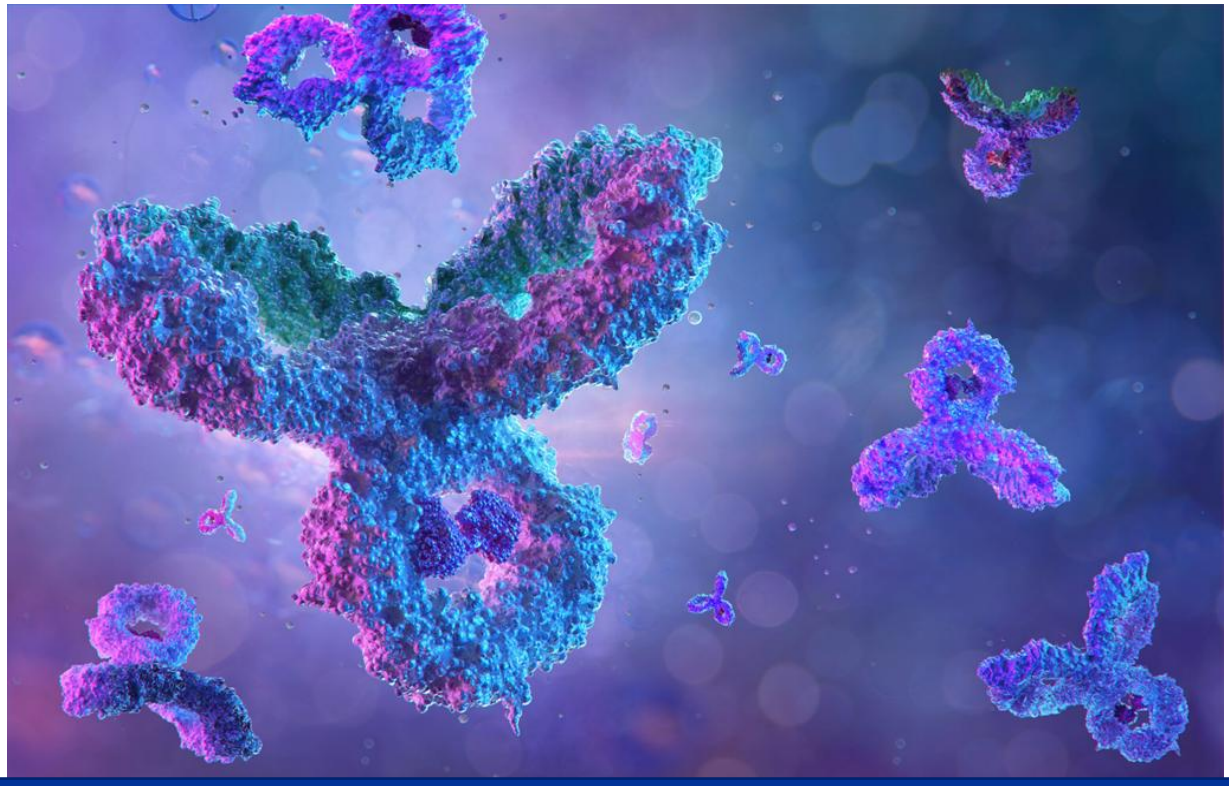
EMA/88993/2025
21 November 2025



Workshop - Challenges in drug development, regulation and clinical practice for immunoglobulins

5th March 2025 (14 pm to 18 pm, CET)

Virtual meeting

Report on EMA workshop on the challenges in drug development, regulation and clinical practice for immunoglobulins

Held virtually on 5 March 2025

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1. Introduction

Immunoglobulins were first used as replacement therapy in patients with humoral immunodeficiency and are now used for both primary immunodeficiencies (PID) and several secondary immunodeficiencies. They are also used for immunomodulatory indications in patients with primary immune thrombocytopenia (ITP), Guillain-Barré syndrome (GBS), Kawasaki's disease, multifocal motor neuropathy (MMN), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

The European Medicines Agency (EMA) has published guidelines for the clinical investigation of human normal immunoglobulin for intravenous use with regards to the use of immunoglobulins in CIDP and GBS.[1,2] Following the release for public consultation of the EMA guideline on the core summary of product characteristics (SmPC) for subcutaneous and intramuscular human normal immunoglobulin medicines, EMA organised a virtual workshop to get perspectives of stakeholders on use of immunoglobulins in both established and new indications as well as the data needed and clinical requirements for the marketing authorisation of these products.

