Original Research

European Journal of ONCOLOGY PHARMACY

OPEN

Evaluation of post-production handling practices of monoclonal antibodies throughout the world

Rana Fayek, BSc[a], Mostafa Soleyman, PharmD[a], Wim Jiskoot, PharmD, PhD[b], Mirjam Crul, PharmD, PhD[a,*]

Abstract

Introduction: This survey aimed to create a snapshot of the post-production handling of monoclonal antibodies in daily practice in health-care facilities in several parts of the world.

Methods: A worldwide web-based survey was distributed among pharmacists between November and December 2020.

The questions were categorized in sections related to storage conditions, reconstitution practices including the use of medical devices, administration practices, transportation, visual examination and shelf-life of mAbs, education of health-care professionals, and patient's home-administration.

Results: A total of 247 responders from 37 countries around the world participated in the survey. Hospital pharmacists were the largest group of respondents (92%). Most of the respondents (92%) reported that they store the mAbs at 2 to 8°C and 71% protect the prepared ready-to-administer mAbs from light by secondary packaging. The participants used spikes (38%), closed system transfer devices (CSTDs) (12%), and needles (22%) or a combination of these (28%) as a medical device, and 89% perform the reconstitution practices manually, versus 4% by semi-automatic pump system, 1% by robot, and 5% by a combination of these reconstitution methods. The respondents reported that in their institution, after compounding mAbs are transported via a logistic employee on foot at ambient temperature (59%) or in a cool-box (20%), or via the tube system (7%). More than half (64%) do not have written guidelines for transportation, but 86% perform a visual examination for particles of prepared mAbs before administration. Furthermore, 52% of the responders answered that nurses as well as pharmacists and pharmacy assistants receive staff training on the potential risks of mAb handling.

Conclusion: There is a high level of variability in daily practices of mAb handling in pharmacies worldwide.

Keywords: compounding, monoclonal antibodies, pharmacies, post-production handling, stability, survey, worldwide

1. Introduction

Monoclonal antibodies (mAbs) are protein drugs that are susceptible to different forms of stress. Research has shown that exposure to different environmental stress factors can lead to protein degradation and aggregation as a result of incorrect handling.[1] Aggregates can have a negative effect on the clinical efficacy of the drugs as they reduce the ability of the mAbs to bind to their target receptors. In addition, aggregates and sub-visible particles can cause immunogenicity,[2–5] which may compromise both safety and efficacy. Once a mAb is produced and shipped by the manufacturer, there are few controls over the many factors that may affect the structural integrity of the protein and the overall quality of the product. Remarkably, it seems that there is a general lack of strict procedures for post-production handling of mAbs in pharmacies from a protein stability point of view.[1] Since post-production handling is essential and no strict procedures are available yet, it is very important to investigate which practices in post-production handling are widely used and to identify potential risks.

Previously, Kiese et al investigated the effect of shaking and stirring on the aggregation behaviour of mAbs (immunoglobulin [IgG]1) and showed that both forms of mechanical stress resulted in formation of aggregates.[6] More recent studies have shown that mechanical stress is the most common form of stress to which a protein drug can be subjected during its entire life cycle.[1,7–11] In addition, reconstitution or compounding practices can have varying effects on the protein stability. Notably, the presence of air or headspace during mechanical stress can accelerate protein aggregation.[10–12] Hernández-Jiménez et al investigated five therapeutic mAbs under various controlled stresses, such as freeze–thaw cycles, and performed long-term stability studies on previously opened vials. The results indicated that the tendency to aggregate depends not only on the specific stress conditions, but also on the concentration and nature of the mAb, even though they all have a similar IgG1-structure.[13] Another study examined the effect of elastomeric surfaces of final drug vehicles on protein stability.[14]

From these studies one can conclude that compounding materials may affect protein stability, implying that repackaging of mAbs also may compromise product quality. For instance, Liu et al investigated the levels of sub-visible particles (silicone oil

The study was funded by the Amsterdam University Medical Center. Publication was funded by the Institute for Applied Health Care Sciences (IFAHS) in Hamburg, Germany.

The authors declare no conflict of interest.

[a] Department of Clinical Pharmacology and Pharmacy, Amsterdam University Medical Center, Amsterdam, [b] Division of Biotherapeutics, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands.

[*] Correspondence: Mirjam Crul, Amsterdam University Medical Center, de Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands (e-mail: m.crul@amsterdamumc.nl).

