EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Brussels,
SANTÉ

Meeting between International Plasma Fractionators Association (IPFA) and DG SANTE B4

17 April 2018

Summary Minutes

Participants:

IPFA: Francoise Rossi, Paul Strengers

DG SANTE (Unit B4): Stefaan Van der Spiegel, Deirdre Fehily and Ingrida Pucinskaite-Kubik.

IPFA had requested the meeting with DG SANTE and the topics discussed were the following:

- General update on recent developments
- IPFA input to the evaluation of the Blood Directives
- Strategic independence of European plasma supply
- Regulatory strategies for small volumes of EU plasma offered for fractionation
- Triton X on the Reach list.

Discussion points:

1. IPFA representatives complimented DG SANTE for the Stakeholder Event in September 2017, which they considered to have been organised in an open and effective manner[1]. They had also appreciated the focused meeting with blood stakeholders in June 2017 where the topics of donor safety and plasma supply had been discussed in detail[2].

2. They updated DG SANTE on some of their recent publications, including one on the clinical use of plasma derived medicinal products[3] and one on plasma as a strategic resource[4].

3. They also informed DG SANTE regarding the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) published in the New England Journal of Medicine that demonstrates that patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII[5]. Although this

[1] https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170920_sr_en.pdf
[2] https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170623_sr_en.pdf
[3] Strengers PF. Ann Blood 2017;2:20.
[4] Strenger FW, Klein HG Transfusion 2016; 56(12): 3133-3137
[5] Peyvandi F et al. N Engl J Med 2016; 374;21

evidence has not been accepted as conclusive by EMA at this time, the impact could be significant in terms of increased clinical demand for plasma-derived products in the future.

4. The importance of European registries for the follow up of patients with specific conditions such as haemophilia was discussed as important for demonstrating efficacy. They described a situation with many national haemophilia registries (France, UK) and noted the potential benefit of having an EU wide registry for aggregation of data.

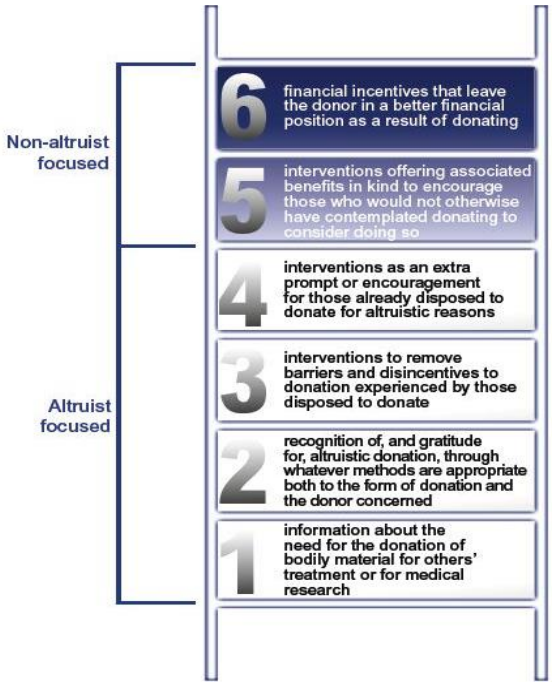
5. IPFA had provided DG SANTE with a document summarising their proposals for a possible revision of the Directives. The Commission clarified that the current initiative relates solely to gathering views and evidence on the current legislation on blood and tissues and cells (BTC) to evaluate whether it achieved its original objectives and is still fit for purpose. Any decision to revise the legislation would be taken only when the current Evaluation has been completed and published. DG SANTE further informed IPFA representatives on the timeline of the evaluation – with the publication of the summary of the open public consultation in mid-April, submission of the external contractor study mid-2018 and publication of the final Evaluation Report bringing together all inputs by the end of 2018.