The virtual workshop, held on 5 March 2025, was attended by healthcare professionals, industry and health technology assessment (HTA) bodies. This report summarises the key aspects discussed and the views expressed should not be understood as being the official views of EMA or its scientific committees.

The presentations of the speakers and video recording of the workshop are published on EMA's website.

2. Welcome and opening speech

Opening remarks

Daniela Philadelphy, the Austrian member of the Committee for Medicinal Products for Human Use (CHMP) and the Chair of the Haematology Working Party, welcomed attendees to the workshop, noting that immunoglobulins play a crucial role in medicine and offer a wide range of therapeutic options.

She explained that the focus of the workshop was the clinical aspects and clinical use of immunoglobulins. She also explained that the two guidelines EMA developed concern the clinical requirements to support marketing authorisation applications (MAAs) in the EU and are not clinical treatment guidelines.

As a new guideline on the core SmPC for subcutaneous and intramuscular human normal immunoglobulin medicines was out for public consultation, she noted that the workshop aimed to get stakeholder input to understand more about the clinical use of immunoglobulins. While the workshop would discuss different aspects and different stakeholder perspectives, the common overarching goal was to enable patient access to medicines that are safe, effective and of high quality.

[1] European Medicines Agency. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94033/2007 rev 4. Published December 2021. Accessed November 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-4_en.pdf

[2] European Medicines Agency. Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). EMA/CHMP/BPWP/410415/2011 rev 2. Published June 2025. Accessed November 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-human-normal-immunoglobulin-subcutaneous-or-intramuscular-administration-scig-imig-revision-2_en.pdf

Outline of the workshop

Caroline Voltz of EMA's office of advanced therapies and haemato-oncology diseases explained the outline of the workshop and how the day would be run. The workshop would have a session on clinical perspectives on the use of immunoglobulins, followed by another on additional perspectives, including those from industry and HTA bodies.

A panel discussion would provide the opportunity for more interactive deliberations on the use of immunoglobulins from a regulatory and clinical perspective, the clinical development of immunoglobulins and the need to update and amend the existing EMA clinical guidelines.

Authorised medicines and regulatory considerations

Claudia Gramiccioni of the Italian medicines regulator (AIFA) and Haematology Working Party gave an overview of the current authorised indications for immunoglobulin medicines in the EU which fall into two main categories: replacement therapies (primary immunodeficiencies and secondary immunodeficiencies) and immunomodulatory indications.

She provided a list of authorised immunoglobulins and their indications and explained the clinical data needed to obtain a marketing authorisation and the role of post-marketing surveillance in ensuring ongoing safety and efficacy.

She also highlighted recent updates to the guideline for subcutaneous and intramuscular immunoglobulins and core SmPC with regard to the chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) indication.

3. Session on clinical perspectives on the use of immunoglobulins

Clinical considerations on the use of IgG in primary immunodeficiencies (replacement therapy)

Dr Maria Pia Cicalese of the San Raffaele Scientific Institute and Vita-Salute San Raffaele University provided an overview of the use of immunoglobulins in patients with primary immunodeficiencies (PIDs). She highlighted the differences between treatment with intravenous Ig and subcutaneous Ig. Her presentation covered patient selection criteria, dosing strategies and monitoring protocols.

Emphasis was placed on monitoring serum IgG levels leading to individualisation of treatment plans to optimise patient outcomes and the importance of early intervention to prevent severe and recurrent infections. She mentioned that monitoring serum IgG levels has been an integral part of diagnosing PIDs and determining or adjusting IgG dosing schemes in patient care to meet individual needs. The frequency and doses of intravenous immunoglobulin and subcutaneous immunoglobulin (including hyaluronidase-facilitated subcutaneous immunoglobulins) require rigorous evaluation to provide optimum therapeutic benefit to patients with PIDs.

Clinical considerations on the use of IgG in secondary immunodeficiencies

Dr Peter Asdahl from the Aarhus University Hospital, Denmark, addressed the use of immunoglobulin therapy in secondary immunodeficiencies resulting from a disease or following a treatment. Dr Asdahl discussed risk assessment methodologies, indications for initiating immunoglobulin therapy, patient selection and the balance between potential benefits and risks.