EJOP (2021) 4:3

Received: 8 February 2021 / Received in final form: 31 March 2021 / Accepted: 20 April 2021

http://dx.doi.org/10.1097/OP9.0000000000000031

microdroplets) in bevacizumab in plastic syringes and performed controlled laboratory experiments with repackaged bevacizumab to quantify protein aggregation. They concluded that bevacizumab repackaged in plastic syringes was contaminated by silicone oil microdroplets and could contain protein aggregates. In addition, the use of filters and silicone-lubricated syringes may contribute to increased particle counts.[15] Additionally, Krayukhina et al showed the amount of aggregated protein and number of sub-visible particles were similar between unlubricated polymer-based and glass syringes, but significant protein loss was observed for lubricated glass syringes.[16] Furthermore, Crul et al studied the impact of sub-visible particles on the shelf-life of repackaged bevacizumab. These authors concluded that the number of particles increased due to the repackaging process, but no considerable increase was observed during storage for up to 37 days.[17]

In recent years, several studies have been published on the use of a closed system transfer device (CSTD) for biologic products and focused on the benefits and shortcomings of these devices.[18–21] Petoskey et al indicated that CSTDs may introduce sub-visible particles into an antibody-drug conjugate (ADC) formulation. They showed that these devices may increase the risk for patients from manipulating the final drug product through the introduction of sub-visible particles and generation of visible particles directly before administration.[20] Furthermore, Besheer et al demonstrated that the majority of CSTDs can have leaks, varying in size and that some of them produced visible and sub-visible particles, both due to silicone oil and particle contamination of the device.[21]

The studies above collectively demonstrate that proper storage and handling of mAb products throughout their life span, including all steps from transport from the manufacturer through handling in the pharmacy up until administration to the patient, is pivotal. In order to gain insight into the compounding and handling practices for mAbs by pharmacy, nursing and medical personnel, a few investigations have been conducted. First, Alexander et al investigated current practices, beliefs, and attitudes regarding the handling of mAbs by Australian medical personnel and pharmacists. They concluded that mAbs are treated according to cytotoxic drug standards and often without formal guidelines.[22] Secondly, Crul et al reported compounding practices of mAbs across Europe via an email survey. The results of the survey provided a clear impression of the variety of device use in practice across Europe.[23] Lastly, a small pilot study examined the procedures in one hospital pharmacy in the Netherlands about the handling of biologicals and identified several issues that might have jeopardized product quality, including a lack of visual inspection of the contents of a vial and an IV infusion bag, vigorous manual agitation of a vial, formation of air bubbles in a syringe and careless handling of a biologic-containing IV infusion bag.[24]

The study presented here was performed to gain insight into the practices in place for handling mAbs in several parts of the world and to identify potential risks associated with these real-world practices.

2. Methods

2.1. Study design and study population

In November 2020, a worldwide web-based survey about post-production handling of mAbs was conducted. Completion of the questionnaire was made possible during 1 month (from November 1 until December 1). The survey tool Google Forms was used to build the questionnaire. The study population consisted of pharmacists working in hospitals, outpatient clinics or community pharmacies in various countries around the world. This study was performed in collaboration with the European Society of Oncology Pharmacy (ESOP). The participants were invited to participate in the survey via the ESOP newsletter. This newsletter was sent to ~3500 pharmacists/members from 62 countries around the world. The number of participating pharmacists was not limited per country and there were no exclusion criteria for the selected population. Participation in the survey was completely voluntary and the results were processed anonymously.

2.2. Categorization of the questions

The questionnaire (see Appendix 1) was constructed by looking at the important points of discussion and future perspectives of the currently available literature data on protein drug stability risks. The questionnaire consisted of a total of 17 questions and, if applicable, 7 sub-questions, which could be completed within a maximum of 10 min. The 17 questions included 2 baseline and 15 substantive questions. The baseline questions were related to the country where the respondents reside, where they work and what profession they have. Furthermore, substantive questions were categorized in sections related to storage condition (Q3–5), reconstitution practices including the use of medical devices for reconstitution and administration (Q6–9), transportation (Q10–11), visual examination and shelf-life of mAbs (Q12–13), education of health-care professionals (Q14), and patient's self-administration of mAbs (Q15–17).

2.3. Validation and testing of the questionnaire

After completing the outline of the questionnaire, it was validated by experts from four countries before sending to participants. The aim of this validation was to verify the relevance, feasibility, and clarity of the questions. After approval of the questions by the experts, the link to the questionnaire was sent by e-mail to 25 pharmacy students and residents in the Netherlands. This pilot test ensured that all participants clearly understood the questionnaire and that no technical issues with Google Forms were overseen.

2.4. Completing the data for analysis

The survey responses in Google Forms were automatically sorted into an excel file by question. Since the 17 main questions of the questionnaire were made compulsory for participants to be able to proceed to the next question, there were no incomplete surveys to exclude from the analysis. Data analysis was performed using Excel (Microsoft Office 2016, Microsoft, Redmond, WA).