6. With regard to the EU Blood Directives, IPFA underlined that the source material for the manufacturing of plasma-derived medicinal products, as a Substance of Human Origin (SoHO), falls under the EU Blood directive for donation, procurement and testing and that this implies various ethical and safety considerations. IPFA considers that the regulation of the collection of human plasma should be consistent with wider SoHO regulations and proposed that a definition for SoHO should be included in the legislation for greater clarity.

7. IPFA stressed that, in their view, measures should be taken by governments or regulatory bodies to mitigate the risk of dependency of supply of plasma on any single country or region. IPFA describes this approach as 'strategic independence of plasma'. Given the current dependency on US plasma for the global plasma supply, IPFA promotes for Europe strategic independency of plasma in order to avoid the risk of shortages in case of adverse events in the US plasma supply. The current US plasma supply is covering global needs but IPFA considers that the potential risk should be addressed by European blood establishments by significantly increasing their plasma collections in order to create a balance for future supply security for the EU. Current examples of countries with a plasma supply strategy, independent from whole blood collections, were listed as Canada, Australia and the Netherlands. IPFA considers that the supply security should be addressed in the EU legislation. It was discussed whether targets should be set for the degree of PDMP self-sufficiency from European plasma, which could be expressed as a percentage of supply or as International Units of each PDMP per capita. IPFA confirmed that initiatives with blood collectors to move towards increased plasma collections in the public sector do exist, in some cases supported by IPFA workshops and other means, although it was noted that the costs involved for blood establishments may be a significant barrier.

8. IPFA expressed the view that the same legislative framework is needed for plasma for fractionation, whether it is provided as plasmapheresis plasma (also commonly called source plasma) or as recovered plasma. They consider that specific technical requirements, separate from those for transfusion products, should be applied in the EU Blood legislation to plasma for fractionation, whatever its origin of collection. An illustrative example provided was the requirement for HTLV I and II testing, which IPFA stated is of relevance for blood for transfusion but not for plasma for fractionation.

9. IPFA considers that the concept of Voluntary Unpaid Donation (VUD) is not sufficiently clear in the legislation and suggested adopting new definitions for remuneration / non-remuneration. They proposed adopting the scale published in the Nuffield Council of Bioethics report on Human Body Donations for Medicine and Research[6] and, in this way, distinguishing between non-altruistic-focused and altruistic-focused practices (see figure copied from the Nuffield report). IPFA recommends that levels 1, 2, 3 and 4 are consistent with the definition of non-remuneration and 5 and 6 are consistent with the definition of remuneration. IPFA supports the advocacy of promotion of non-remuneration in the EU legislation but notes that strategies must be found to motivate donors and increase plasma collections without compromising the safety of the donors.



10. IPFA proposed that the EU Commission explore options for more flexible updating of the technical requirements on blood and plasma to reflect scientific and technical advances in a timely manner. Specifically, they propose legal cross-referencing to the EDQM/Council of Europe Guide.

11. IPFA stressed that deferral for plasma donors should be evidence-based and that the current rules should be reviewed. As an example, they urged that individual MSM national deferral policies (deferral of men having sex with men) should be considered by the European regulation as bringing the same level of quality of plasma for fractionation. They consider that the MSM rules represent an example of urgent need for harmonisation throughout Europe. They would wish to see EMA make a statement on the equivalent safety and quality of plasma collected under different MSM national acceptance criteria.

12. IPFA expressed the view that the outcomes of some incremental blood safety interventions for the avoidance of transfusion-transmitted infection are not cost-effective when measured by QUALYs or other measures of public health benefit, e.g. yield of increased safety vs cost for NAT testing. They consider that the cost efficiency of additional biological safety

[6] http://nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf

measures should be assessed and weighed against availability of plasma and plasma derived medicinal products as well as compared with other costs of health care interventions.

13. IPFA also shared the following views on some specific technical issues:

    (a) The competence of experienced nurses should be recognized as appropriate for oversight at collection sessions without compromising safety.
    (b) Epidemiological data collection (prospective donor testing results) should be aggregated at the level of organisations to allow meaningful epidemiological statistics to be published.
    (c) Safe plasmapheresis frequency per year is not known and an assessment should be performed on a European basis.