Case studies were presented to illustrate decision-making processes in clinical practice. He provided the example of secondary hypogammaglobulinemia which has disease-related factors (such as multiple myeloma, chronic lymphocytic leukaemia or lymphoma) and treatment-related factors (such as monoclonal antibodies targeting plasma cells or B-cells, CAR-T cells, bispecific T-cell engagers, lymphocyte-directed chemotherapy, long-term high-dose steroids, allo-haematopoietic stem cell transplant). He indicated that future studies should compare different interventions such as the use of immunoglobulins, antibiotics and vaccinations, using standardised definitions of infection outcomes and incorporate cost-effectiveness analyses. In addition, there are unanswered questions concerning the optimal dosing of immunoglobulins, route of administration, alternative prophylaxis and the duration of therapy. It was stressed that more trials are needed to address these aspects.

Intravenous Ig therapy in immune thrombocytopenia and foetal and neonatal alloimmune thrombocytopenia (FNAIT)

Professor Jaap Jan Zwaginga, chairman of the Benign Hematologic Diseases Working Party of the Dutch Haematology Association gave a presentation on the use of intravenous immunoglobulin therapy for treating immune thrombocytopenia. Treatment for acute bleeding includes high dose corticosteroids and intravenous immunoglobulin.

Topics covered included mechanisms of action, clinical trial data supporting efficacy and clinical guidelines for managing these conditions with intravenous immunoglobulin. The importance of timely diagnosis and intervention to prevent complications was also emphasised. He also spoke about foetal and neonatal alloimmune thrombocytopenia and treatment guidelines; he also suggested that pregnant women could be tested for HPA-1a antibodies to prevent complications. HPA-1a immunisation causes severe bleeding in 11 in 10,000 pregnancies of HPA-1a negative women.

Clinical considerations on the use of IgG in Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP)

Dr Yuri Falzone discussed the therapeutic role of immunoglobulin in managing inflammatory neuropathies focusing on acute GBS and chronic CIDP. With regards to GBS, 2 patients out of 3 report symptoms of a respiratory or gastrointestinal tract infection before the onset of GBS. The clinical manifestations are characterised by subacute progressive muscle paralysis which may progress to respiratory failure. It is a monophasic disease, and patients typically recover within 2-3 weeks from the onset of symptoms.

The immunomodulatory mechanism of action of immunoglobulins includes anti-idiotypic activity, saturation of the neonatal Fc receptor, inhibition of complement pathways, inhibitory FcyRIIB and macrophage activation and suppression of co-stimulatory and adhesion molecules.

The first therapy given for GBS was plasma exchange in 1987 and this comes with a higher risk of adverse events than intravenous Ig. Studies showed that combining plasma exchange with intravenous immunoglobulin was not superior to single treatments. No superiority in efficacy has been demonstrated for administering a second course of intravenous immunoglobulin compared to a single course of administration.

With regard to CIDP, several phenotypes were described which involved either motor or sensory dysfunction, reflecting the clinical heterogeneity of CIDP. First-line treatments include corticosteroids. Overall, corticosteroids are widely used in clinical practice with low quality evidence from randomised controlled trials. With regards to the intravenous Ig, a randomised controlled trial including 45 CIDP patients compared the long-term effects of intravenous immunoglobulins with intravenous corticosteroids to investigate as a primary outcome the difference in the proportion of patients

discontinuing treatment with intravenous immunoglobulin or intravenous methylprednisolone during the 6 months. A higher percentage stopped intravenous methylprednisolone. International guidelines weakly recommend either intravenous immunoglobulin or corticosteroid treatment because of a lack of data. International guidelines strongly recommended using subcutaneous immunoglobulin for maintenance treatment in CIDP. Finally, Dr Falzone stressed the importance of tailoring therapy to the individual patient's response considering the high variability of patients' responses.

Clinical considerations on the use of IgG in neuropathies

Professor Helmar Lehmann, Director of the Klinik für Neurologie und Geriatrie, expanded on the use of immunoglobulin therapy in various neuropathies beyond GBS and CIDP, namely multifocal motor neuropathy (MMN) and paraproteinaemic polyneuropathy. Treatment of immune-mediated neuropathies include plasma exchange for GBS, CIDP and paraproteinaemic polyneuropathy and steroids for CIDP and paraproteinaemic polyneuropathy. Intravenous immunoglobulin treatments are given in all these conditions.