3. Results

3.1. Characterization of the participants

A total of 247 respondents from 37 countries participated in the survey (Fig. 1, Appendix 2). The majority of the respondents who participated in the questionnaire were hospital pharmacists (n = 227, 92%), followed by community pharmacists (n = 8, 3%), oncology pharmacists (n = 7, 3%) and others such as quality officers or trial coordinators (n = 5, 2%). Oncology pharmacists are pharmacists that have a specialisation in the field of oncology. The hospital pharmacists worked in a general hospital (n = 118, 52%), an academic hospital (n = 69, 30%) or a dedicated cancer

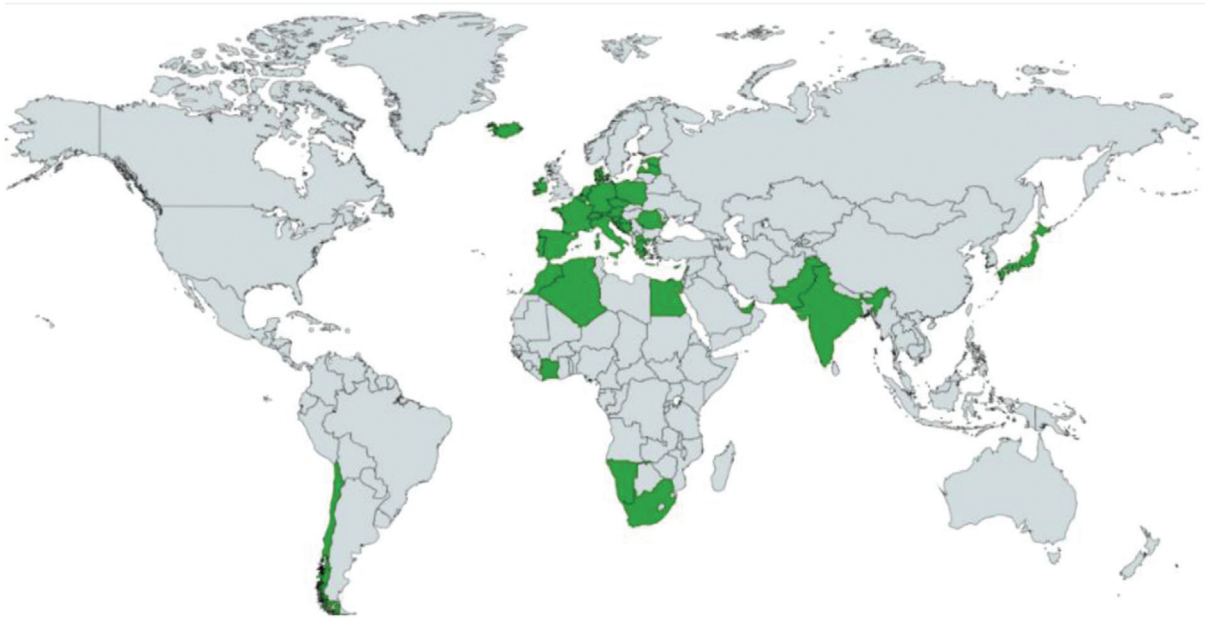

Figure 1. Overview of the participating countries in green.

clinic (n = 35, 16%). The remaining 2% did not specify their place of work.

3.2. Storage and compounding in the pharmacy

The participants were asked three questions to evaluate the storage conditions of the mAbs. The majority of the pharmacists (92%) answered that they store the mAbs at 2 to 8°C and they are using temperature loggers for measuring storage conditions. One participant answered that mAbs are stored below 0 degrees Celsius in his hospital. Furthermore, 149 pharmacists (60%) responded that they validate the temperature loggers annually. Remarkably, several pharmacists (n = 22, 9%) replied that they do not validate the temperature loggers at all. Finally, 175 of the pharmacists (71%) answered that the prepared ready-to-administer mAbs are protected from light by secondary packaging. However, a quarter (n = 61, 25%) of pharmacists replied that they do not take measures to protect prepared mAbs from light (Fig. 2).

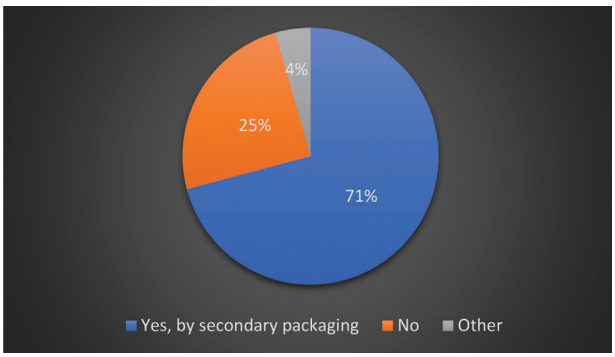

Figure 2. Visual summary of the responses (n = 247) to question Q5 of the survey: Light exposure can be an aspect leading to protein aggregation. Are some of the prepared ready-to administer mAbs intentionally protected from light?

The next section of the questionnaire consisted of questions regarding reconstitution practices including the use of medical devices. Reported devices are spikes (38%), CSTDs (12%), and needles (22%). The other 28% used a combination of these devices depending on the type of mAb and working conditions. The majority perform reconstitution manually (n = 220, 89%), versus some by semi-automatic pump systems (n = 10, 4%) and by robot (n = 3, 1%). An overview of the devices in use is given in Table 1.

In addition, the pharmacists were asked three questions on the administration of the mAbs. More than half of the respondents (63%) answered that they attach an administering side-line at the compounding site to the infusion bag, 29% answered that the side-line is attached at the administration site and 8% do not use any side-lines. Furthermore, (90%) of the participants fill the administration line by sodium chloride 0.9% or dextrose 5%. Finally, 61% of the participants do not remove residual headspace/air of the infusion bag (Fig. 3). Interestingly, 8% even add extra air to compensate for dead volume of the filter and side-line.

