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Quality and safety for substances of human origins: scientific evidence and the new EU regulations

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INTRODUCTION

In December 2023, the Council of the European Union (EU) and the European Parliament reached consensus on a new 'Regulation on standards of quality and safety for substances of human origin intended for human application' (SoHOs).[1] These substances encompass human-origin materials, including blood, plasma, skin, corneas, embryos, sperm, breast milk and microbiota (but not solid organs), all of which play a crucial role in life-saving medical procedures. The main objectives of the new regulation are (1) to ensure EU self-sufficiency and (2) to guarantee safety. The regulation establishes common EU-wide safety procedures, oversight protocols and donor safeguards.

Throughout the discussions, one of the most controversial aspects has been the compensation of donors. The objective of ensuring EU self-sufficiency directly responds to the EU's heavy reliance on imported plasma for the production of therapies, notably from the USA, where plasma donors receive compensation. The EU regulation, however, considers the 'voluntary and unpaid donation' of SoHOs, rooted in the principle of 'non-commercialization of the human body', as essential to ensure safe supply. The proposed regulation states that '*donation of SoHO should be voluntary and unpaid*', and that compensation is only allowed '*to prevent that SoHO donors are financially disadvantaged by their donation*'. The EU is concerned that the increasing commercialisation and globalisation of blood plasma may intensify the pressure on individuals to donate, with negative consequences on the safety of the supply. However, the new EU regulation, although based on long-standing principles, is not in line with current evidence, in particular on the safety and efficacy of paid plasma donations, and is largely at odds with the objectives of achieving self-sufficiency in SoHOs and serving donors and patients who rely on these vital resources.

SUMMARY BOX

⇒ The new European Union (EU) 'Regulation on standards of quality and safety for substances of human origin (SoHOs) intended for human application' is based on a long-standing diffidence towards offering compensation to donors of SoHOs.
⇒ We point to recent, growing empirical evidence indicating that carefully designed compensation can increase the supply of SoHOs without negatively affecting quality and safety. We also elaborate arguments that address some of the moral concerns that motivate the aversion to payments.
⇒ As member states proceed to adopt the new EU regulation, our article may provide insights on how to achieve both self-sufficiency and safety.

SAFETY AND DONOR'S COMPENSATION

Since Titmuss' 1971 book, *The Gift Relationship*,[2] there has been a lingering concern that remunerated donors may compromise blood safety, because the expectation of a financial return may lead to unreliable personal information reporting and therefore increase the risk of transmissible diseases such as hepatitis or HIV. Titmuss reported American studies showing that hepatitis was more prevalent in blood supplied from paid than from unpaid donors. Generally, these studies were based on small samples and did not adequately account for potentially confounding factors that were unevenly distributed between compensated and non-compensated groups, such as the prevalence of first-time donors and the inclusion of inmates. Furthermore, the evidence predates the development of tests for the presence of hepatitis and HIV in the blood supply.[3] Recent studies and reviews of the evidence over the last 40 years

have concluded that the statistically sound, field-based evidence from large, representative samples shows that properly devised rewards increase supply without compromising the quality and safety of blood and blood components.[4]

Today, plasma-derived therapeutical products from both paid and unpaid donors are safe, thanks to stringent regulatory measures that rely on scientific advances in testing, require rigorous donor selection and mandate thorough inspections of collection and manufacturing facilities. These measures include production processes capable of inactivating or removing a range of known and unknown infective agents.[5] Prevalent industry standards ensure that plasma originates from low-risk donors, for example, it is standard procedure not to use a person's first donation but to use their plasma only if it passes tests starting from the second donation. These standards have made US plasma-derived products safe for decades.[6]

MORAL CONCERNS: COERCION, EXPLOITATION, COMMODIFICATION

The WHO classifies donors into three categories: voluntary unpaid, family/replacement and paid.[7] This classification is misleading: it implicitly assumes only unpaid donations to be 'voluntary', suggesting paid donations are coerced. The implication that compensation negates voluntariness is not only a potentially stigmatising claim; it is also at odds with common ethics and practice elsewhere, where *not* paying for a service is associated with exploitation, especially of those in more vulnerable socioeconomic conditions. To protect individuals from exploitation, labour laws around the world have introduced minimum compensation requirements rather than caps on earnings. To rely solely on altruism in these areas would be exploitative and eventually lead to a collapse in provision. In addition, payment bans on donors, even if intended to protect against undue inducements, raise concerns about price fixing to the benefit of non-donors.[8]

The commodification of the human body, that is, the transformation of a person or their parts into goods to be traded, is another ethical concern related to compensation for SoHOs. However, this can be immensely valuable to patients. For instance, approximately 1200 plasma donations are needed to produce the annual supply of clotting factor necessary for a single patient with haemophilia. This system of commodification has proved to be life-saving on a global scale.[9] Vilifying certain types of donations overlooks the benefits that compensation together with careful regulation can bring to the efficiency and reliability of blood supply.

