often used which may present risks for sensitive PDs relating to compatibility with the CSTD⁴⁴ potentially leading to aggregation and other stability issues.^{45,46} In the cleanroom CSTD are not used in the reconstitution step.

All the retrieved PDs are placed on a ward trolley and transported to the patient's room as the last step of the HBT chain. Each drug is handled depending on specific requirements such as protection from light, temperature, route of administration, frequency and time.

Before administration, the nurse verifies the patient identification number and has a short interview with the patient to check symptoms and related health issues.

During administration, protective clothes are worn by the nurse since hazardous drugs may be administered. As soon as the treatment starts, the nurse checks the patient's condition frequently. If there is any adverse event or unexpected intolerance to the treatment, the doctor is called.

Special Considerations for Investigational Medicinal Products

In Uppsala, there are approximately 100 clinical studies ongoing, of which 50 have investigational medicinal products (IMP) that are protein based, predominantly mAbs. The clinical trial unit is situated at the entrance C7 (Fig. 1, far left part where the arrows start). The IMP logistics are strictly regulated with an estimated 90% of shipments coming to the hospital with in-container temperature monitoring (datalogger) and validated boxes. Upon arrival, a standardised checklist is used to document any deviations such as damage to container, out-of-specification storage etc. PDs are placed in the quarantine area of the clinical trial unit awaiting release. No system is in place to measure, control or prevent vibration or shaking effects on protein drugs. Within-hospital transport is performed indoors with temperature validated boxes (2–8 °C, temperature validation approved for 36 h use) for PDs that should have cool storage without datalogger. For light-sensitive material, black re-sealable sliding channel storage bags are used when reconstitution should take place in the pharmacy cleanroom.

Identified Risks and Mitigation Strategies

Based on findings from the Gemba Walk the major risk factors of the PD handling in Uppsala University Hospital were identified. The scores of the FMEA risk management for the four sections of the supply chain can be seen in the Fig. 3A and further described in Table 4. It is prominent that most of the high-risk factors are found in the patient administration section and as expected, the cleanroom section has no high-risk numbers due to the many control steps. To discuss one example, it was seen that porters from different organisations may accidentally drop boxes with infusion bags or the boxes may fall from trollies. Being ignorant of the sensitivity of its contents, porters would likely only report broken glass containers so as long as soft plastic infusion bags are dropped there will be no reports. This risk was calculated as Severity 5, likelihood of Occurrence 3 and Detection 5 with the resulting risk RPN number equals 75.

The high-risk factors originating in the distributor section were found during the process of packing the PDs into boxes and the road transport by truck to the hospital. The risks originate from careless manual handling or inadequate protection against shock and vibration. It should however be highlighted that the distributor operations are fully complying with regulations and current guidelines, so the

risks described are still theoretical emanating from the early concerns of post-production handling. If the PD is licensed, the formulation is likely so well-developed and studied that the stability is maintained even under sub-optimal conditions.

Moving to the transport inside the hospital the risk factors were seen to originate from the electric car with cage trollies transportation underground to each ward. The risks in this section are shaking, lack of temperature control and careless handling. When the boxes are accidentally dropped by porters during the distribution, transportation and delivering inside the hospital, the vials or containers with PDs can impact with the solid surface and consequently be exposed to mechanical shock. Rarely, the vials in a box are checked after dropping. The main risk resulting from dropping the vials or containers is cavitation, overlooking that this factor tends to enhance aggregation.^{47,48}

As mentioned previously, the pharmacy cleanroom was the most regulated process covered in the Gemba Walk with no risk factor above the RPN sum 45.

The last section of the Gemba Walk, the patient administration, involved reconstituted PDs, nurses and patients. High risks were found during the process of handling the PDs from the cleanroom by nurses and transport to the patient room. The potential risks identified in each step are: i) product shaking and ii) careless manual handling. Moreover, during the administration mistakes such as inappropriate storage conditions, unsupported simultaneous intravenous Y-site administration, incompatibilities with administration material sets are also potentially occurring. For the Oncological/Haematological daycare ward, Y-site administration never takes place according to interviews with nurses, so this issue is likely more relevant in wards with more complex simultaneously medication treatments (i.e. in the ICUs or the pediatric oncology department).