3.3. Transportation within the hospital

For this section, two questions were asked about transportation of mAbs and written guidelines regarding transportation. A majority of 146 pharmacists (59%) stated that the mAbs after compounding are currently transported via a logistic employee on foot at ambient temperature. Other practices are transportation on foot in a cool-box (n = 49, 20%) or via the tube system (n = 18, 7%); the rest use a combination of the different transportation methods (Fig. 4). A relatively high number of the pharmacists (n = 158, 64%) indicated that they do not have any written guidelines for the transportation of mAbs in their institution.

3.4. Visual inspections and shelf-life of mAbs

The participants were asked if they perform visual examination for particles of the prepared mAbs before administrations. Most

Table 1

Overview of the name/brand of devices and in-line filters, which the respondents reported in the questionnaire.

	Name and brand of devices	Name and brand of in-line filters
1	BD Phaseal CSTD	BBraun
2	Cyto set	BD Phaseal secondary set with filter
3	BD spike	Bexen
4	Biokon chemo-clave	Bodyguard 1.2 nm
5	Care fusion (R)	0,22 micro filtre ref CHD506
6	Chemo spike codan	Carefusion
7	Chemolock	Codan
8	Codan spike swan	Codan connect-Z iv star
9	Codan micro spike	Codan ref 76.447
10	Codan (swan lock)	Cyto ad z inline
11	Codan (chemoprotect)	Cyto set mix 0,2 micro filtre
12	Equashield	Cyto set mix sterfix
13	Extra spike plus – Fresenius kabi	Cyto-set Braun
14	Fasyl	VAR7
15	Hospira	Filtre IVEX
16	ICU medical	Fresenius Kabi
17	ICU- 034-CS-51	FSK volumat filtre line
18	ICU CH70	Grobir inline filtre
19	ICU Claves	ICU medical extension filtre 0,2 µ ref 011-H3669
20	ICU- 034-CH-70	ICU mediplast
21	BBraun mini spike	Infusomat Space Line
22	Needle with side hole	Fresenius, Ref. M77460070
23	Becton Dickinson needle	Pharmassure
24	Tevadaptor	Rowe-Med
25	Texium	Sterifix
26	Vialvent (Millipore)	Vary
27	Yukon	Whatman

of the respondents (n = 213, 86%) replied that they do. Another question of the survey was about the determination of the shelf-life of mAbs (Fig. 5). Most of the respondents (n = 161, 65%) indicated using literature data, such as Stabilis[25] and Trissel[26] as the sources they might consult to determine the shelf-life of the prepared mAbs. Also, pharmacists use the summary of product characteristics (SmPC) (n = 72, 29%) or results from their own stability tests (n = 8, 3%).

3.5. Staff training and patient's home-administration

The last section of the questionnaire consisted of questions about which health-care professionals are receiving staff training on the potential risks of mAb handling and about patient's self-administration of mAbs at home. A slight majority of 52% of the respondents answered that nurses as well as pharmacists and pharmacy assistants receive staff training. However, 27% of the participants answered that the staff do not receive any training. In the remainder (21%), staff training is only available for some but not all of the health-care professionals. Furthermore, the majority of the respondents (n = 206, 83%) answered that mAbs are not dispensed by the pharmacy to patients for self-administration at home. However, when self-administration home treatment programs are in place, in most cases pharmacists instruct the patients and inform them about handling and administration of the mAbs (Fig. 6). Also (n = 37, 90%) inform the patients on how to store the mAbs at home. The total number of participants who answered this sub-question was 41.

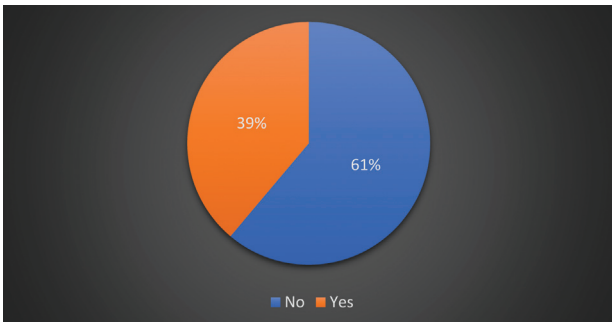

Figure 3. Visual summary of the responses (n = 175) to sub-question Q8c of the survey: Do you remove the residual headspace/air from the bag?

