Topic: Handling of protein drug products and stability concerns

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

In the past two decades, protein pharmaceuticals have become the fastest growing class of therapeutics owing to their beneficial impacts on the treatment of severe and life-threatening conditions and diseases. Development and manufacturing of protein pharmaceuticals is, however, challenging and requires overcoming various manufacturing hurdles such as issues with the purity of the protein product. The safety and efficacy of protein pharmaceuticals depend sensitively on their purity. Impurities in marketed protein pharmaceuticals may be present due to limitations in manufacturing processes or may also be a result of degradation processes occurring not only during manufacturing, but also during long-term storage of the bulk drug substance and/or final drug product (DP) [1]. Impurities within therapeutic protein products can cause severe adverse drug reactions (ADRs) in patients, that may be acute, as is the case for infusion-induced anaphylaxis and pseudo-allergy responses, which may even result in patient death, or long-term like unwanted immunogenicity.

Physical aggregation and chemical degradation can occur throughout a protein product's life history, and even modest environmental stresses can cause extensive damage. Development of effective upstream and downstream processes as well as robust formulations and filling processes are crucial for maintaining product quality, and hence, for the safety and efficacy of protein pharmaceuticals. The pharmaceutical industry has made great progress in improving bulk and DP manufacturing as well as storage and transportation conditions to minimise the level of degradation. However, there exists only low control over the many factors that may affect product quality after the protein pharmaceuticals are released and shipped. Routine handling or unintentional mishandling of therapeutic protein products may cause protein degradation that remains unnoticed but can potentially compromise the clinical safety and efficacy of the product [2]. Storage of the DP outside the recommended condition ranges, use of incompatible supply and/or technology, careless handling of drug during preparation for administration and during delivery to patient are just a few examples of mentioned (mis)handling [3].

There has been increasing expression of concern in the past decade regarding the significance of the post-production handling of protein pharmaceuticals. At the same time, studies revealed that the consequences of presence of impurities in DP can be severe. Potentially high likelihood and/or severity in consequences in combination with the low level of control over the processes by the industry make these concerns a significant risk that needs to be addressed in a public-private partnership including all relevant stakeholders.

DPs as described above are handled in pharmacies, hospitals and by patients after they have been released by the manufacturer. It is therefore outside the scope of full control of the pharmaceutical industry although the manufacturers influence the process by trying to consider the human factors, by providing training and instructions as well as making more robust DPs that should withstand a certain level of stress during usage. Understanding the handling conditions requires assistance from the experts in pharmacies, medical institutions as well as organisations that can gather and document information on the patients' side, e.g. academic and research organisations or structured patients communities, all of which are envisioned to become part of the applicant consortium.

Alongside a good understanding of the various (and probably most common) handling steps and the stresses they imply for protein drugs, there is a need for research in estimating the impact of each handling step on DP quality and potentially the safety and efficacy of the drug.

It is only through the above-mentioned process that the risky handling steps are identified and addressed. Working out a meaningful framework for sharing the information between the manufacturer and the healthcare professionals and/or patients (that might go beyond the current communication channels and exchange of standard pharmacy manuals and training) is only possible through close collaboration among all involved. A consortium comprised of the pharmaceutical industry, medical institutions, pharmacies, academia and SMEs and potentially patient organisations can fully address all the aspects of the complex topic and help to develop technological and process solutions.

Scope

The first objective of this topic is **to improve the understanding of real-world stressful drug product handling steps** and their **effects on protein product quality**.

- All protein pharmaceuticals are considered to be within the scope of the topic;
- All handling steps for preparation, transport and administration should be addressed:
    - Studying the effects of the handling steps on drug product quality is in the scope of the topic;
    - Supplies that are used for handling of the protein pharmaceuticals are also to be investigated and evaluated. Evaluation of new technologies that are used to handle protein pharmaceuticals such as closed-system transfer devices are of interest;
    - Handling practices include the ones that are performed by healthcare professionals in hospital and compounding pharmacies and the ones in hands of patients. The understanding should be as thorough as possible and can, among other ways, be obtained by the use of new technologies and digital tools that record details visually or by sensors of conditioning parameters during storage and administration processes;
    - Routine handling procedures, i.e. the ones that are currently used as standard procedures for protein drug products in pharmacies and by patients should be addressed.
- These risks associated with the handling of protein DPs should be assessed and potential solutions developed;
- Mishandling cases with high level of likelihood or severe impacts should also be examined.

The second objective of this topic is to use this understanding for **development of guidelines and operating processes** to **improve the DP robustness and pharma processes**, and to develop **more efficient training** (see Figure 1)

- Improving the in-use studies and other processes in development of protein pharmaceuticals is in the scope of the topic;
- Innovative solutions that help ensuring the stability of DP during handling are welcome;
- Improving the training materials and improving the handling culture are in the scope of the topic. Training aspects should cover training for professionals and patients;

- Utilisation of technologic tools (video, webinar, online media and creative manuals) for development of novel training methods and materials is within the scope of the topic.