The risk factors found during the Gemba Walk and the FMEA can be reduced by implementing different actions such as validated protocol posters, bar code system track, continuous training, shock absorbing packaging, robotic preparation, among others. These improvements are presented in the Double Diamond model (Fig. 4).

The Double Diamond is a way to represent our findings during the whole process and the solutions that we suggest. The divergent part of the first diamond is the *Discovery* phase. This first step shows the methods we applied to explore, analyze and understand the problem by statistical analysis, the Gemba Walk and the FMEA. The *Define* phase is the convergent part of the first diamond where we have collected the most important findings and knowledge of the discovery phase to highlight the risk factors in the supply chain (shaking, light exposure, road transport and temperature) that may have an impact to the protein drug and consequently to patient safety.

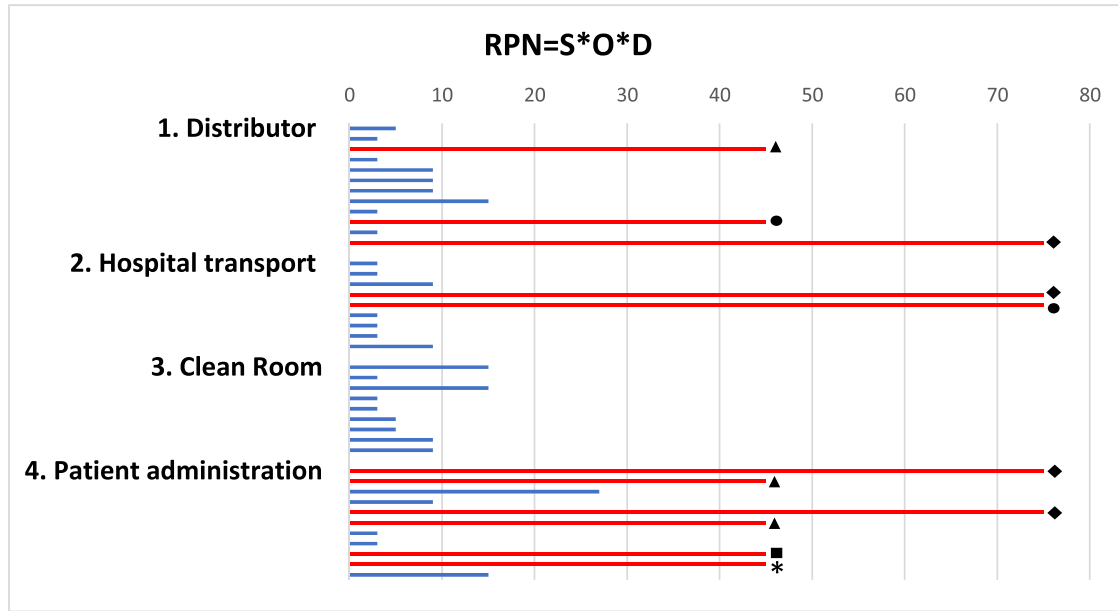
From the research conducted in the first diamond, we found that the main problem comes from inappropriate handling, awareness of diversity of professionals involved and lack of knowledge.

The *Develop* phase is the divergent part of the second diamond where we suggest different actions and ideas (yellow areas) to improve and reduce the problem. In the ideal situation (simulation) that all the actions could be carried out, we can see in the Fig. 3B that in every step of the flowchart the risk factors would be under score 45, considering that the risk zero does not exist and therefore, there will be always a minimal risk. The requirements to implement each action differ, and the potential success is in reality limited by factors such as available resources, as well as ethical, legal and technical hurdles.

Following the *TOP principle* as an implementation plan,⁴⁹ the best solution is:

- *Technical* for example implementing modern cars, more advanced boxes, bar code system tracking, labels with logging possibilities etc. Since this involves financial and legal aspects among others, the technical solution may only be possible in a long-term perspective.