4. Discussion

The aim of this research was to create a snapshot of the post-production handling of mAbs in several parts of the world and to provide more insight into potential risks that are associated with post-production handling of mAbs in daily practice in pharmacies. The outcomes of this study show a high level of variability in daily handling practices of mAbs. There is a general lack of appropriate guidelines for handling of mAbs in hospitals and outpatient clinics. The results that were found in this study reinforce and confirm previous studies.[22–24]

Our study highlights the potential risks that are associated with post-production handling of mAbs. First, appropriate storage conditions with regard to temperature are pivotal. Although most pharmacists store the vials of mAbs refrigerated, not all use temperature loggers or validate their temperature loggers to ensure that the refrigerator remains within the 2 to 8°C range at all times. Thus, unnoticed temperature deviations can occur during storage. Secondly, compounding is performed by using a variety of devices and equipment. The material of such devices can interact with the protein, which may lead to particle formation below the visual range.[13,18] This may result in either a loss of active protein and thus administration of a lower dose, and/or in aggregation that may potentially lead to an immune response. Thirdly, ready-to-administer mAbs are transported within the facility to the ward or administration site. Most pharmacists reported that this transport is done by logistic employees on foot at ambient temperature. Although this poses a potential stability risk, this transport is presumably often short in duration, generally within one building or to adjacent buildings. Hence, we deem this risk of minor importance. The presence of air in ready-to-administer infusion bags might be of greater concern, because the air liquid interface is a well-known site where aggregation can start.[7] In our survey, 61% of pharmacists reported that they do not remove residual air. Some respondents even add extra air to the infusion bag, to allow for administration of the full dose when using an in-line filter. In addition, a quarter of the responders do not keep the prepared mAbs protected from light, which can also lead to protein aggregation.[1] Fourthly, 14% of the pharmacists do not perform visual examination for particles of the prepared mAbs before administration. This is a major risk, since visible particles may lead to safety issues, including immune reactions.[2–5,15,17,27] This can easily be avoided as it does not take much time to realise visual examination. Finally, there is a lack of training of health-care staff on the proper handling of mAbs. This may result in instability and aggregation of the mAbs by inaccurate handling by health-care professionals.

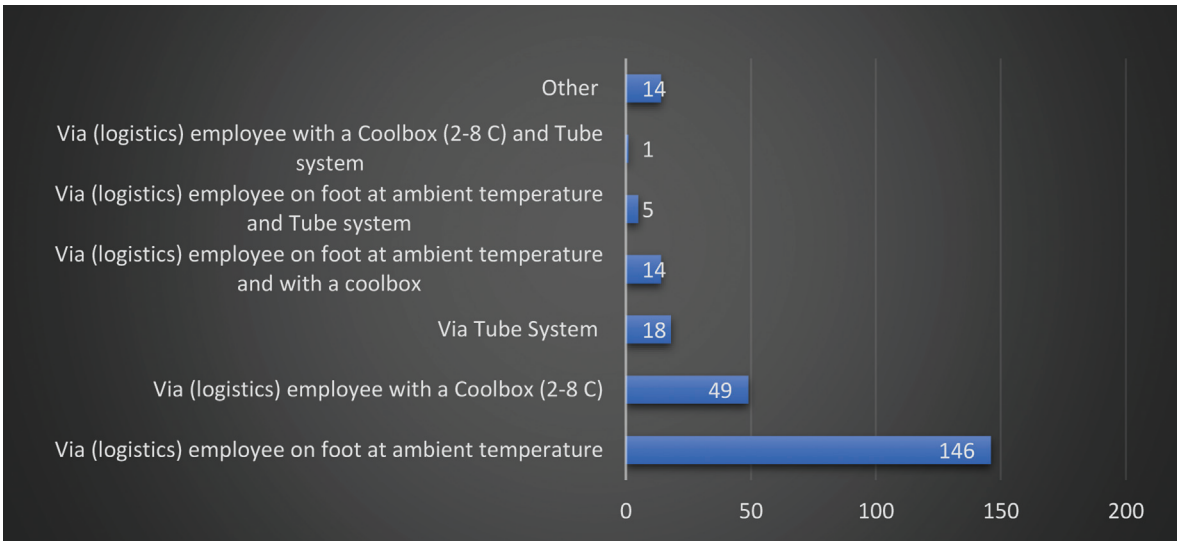

Figure 4. Visual summary of the responses (n = 247) to question Q10 of the survey: How are monoclonal antibodies transported after compounding within the institution where you work?

This is the first published study reporting real-world post-production handling of mAbs throughout the world, with almost 250 participants dealing with mAbs at their workplace. A limitation of this study was that some countries are better represented in the survey than others, with many countries not represented at all. Moreover, voluntary participation can provide bias. For instance, professionals who know that their work practices are not so well organized might be less inclined to participate. Furthermore, to get a high-response rate, we had to limit the number of questions so that participants could complete the survey within a short time. As a result, we were not able to investigate all the possible practices in great depth.

Future research is strongly recommended in this area. In particular, more attention should be paid to the consequences of the different real-world mAb handling practices on product quality, for example through the actual measurement of aggregation and particle formation. Specifically, reports on introduction of particles through the use of devices is of great concern. In addition, it is important to gain more insight into the content, effect and education of the staff training of health-care professionals. Finally, this article illustrates the need for more attention to informing and instructing patients who take mAbs home for self-administration.