14. On the subject of GMP and inspections, IPFA noted that GMP requirements apply according to activities of blood collection centres, i.e. covering processing, storage, and some of the testing activities. For the plasma 'collection' activity, the Directive on Good Practices Guidelines7 should apply and should be accepted by all inspectors as complying with the requirements of GMP. They also consider that risk-based management of inspections should be generalised for all European blood establishments. The consider that the quality assessment/inspection of fixed and mobile blood collection centres which are working under the same overall quality management system should recognise these common quality assurance procedures and they consider that the interpretation of the European Commission included in GMP Annex 14 with regards to contract manufacturing should appear per se in the blood legislation.

15. IPFA recommends that Member States fully transpose the EU requirements, as adopted at EU level, and without applying more stringent rules unless justified by scientific evidence. This was highlighted as a step towards facilitating free movement of plasma and achieving strategic independence.

16. IPFA believes the matter needs clarification in the Blood Directive from an ethical point of view, Furthermore, IPFA noted that there is evidence that a set maximum payment, as applied in some Member States, has different values in different countries and might constitute reimbursement in one but a significant sum of payment in another. This could result in certain groups of citizens donating at a disproportionately high rate. IPFA remarked the number of donations during the period of donation and not per year should be defined in order to avoid high frequency donation. IPFA supports the advocacy of VUD as the best basis for plasma collection.

17. The **technical requirements** currently laid out in the Blood Directive need to be more flexible in IPFA's views as to reflect scientific and technical advancements through, for example referencing the EDQM guide in the legislation. Further, IPFA recommends that deferral for plasma donors should be evidence-based and reviewed; MSM is an example for urgent need for harmonisation throughout Europe to which EMA's help is required in issuing a statement on the equivalent safety and quality of plasma collected from different MSM national requirements for acceptance criteria. As EMA has not gotten back to IPFA yet, DG SANTE was asked to follow up on the matter. Additionally, IPFA is particularly interested in the following points:

    (a) The cost efficiency assessment of additional biological safety measures

7 Directive 2016/1214/EC amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments

(b) The recognition of experienced nurses to overseeing collection activities

(c) The epidemiological data gathering at organisation level to allow meaningful epidemiological statistics

(d) The assessment of plasmapheresis donation frequencies should be performed to increase donor safety and maximise supply capabilities, an

(e) The role of EMA that is currently responsible for the starting material of PDMPs, however not involved in the EU Blood Directive.

18. In IPFA's opinion, the Directive on Good Practices should apply to all plasma "collection" activities and accepted by all inspectors. Further, IPFA recommends risk based management of inspections, the recognition of common quality assurance procedures taking place in fixed and mobile blood collection centres by the regulations on quality assessment and the per se inclusion of the European Commission's interpretation regarding GMP in Annex 14 in EU Blood Regulation. Finally, IPFA recommends that MS fully transpose the EU provisions without increasing the technical requirements – therefore facilitating free movement of goods. To have consistent implementation of the Blood Directive across the EU, IPFA proposes that the Blood Directive that covers all aspects of Blood, cells and plasma should be uniformly transposed without deviation by the MS, unless justified by scientific evidence. This process of harmonization is perceived as being essential to IPFA in ensuring the security of supply across the EU and support the development of Strategic Independence.

19. IPFA highlighted the challenge of accepting small volumes of plasma for contract manufacturing from smaller countries, stressing that, for cost-effectiveness, if would be necessary to pool those donations with donations from other countries.

20. On the topic of Triton-X, IPFA explained the critical impact of putting this product (critical for the safety of plasma-derived medicinal product manufacture and with no current alternative) on the Reach list has been communicated to the relevant DG in the European Commission and a response is awaited.

21. Both parties expressed their appreciation for the open and constructive discussions.