MMN is rare and electrophysiologically characterised by the presence of persistent conduction blocks in motor nerves. Intravenous immunoglobulin is the mainstay of MMN treatment although only a few studies support its use with mixed results. Intravenous immunoglobulin can also be given to patients with paraproteinaemic neuropathy, which has a malignant underlying disease in about a third of cases (such as multiple myeloma, osteosclerotic myeloma, Waldenström's disease, primary amyloidosis and cryoglobulinaemia). Treatment preferably includes rituximab but intravenous immunoglobulin is sometimes given despite the lack of data from randomised controlled trials and the fact that the use of intravenous immunoglobulin in this condition is not well established. Plasma exchange has also been used since the 1990s but it is not a long-term treatment.

Professor Lehmann emphasised the importance of a multidisciplinary approach in managing these complex conditions to enhance patient care.

4. Session on additional perspectives

PPTA's perspective on clinical development and clinical use

Dr James Knowles, representing the Plasma Protein Therapeutics Association (PPTA) discussed the association's commitment to ensure availability of immunoglobulins to patients. For decades immunoglobulin replacement therapy has been a lifesaving treatment to prevent life-threatening microbial infections in immunocompromised individuals with antibody deficiency. He commented on the update of the guideline for subcutaneous immunoglobulin, extrapolation from PID to SID is supported. He also recommended the development of a standard mechanism of action statement on immunomodulatory actions of immunoglobulin in the Core SmPC. He also welcomed the inclusion of CIDP in the guideline and proposed extending the indications to include MMN. Overall, he supported the revision of the guideline to enable patients' access to safe and effective immunoglobulins.

EuropaBio's perspective on clinical development and clinical use

Dr Via Katkade, the EuropaBio representative, detailed the differences in mechanisms of action in terms of immune replacement therapy and immunomodulation. Potential mechanisms by which immunoglobulins exert immunomodulatory effects include neutralisation of autoantibodies, blockade and modulation of Fcγ receptors, inhibition of complement activation and fragment scavenging, saturation of the neonatal Fc receptor (FcRn) leading to accelerated clearance of pathogenic immunoglobulins, and activation of regulatory T cells.

He noted that the proposed changes in the guidelines and said that EuropaBio supported the extrapolation from PID to SID due to the similarities between the two diseases. On the contrary, the extrapolation to CIDP (immunomodulatory condition) was not supported due to differences in mechanisms and the need for higher doses for CIDP. Efficacy, safety and patient convenience cannot be extrapolated from PID trial data. Although there is an unmet medical need for additional therapies in CIDP, therapies should be evidence-based and supported by data such as those from product specific randomised controlled studies.

With regard to hepatitis A, EuropaBio considerations include the product availability and need for products declining due to effective vaccination, the ability of manufacturers to meet EMA titre requirements and EMA's thinking on flexibility regarding titres and volumes would be helpful as guidance for manufacturers.

IPFA's perspective on clinical development and clinical use

Dr Karen Pinachyan, the representative of the International Plasma and Fractionation Association (IPFA), discussed the dynamic balance between patient access and reward for innovation. He also detailed the very special situation of immunoglobulins, explaining that some agencies issued national recommendations with regard to prioritisation of indications due to shortages.

He mentioned the very costly clinical studies in a situation of regular supply challenges and stated that the country-level market access process does not consider the available evidence for price differentiation. He mentioned the need for a collaborative approach to clinical development including the anticipation of potential iatrogenic side effects of other medicines. He also called for an innovative approach to evidence generation and consideration, including the use of all available evidence and the use of real-world evidence to clarify or confirm core SmPC indications and provide clinical use guidance such as guidance on dosing.

Perspective of health technology assessment bodies

Dr Anja Schiel, the HTA representative, addressed the assessment of immunoglobulin therapies from a health economics and outcomes research standpoint. The presentation covered methodologies for evaluating the cost-effectiveness of immunoglobulin treatments, considering both direct and indirect healthcare costs. She highlighted the differences between PID and SID and the increased use of immunoglobulins. She also emphasised the importance of clinical evidence of sufficient robustness in informing HTA decisions and the need for comprehensive data on patient outcomes.

For PID, she highlighted that the evidence on efficacy is rather 'historical'. Patients have been treated since 1952 and not many clinical trials have been performed although the use has been established. For SID, the evidence on the efficacy of immunoglobulin is at best weak and contradictory. Numbers needed to treat to prevent one serious infection have been assessed as being rather large.