In conclusion, the results of our survey show that there is a high level of variability in daily practices of mAbs in pharmacies

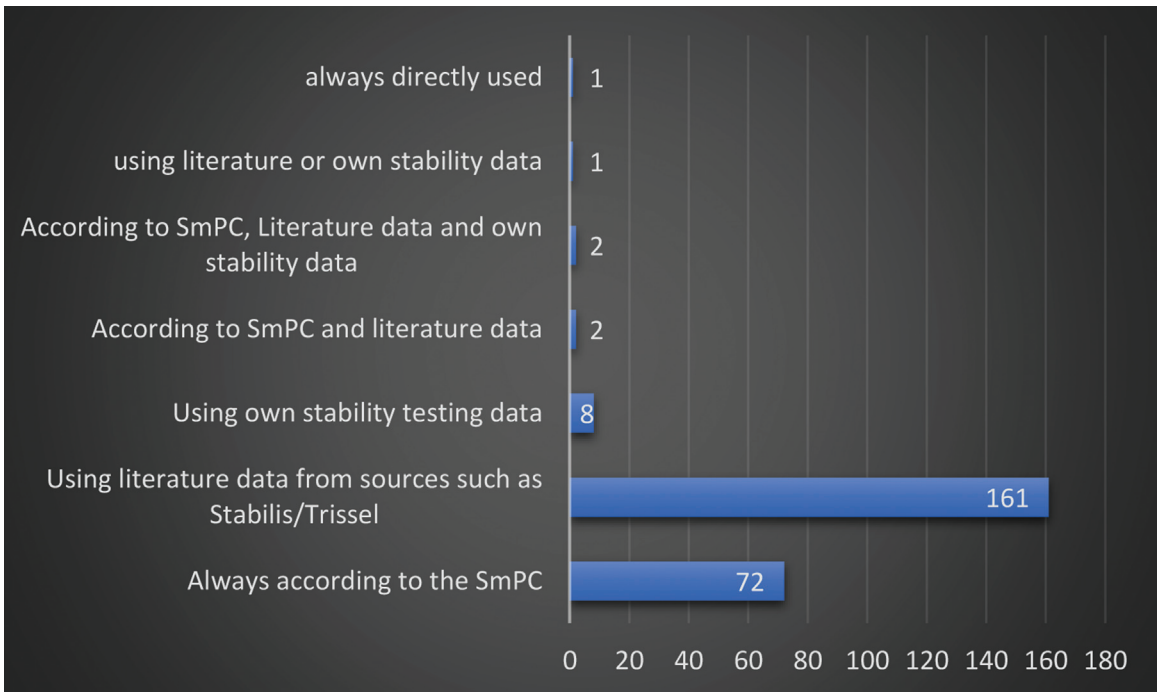

Figure 5. Visual summary of the responses (n = 247) to question Q13 of the survey: How is the shelf-life of the monoclonal antibodies determined?

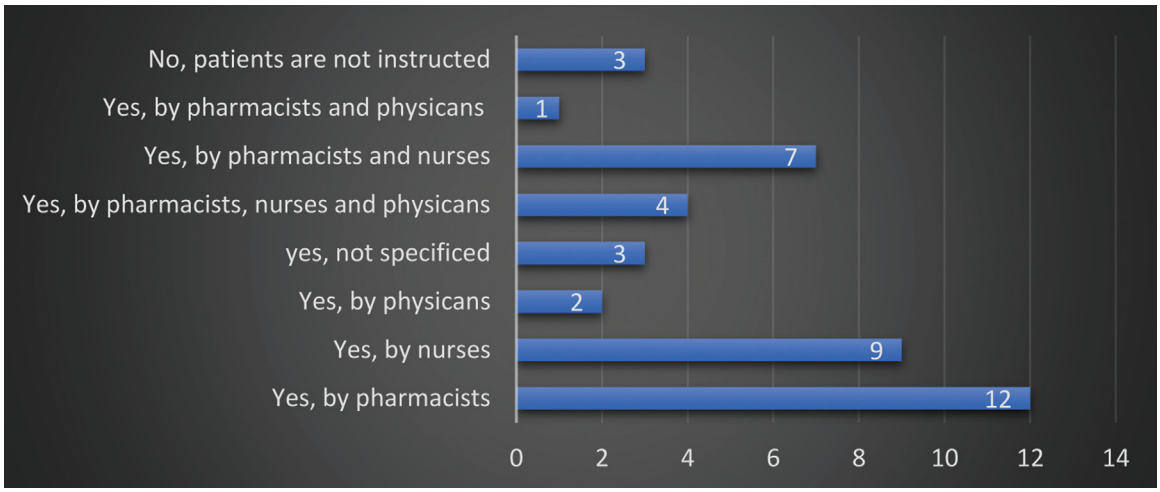

Figure 6. Visual summary of the responses to question Q15 of the survey: Are patients instructed on handling and administration of the monoclonal antibodies?

worldwide. Inappropriate handling has been reported in our survey in each stage of the drug's post-production life-cycle: from transport to storage to compounding and administration. Therefore, the need to perform studies in this area remains paramount and the development of handling guidelines for health-care professionals is warranted.