A)



B)

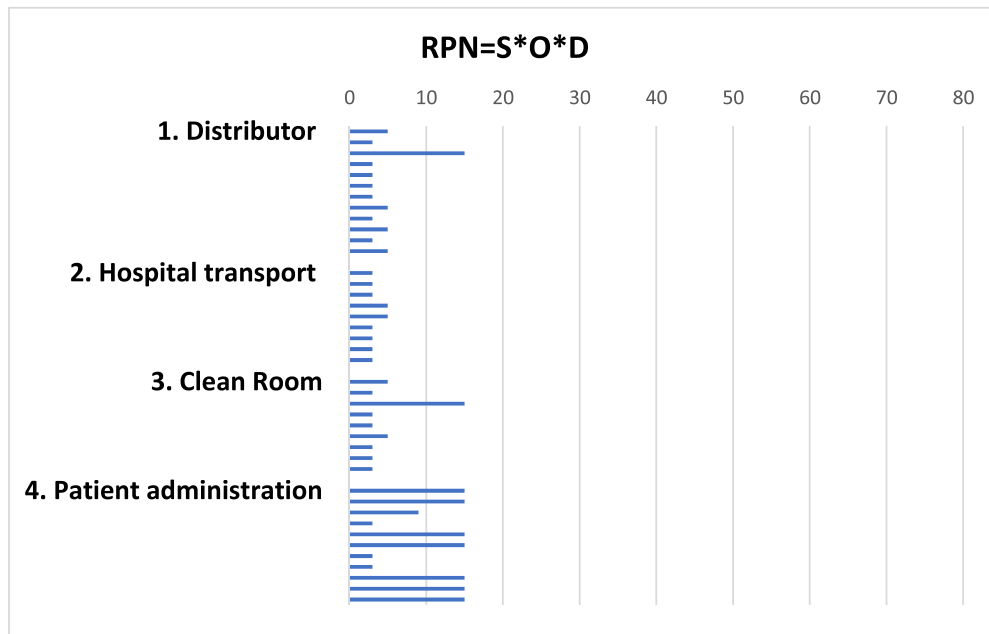


Figure 3. Risk Priority Number (RPN) to the risk factors found in each step of the Gemba walk (A) and after simulating implementing improvements (B). RPN calculated by multiplying Severity (S), Occurrence (O) and Detection (D). Red bars for RPN ≥ 45 (high-risk). Risks are described as: Inappropriate handling–exposure to light, no temperature control and shaking (▲), Drop or miss boxes from the initial order (●), Risks from road and indoor transport (◆) Unsupported Y-site IV administration (■) Inappropriate storage conditions during administration (*).

- *Organizational* which consist of changing the process and involves reviewing protocols and communication with the personnel involved. This solution is not as effective as the Technical, but it is faster and the requirements to implement are simpler.
- *Personnel* based on continuous training and personally educating workers, which is likely less successful but is the fastest and easiest.

Focusing on the *Deliver phase* that is the last convergent part of the Double Diamond and taking into account the *TOP principle*, it can

be appreciated that the following actions should be prioritized: validated protocol posters, continuous training and robotic preparation. Based on the resources in Uppsala University Hospital, implementation of these three actions is promising and can be used as a bridge for long-term improvements.

What stands out from the Double Diamond method is that it is a feedback cycle which means it does not finish by implementing the actions proposed, but rather by reassessing and introducing additional measures and improvements. Every big change requires small steps before achieving the main goal, which in this research is the

Table 4
Risk factors from FMEA above score 45 based on the Gemba Walk.

PROCESS STEP	ERROR
1.2 Separate the protein drugs in different boxes 1.3 Transport the protein drugs by truck to the hospital	Low handling care (exposure to light, shaking, temperature, dropping of box) Drop/miss boxes from the initial order Shaking, changes of speed, long travel time (risks from the road transport)
2.2 Transport the protein drugs to each ward	Shaking, no temperature control Drop from the cage trolley
4.1 Handling of protein drugs from the cleanroom	Product shaking Inappropriate handling
4.3 Transport to the ward / patient room	Product shaking Inappropriate handling
4.4 Administration to the patient	Unsupported Y-site IV administration Inappropriate storage conditions around/during administration