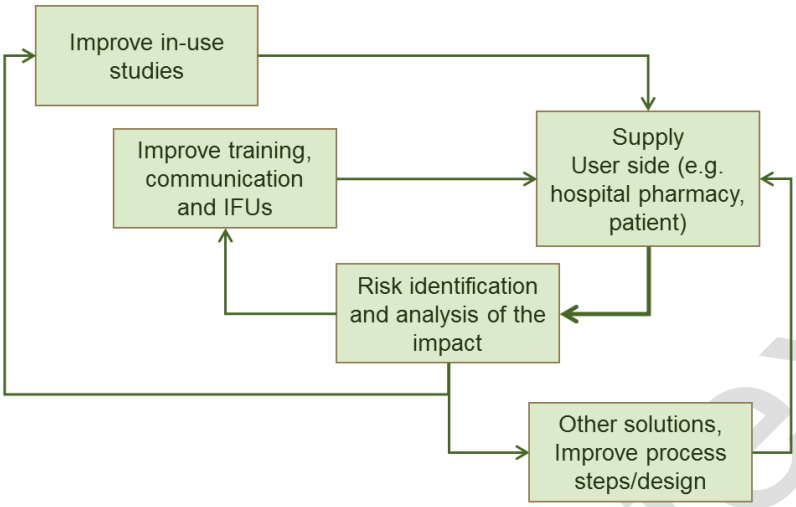

Figure 1: Good understanding of the drug product handling at the user side can lead to formulation of various solutions

Expected key deliverables

The expected deliverables from the project are the following:

Clear insight into the drug product handling procedures and their impact:

- Detailed outlining of the handling procedures in pharmacies and at homes including all steps (irrespective of the delivery method/device);
- Evaluation of the real impact of handling steps on stability of protein DP;
- Outlining of the protein drug preparation and administration supplies available to pharmacies, and clinics considering the major geographic markets investigated in the project;
- Assessment of the potential impacts on delivered dose;
- Estimation of the potential impacts on clinical safety and efficacy.

Improved protein drug product development processes

- Tools and methods to improve DP robustness (rational and realistic in-use studies);
- Determination of critical parameters, improvements in processes and definition of DP handling requirements.

Improved training on drug product handling

- Improved professional user training including development of training materials (e.g. videos) that can be used to educate and as reference in pharmacy manuals/instructions;
- Improved patient/caregiver training (at both strategy and execution levels).

These key deliverables lead to improvements in assessment and management of the risks associated with handling of protein drug products and improved efficacy and safety of protein drug products for patients.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- Through this project, a better understanding of the handling procedures and associated stresses in hospitals and in the hands of patients will be obtained. The project will assess the risks associated with these handling steps and provide solutions to ensure a high-quality delivery and administration of protein DP;

- The project will help involved pharmaceutical companies to improve their processes towards development of more robust DPs that withstand the handling stresses;

- At the same time, access to the resulting improved methods to influence the handling culture can be used by both private and public sectors in the interest of patients. Foremost amongst the expected impacts, is the improved training for professionals and patient/caregivers to ensure the stability of protein DP. This will have global effects on the manufacturer side as well as the user side at pharmacies, hospitals and with patients, thus providing benefits to all healthcare stakeholders;

- Generation of knowledge in the area of stress-stability will help all the stakeholders involved and can be directly applied to the design of the processes and the addressing of important but challenging issues around the development of therapeutics and delivery to patients;

- Overall, the project is expected to lead to improvements in the safety and efficacy of protein drug therapies.

In their proposals, applicants should outline how the project plans to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, health technology assessment agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact on competitiveness and growth of companies including SMEs;

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards[1];

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures[2].

- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[2]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

[1] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[2] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Industry consortium

The industry consortium (EFPIA) plan to contribute the following expertise and assets:

Resources and expertise in:

- the development and manufacturing of biologics;
- formulation and process development;
- clinical processes;
- protein and biologics analytic;

as well as interaction with public health stakeholders and authorities.

Indicative duration of the action

The indicative duration of the action is 48 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture [which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate, the following expertise:

- A global understanding of the protein DP handling providing first-hand knowledge; The applicant consortium can also assign an expert advisory board to cover the needs of their proposal;
- The capacity to investigate the real-world handling procedures in hospitals, pharmacies and at homes and assess their impact on the stability and potentially on safety and efficacy of protein pharmaceuticals;
- Expertise in the available methods of communication and training for handling of protein DPs and have a strong capacity to come up with novel training concepts and materials;
- The ability to implement new technologies to achieve relevant data for handling conditions and also to produce novel and efficient training materials and methods;
- Supporting industry partners to address the challenge and influence the process of handling of protein DP.
- The participation of SMEs adding value in the field by novel monitoring concepts, training tools is highly encouraged.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

It may also require mobilising, as appropriate, the following resources:

- Utilisation of expertise and resources, including data from past investigations or existing frameworks such as the AAPS community on DP handling;
- Use of experiences or technologies from SMEs that have been developed for other purposes but can be of use for this project;
- Networks and ecosystems involving the applicants to be leveraged.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided above.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[3]

[3] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[4] and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[5]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

References

[1] Nejadnik M.R., Randolph T.W., Volkin D.B., Schöneich C., Carpenter J.F., Crommelin D.J.A., Jiskoot W.: Postproduction Handling and Administration of Protein Pharmaceuticals and Potential Instability Issues; J Pharm Sci. 2018 Aug 107:2013-2019

[2] Jiskoot W., Nejadnik M.R., Sediq A.S.: Potential Issues With the Handling of Biologicals in a Hospital; J Pharm Sci. 2017 Jun 106:1688-1689

[3] Vlieland N.D., Gardarsdottir H., Bouvy M.L., Egberts T.C., van den Bemt B.J.: The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range; Rheumatology (Oxford) 2016 Apr 55:704-709

[4] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[5] http://www.corbel-project.eu/about-corbel/research-infrastructures.html