Acknowledgments

We are grateful to Prof. A. Astier, Prof. N. Navas Iglesias, Prof A. Salmeron, and Mrs. M. Saar respectively from France, Spain, and Estonia, for commenting on and validating the questionnaire. We are also grateful for all colleagues who participated in the survey.

References

1 Nejadnik RM, Randolph TW, Volkin DB, et al. Postproduction handling and administration of protein pharmaceuticals and potential instability issues. *J Pharm Sci* 2018; 107:2013–2019.
2 Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. *Nat Rev Drug Discov* 2014; 13:655–672.
3 Rosenberg AS. Effects of protein aggregates: an immunologic perspective. *AAPS J* 2006; 8:E501–E507.
4 Hermeling S, Crommelin DJA, Schellekens H, et al. Structure-immunogenicity relationships of therapeutic proteins. *Pharm Res* 2004; 21:897–903.
5 Moussa EM, Panchal JP, Moorthy BS, et al. Immunogenicity of therapeutic protein aggregates. *J Pharm Sci* 2016; 105:417–430.
6 Kiese S, Pappenberger A, Friess W, et al. Shaken, not stirred: mechanical stress testing of an IgG1 antibody. *J Pharm Sci* 2008; 97:4347–4366.
7 Siska C, Harber P, Kerwin BA. Shocking data on parcel shipments of protein solutions. *J Pharm Sci* 2020; 109:690–695.
8 Fleischman ML, Chung J, Paul EP, et al. Shipping-induced aggregation in therapeutic antibodies: utilization of a scale-down model to assess degradation in monoclonal antibodies. *J Pharm Sci* 2017; 106: 994–1000.
9 Randoph TW, Schiltz E, Sederstorm D, et al. Do not drop: mechanical shock in vials causes cavitation, protein aggregation, and particle formation. *J Pharm Sci* 2015; 104:602–611.
10 Torisu T, Maruno T, Hamaji Y, et al. Synergistic Effect of cavitation and agitation on protein aggregation. *J Pharm Sci* 2017; 106:521–529.
11 Duerkop M, Berger E, Dürauer A, et al. Impact of cavitation, high shear stress and air/liquid interfaces on protein aggregation. *Biotechnol J* 2018; 13:e1800062.
12 Ghazvini S, Kalonia C, Volkin DB, et al. Evaluating the role of the air-solution interface on the mechanism of sub-visible particle formation caused by mechanical agitation for an IgG1 mAb. *J Pharm Sci* 2016; 105:1643–1656.
13 Hernández-Jiménez J, Martínez-Ortega A, Salmerón-García A, et al. Study of aggregation in therapeutic monoclonal antibodies subjected to stress and long-term stability tests by analyzing size exclusion liquid chromatographic profiles. *Int J Biol Macromol* 2018; 15:511–524.
14 Singh R, Waxman L, Fang L, et al. An investigation to examine the effect of the elastomeric surface treatment on protein stability. *PDA J Pharm Sci Technol* 2020; 21: doi: 10.5731/pdajpst.2020.012120.
15 Liu L, Ammar DA, Ross LA, et al. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. *Invest Ophthalmol* 2011; 52:1023–1034.
16 Krayukhina E, Tsumoto K, Uchiyama S, et al. Effects of syringe material and silicone oil lubrication on the stability of pharmaceutical proteins. *J Pharm Sci* 2015; 104:527–535.
17 Crul M, Zandvliet A, Moes JR, et al. Bevacizumab for intravitreal injection: impact of sub-visible particles on the shelf-life of repackaged bevacizumab. *J Ocular Pharmacol Ther* 2019; 35:372–375.
18 Sreedhara A, Zamiri C, Goswami S, et al. Challenges of using closed system transfer devices with biological drug products: an industry perspective. *J Pharm Sci* 2020; 109:22–29.
19 Meade E. Use of closed-system drug transfer devices in the handling and administration of MABs. *Br J Nurs* 2015; 24 (16 Suppl 1):S21–27.
20 Petoskey F, Kwok SC, Jackson W, et al. Overcoming challenges of implementing closed system transfer device clinical in-use compatibility testing for drug development of antibody drug conjugates. *J Pharm Sci* 2020; 109:761–768.
21 Besheer A, Mahler HC, Matter-Schwald A, et al. Evaluation of different quality-relevant aspects of Closed System Transfer Devices (CSTDs). *Pharm Res* 2020; 37:81.
22 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; 22:219–227.
23 Crul M, Franki AS, Simons K. Preparation of monoclonal antibodies: practice across Europe. *Eur J Oncol Pharm* 2012; 5:6–8.
24 Jiskoot W, Nejadnik MR, Sediq AS. Potential issues with the handling of biologicals in a hospital. *J Pharm Sci* 2017; 106:1688–1689.
25 Stabilis 4.0. Stability and compatibility of drugs. www.stabilis.org.
26 Trissel L, The Handbook on Injectable Drugs. 20th Edition and previous Editions. American Society of Health System Pharmacists, Bethesda, MD.
27 Mathonet S, Mahler HC, Esswein ST, et al. A biopharmaceutical industry perspective on the control of visible particles in biotechnology-derived injectable drug products. *PDA J Pharm Sci Technol* 2016; 70:392–408.