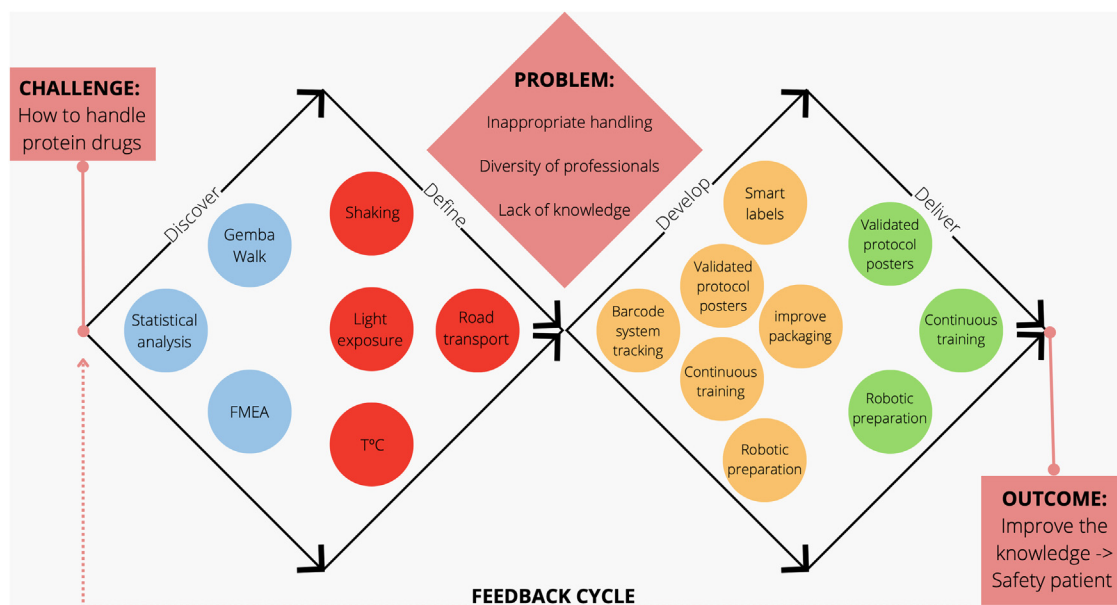


Figure 4. Representation of Double Diamond design to identify challenges, real problem and find the best solution to improve the initial problem.

safe handling of PDs to maintain patient safety. Introducing new solutions and future ideas in the Double Diamond could provide a beneficial impact and the handling be developed in parallel with more findings being presented in the scientific literature.

General Discussion

When performing quality monitoring or when planning PD targeted education, it is necessary to understand that although a great number of PDs are used by few specialists in therapeutic areas such as oncology, hematology or rheumatology, there are examples like insulin that are used in many wards that may be a challenge to properly cover, especially for those rare administration occasions. Also, the drug preparation step is often performed by a great number of nurses, a professional group that is harder to train to the same GMP standard as the pharmacy compounding team.

PDs are likely generally more sensitive to stress after reconstitution than in the state they were formulated from industry. Efforts to prevent stress should thus be focused downstream from cleanroom or ward medication room preparation where transport of RTA PDs to other buildings may be a potentially large risk. Validation of transport solutions (using for example improved packaging) for RTA material is likely a key topic.

It should be noted that a number of limitations were identified for this study. Sales statistics based on number of vials was used to

understand the use but since container size often can differ from a typical patient use, this is rather a rough estimate. Secondly, the observed risks were based on the authors' ideas following literature reviews. The study did not contain any analytical quantifications and the qualitative nature of the study makes it difficult to extrapolate the results to other settings. Lastly, some of the observations e.g. a dropped box, is coincidental and findings depend on the length of the observation period.

The strength of this study is that it shows the actual handling of protein drugs in a large hospital and the compiled findings are likely of great value for members of regulatory bodies, the pharmaceutical industry as well as formulation scientists for designing simulation/real-life studies and evaluating possible increase in particles and aggregation. Also, it presents some tools traditionally used in industry and how they successfully can be applied in a healthcare environment, combining the knowledge and sharing the communication between pharmaceutical industry (EFPIA) partners and hospital pharmacy.

Further investigations are needed to understand the actual effects of the stress risks identified and the generalizability of the findings.

Conclusions

Protein drugs are commonly used in the studied hospital, and they are frequently subjected to a wide range of potential stress factors. By

using *Failure Mode Effects Analysis* risk assessment and the *Double Diamond* methods a structured approach for the analysis and mitigation of stress factors has been presented. By reconstituting according to validated protocols in pharmacy cleanrooms the quality of protein drugs is not jeopardized as long as it is transported and administered to the patient according to well-founded safe procedures. Key tools to reduce failure in these steps are effective communication for correct procedures and continuous education of the involved personnel.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2023.05.003.

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