THE GOAL OF SELF-SUFFICIENCY AND THE BURDEN ON COUNTRIES

The joint focus on self-sufficiency and unpaid donations poses a major tension. At least where plasma for fractionation is concerned, the unpaid-donor system has failed to meet demand. Table 1 indicates that in Europe, countries allowing monetary compensation for donors are the only ones achieving self-sufficiency in plasma collection for the production of immunoglobulin. The plasma sector in countries that compensate plasma donors, notably the USA, serves as supplier to many countries experiencing chronic shortages. The USA alone collects about 70% of the world's plasma supply.[10] A combination of a favourable regulatory environment, an extensive collection network and advanced technological infrastructure contributed to establishing the US position.[11]

More broadly, countries that allow some form of payment for plasma donations—including EU member states Germany, Austria, Hungary and the Czech Republic—account for nearly 90% of the global supply.[12]

The new EU regulation states that '*Compensation may consist of the reimbursement of expenses incurred in connection with SoHO donation or on making good of any losses, preferably based on quantifiable criteria, associated with the donation of SoHO*'. This potentially limits the existing practices of EU countries that allow compensation, as well as other schemes in other jurisdictions. However, national legislation may interpret this regulation with some flexibility, allowing for '*fixed allowances*' or '*non-financial forms of compensation*'. This caveat potentially leaves individual countries the freedom to define what constitutes a quantifiable loss and to decide whether or not to include a form of 'payment' within these parameters. The new dispositions, however, still pose a risk because they do not allow any incentives beyond quantifiable losses, thus overlooking the practicalities of plasma donation—its time-consuming nature and the necessity for large quantities—making donor compensation not just a practical option but often a necessity to meet healthcare demands.

The most serious effects of these provisions will be for low-income countries; the increase in the shortage in the EU due to the reductions of donations following the new regulation would drive up international prices and reduce the affordability of plasma.[13] Plasma supplies from the USA and some European save lives around the world. If this still represents a concern, it can be addressed by proper policies that discourage trade, but the current evidence suggests that this would make things worse for patients in poor countries.[14]

A FALSE DICHOTOMY

An underlying assumption in many discussions about compensation of donors is that it is an inherent feature of the private, for-profit sector, whereas unpaid donations characterise public and non-profit organisations. The opposition to delegating the provision of life-saving human products to for-profit companies may therefore coincide with an aversion to payments. However, nothing prevents publicly owned or non-profit collection agencies from offering economic incentives, with the achievement of social welfare as opposed to private economic return as the main organisational mission.

Table 1 Plasma self-reliance and models of plasma collection[15–19]

Country	Reliance on domestic supply (% of total national need)	Monetary payments allowed	Current payment amount	Other incentives
Austria (2020)	100	Yes	€30–40	–
Czech Republic (2020)	100	Yes	€30–35	–
Germany (2020)	100	Yes	€25	–
Hungary (2020)	100	Yes	€30	–
Latvia (2018)	100	Yes	€17	–
Italy (2018)	76	No	–	Paid leave of absence from work
Slovenia (2017)	54	No	–	Paid leave of absence from work
Belgium (2019)	50	No	–	Paid leave of absence from work
France (2020)	50	No	–	–
Netherlands (2020)	45	No	–	–
Slovakia (2018)	41	No	–	–
Denmark (2018)	34	No	–	–
Spain (2020)	34	No	–	–
Portugal (2018)	22	No	–	Exemption from National Health Service user fees

The table shows, for each country, the percentage of plasma needed for immunoglobulin (Ig) production that is collected domestically. The year in parenthesis is the one to which the data on self-reliance refer. The table then reports whether monetary payments are allowed, the current range of payments per donation and any other incentives in use in each country. In countries that allow payments, plasma collectors offer, in addition to monetary compensation for each donation, additional monetary or in-kind rewards, for example, when a donor reaches a certain number of donations (eg, 5, 10,…), or to first-time donors. The figures reported above do not include these additional rewards.

CONCLUSION

As the EU re-evaluates its healthcare policies, it should consider aligning with evidence-based practices that prioritise donors' well-being and patients' needs, and embrace a global perspective on healthcare provision. The ultimate objective should not merely be self-sufficiency but ensuring the availability of safe, sufficient and accessible SoHOs for all in need. The available evidence suggests that absent stronger individual motivations and incentives, it is unlikely that EU members can achieve self-sufficiency. Economic rewards have proven to be effective in increasing supply of human products, especially whole blood and plasma; the fact that countries that allow payments for plasma donors are net exporters of plasma products (with no loss of safety) further suggests that allowing compensation would increase the availability of plasma for medical use. Of course, there are also other strategies to enhance motivations or reduce disincentives and impediments to donate. Building additional collection centres, running mobile drives more frequently, reducing wait times and improving scheduling would certainly make the donor experience more pleasant and, as such, attract more people to donate. In addition to not being in conflict with providing compensation, however, these strategies are costly and will take time to come into effect.

Following a legal-linguistic revision, the European Parliament and the Council will need to formally adopt the new Regulation by 2027. Although the opportunity for substantial changes seems limited, the period leading up to formal adoption can be critical to the regulation's impact. The interpretation of what compensation will be considered legal under the new EU regulation in each member state will be crucial.

As the EU and its member countries move forward with these new policies, it is imperative to adopt a balanced, empirically sound and research-backed approach that considers multiple aspects and promotes policies to safeguard the interests of donors and patients. The reliance on scientific evidence on the one hand, and the promotion of a broad, open and public debate are essential in order to rely on the best possible information and address the trade-offs and compromises that this policy issue entails.

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Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the

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