Appendix 1: All survey questions.

Questions	Answer options	Number of respondents
.Q1. In which country do you work?	Open Question	N = 247
Q2. What is your profession and specialisation?	A. Hospital pharmacist B. Community pharmacist C. Other:	N = 247
Q2B. If hospital pharmacist, do you work in:	A. General hospital B. Academic hospital C. Dedicated cancer clinic D. Other:	N = 247
Section 1: Storage condition (Q3-Q5)		
Q3. At how many degrees °C are monoclonal antibody vials stored?	A. Under 0°C B. At 2- 8°C C. At temperature controlled room temperature D. At non-temperature controlled room temperature	N = 247
Q4. Do you use temperature loggers for storage?	Yes/No	N = 247
Q4b. How often are temperature loggers validated in the institution where you work?	A. Monthly B. Annually C. Temperature loggers are not validated D. Other, please specify:	N = 228
Q5. Light exposure can be an aspect leading to protein aggregation. Are some of the prepared ready-to-administer mAbs intentionally protected from light?	A. Yes, by secondary packaging B. No C. Other, please specify:	N = 247
Section 2: Reconstitution practices & medical devices (Q6-Q9)		
Q6. What device do you use for reconstitution practices?	A. Needle B. Spike C. Closed system transfer device (CSTD) D. Other, please specify:	N = 247
Q6b. Specify name and brand	Open question	N = 148
Q7. How do you perform the reconstitution practices of mAbs?	A. Manually B. Semi-automatic device C. Robot D. Other, please specify:	N = 247
Q8. Are the infusion bags containing mAbs delivered with a short administering line?	A. Yes, the line is attached at the compounding site B. No, the line is attached at the administration site C. We do not use side lines	N = 247
Q8b. Do you fill the administration line by saline or dextrose ?	Yes/No	N = 176
Q8c. Do you remove the residual headspace/air from the bag?	Yes/No	N = 175
Q9. Are you using in-line filters for the administration of iv mAbs?	Yes/No	N = 247
Q9b. What is the name and brand of the filter?	Open question	N = 116
Q9c. Do you add extra air to the infusion bag to enable administration of the full dose?	A. Yes B. No C. Only for specific medicines	N = 116
Section 3: Transportation within the hospital (Q10-11)		
Q10. How are monoclonal antibodies transported after compounding within the institution where you work?	A. Via tube system B. Via (logistics) employee with a cool-box (2-8 C) C. Via (logistics) employee on foot at ambient temperature D. Other, please specify	N = 247
Q11. Do you have written guidelines for the transportation of mAbs in the institution where you work?	Yes/No	N = 247
Section 4: Visual inspections and shelf-life of mAbs (Q12-13)		
Q12. Before administration, are there visual inspections for visible particles of the prepared mAb?	Yes/No	N = 247
Q13. How is the shelf-life of the monoclonal antibodies determined?	A. Always according to the SmPC B. Using literature data from sources such as Stabilis/Trissel C. Using own stability testing data D. Other, please specify:	N = 247
Section 5: Staff training (Q14)		
Q14. Is there Staff training on the potential risks of MAb handling?	A. Yes, only nurses B. Yes, only pharmacists C. Yes, only pharmacy assistants D. Yes, All the above E. No	N = 247
Section 6: patient's self-administration (Q15-17)		
Q15. Are monoclonal antibodies drugs given to the patient for self-administration at home?	Yes/No	N = 247
Q16. Are patients instructed on handling and administration of the monoclonal antibodies?	Yes/No	N = 41
Q17. Are patients informed of the optimal storage conditions at home for monoclonal antibodies?	Yes/No	N = 41

Appendix 2: Participants per country.

	European continent	African continent	Asian continent	South-America continent	Oceania
.1	Austria (1)	Algeria (1)	India (2)	Chili (5)	New Caledonia (3)
2	Belgium (2)	Côte d'Ivoire (1)	Japan (1)		
3	Bosnia and Herzegovina (1)	Egypt (6)	Lebanon (3)		
4	Croatia (5)	Morocco (2)	Pakistan (1)		
5	Cyprus (1)	Namibia (2)	United Arab Emirates (3)		
6	Czech Republic (2)	South Africa (11)			
7	Denmark (2)				
8	Estonia (3)				
9	France (83)				
10	Germany (3)				
11	Greece (9)				
12	Iceland (1)				
13	Ireland (1)				
14	Italy (9)				
15	Latvia (1)				
16	Netherlands (11)				
17	North Macedonia (1)				
18	Poland (3)				
19	Portugal (3)				
20	Romania (2)				
21	Serbia (1)				
22	Slovenia (1)				
23	Spain (55)				
24	Switzerland (5)				

Numbers of participants are given in parentheses.