She also highlighted that between 1984 and 2004, the annual global use of intravenous immunoglobulins increased from 7,400 to 55,000 kg. By 2018, immunoglobulin production had reached 199,000 kg, about 50,000 kg of which was used in Europe, the second leading user after North America. For PID, she noted that HTA bodies will assess the impact on reduction in frequency of infections, cost-effectiveness needs to be assessed on a case-by-case basis and newborn screening is essential. For SID, HTA assessment is hampered by the poor documentation of efficacy which is outdated. Up to 50% of the clinical use has been reported to be off-label with poor or non-existing evidence of sufficient robustness. Annual mean costs per patient are somewhere between 20,000 to 30,000 euros and can amount to 17% of hospital drug expenditure for Belgium.

Budgetary consequences of the use of immunoglobulins are gaining attention and must be addressed and greater awareness of these consequences among physicians is needed.

Monitoring of supply of immunoglobulins

Klaus Kruttwig, a medicines and medical-devices shortage specialist at EMA, gave a presentation on coordinated medicines shortage management in the EU which aims to improve the availability of medicines authorised in the EU as a key priority for the European medicines regulatory network.

EMA's role in crisis preparedness and management regarding the availability of medicinal products has increased significantly following the outbreak of the COVID-19 pandemic. Regulation (EU) 2022/123 formally established the structures and processes. It provides a framework for activities established by EMA to monitor and mitigate potential and actual shortages of medicines. It has also established the Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG) supported by the Single Point of Contact (SPOC) Working Party (WP) and a network of contact points from pharmaceutical companies. It also foresaw the development of the European Shortages Monitoring Platform (ESMP) which has been operating since January 2025.

The MSSG, supported by the SPOC WP, continues to ensure a robust response to medicine supply issues under preparedness activities or during a major event or public health emergency. It also coordinates urgent actions within the European Union (EU) to manage medicine supply issues. In anticipation of the proposed pharmaceutical legislation the MSSG also engage in shortage prevention activities. The MSSG may provide recommendations to support the strengthening of supply chains of critical medicinal products included in the Union list of critical medicines. EMA continues to monitor shortages of immunoglobulins through the SPOC WP and the MSSG is currently developing a set of recommendations for Rho(D) immune globulins/anti-D immunoglobulins.

5. Panel discussion

The panel, chaired by Daniela Philadelphy and Caroline Voltz, discussed the use of immunoglobulins from a regulatory and clinical perspective, the clinical development of immunoglobulins and the need to update and amend the existing EMA clinical guidelines.

A clinician mentioned that immunoglobulins are used in clinical practice to treat acquired von Willebrand syndrome, a rare, acquired coagulopathy. Due to the rarity of the disease, clinical studies are very hard to perform. EMA indicated that this is currently an off-label use. If an indication is sought, data needs to be submitted for evaluation. It is possible to ask for scientific advice to get advice on the clinical development programme.

A clinical haematologist mentioned some off-label uses for intravenous Ig. It was again emphasised that if an indication is sought, clinical data would need to be provided by companies to be evaluated as part of a marketing authorisation application for an extension of indication. It was highlighted that information on off-label use should be provided in the periodic safety update reports.

A representative of the US Food and Drug Administration (FDA) mentioned that it would be important to investigate target immunoglobulin levels for prevention of infections in PID and in various types of SID.

Several clinicians highlighted the need to focus on optimising the dose and administration schemes before trying to use immunoglobulins in new indications. Standard-of-care treatments also have to be considered. There is wide off-label use despite the supply constraints and the costs associated with these treatments. Collaboration between manufacturers is key to obtaining prospective clinical data as was done during the COVID-19 pandemic with the COVIG Alliance clinical trial.

Participants also emphasised the importance of collecting structured data, noting that real-world evidence could be useful and that the use of DARWIN EU® to obtain real-world data could be further explored. The importance of performing global clinical trials for immunoglobulins was reiterated.

6. Conclusion

These presentations collectively provided a comprehensive overview of the current challenges and considerations in the development, regulation, and clinical application of immunoglobulin therapies. The workshop highlighted the critical importance of multi-stakeholder collaboration in addressing the complex challenges associated with immunoglobulins. Moving forward, the insights gained from this workshop are expected to play a crucial role in shaping the revision of the guideline on subcutaneous and intramuscular immunoglobulins and the core SmPC.