Recommendations to improve the quality and safety of Medical Products of Human Origin

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on behalf of the ICCBBA Board of Directors

Executive summary

In September 2019, ICCBBA organized an international Forum, bringing 90 participants from more than 45 international professional and governmental organizations together to share their views on how to enhance the quality and safety of Medical Products of Human Origin (MPHO). Important topics including traceability, patient safety, ethics, biovigilance and surveillance, and new technologies were based on the WHO Guiding Principles on human cell, tissue and organ transplantation, as endorsed at the Sixty-third World Health Assembly[1]. The goal of the Forum 25 was to identify the current challenges in the area of MPHO and define actions, that will optimize donation and clinical application practices.

This paper describes the overall discussions that took place and identified 16 actions and the involved stakeholders.

It was concluded that while MPHO do already save lives and improve the quality of life for many individuals, it is clear that they are becoming an increasingly important and successful part of the treatment for people worldwide. As the range and reach of MPHO increases, the development and application of reliable traceability systems that preserves individual privacy and yet provide clear documentation of the various steps from donation to use of specific products, is both important and urgent. It is the human product that links a donor to a recipient. The wide variety of products that are possible after a single donation necessitates usage of an unique identifier that will meet public expectations for quality and safety of all MPHO derived from the donation and preserve the intimacy and altruism inherent in organ and tissue donation event.

[1] https://www.who.int/transplantation/en/

Actions:	***Responsibilities:***
1. Implement overarching principles, ethics and guidance across all MPHO within specific jurisdictions	Governments
2. Harmonize the legal oversight of all individual types of MPHO across countries/continents	WHO and regulatory committee/stakeholders
3. Increase donor safety, respect, and privacy and where appropriate perform long-term follow up	Professional organizations
4. Improve traceability tools to ensure rapid tracking from an MPHO to the donation event and ensure effectiveness through audit.	ICCBBA and professional organizations
5. Optimize the rapid tracing of all other MPHO products derived from a donation or donor for the purpose of inspection, quarantine or determination of recipient risk	ICCBBA, regulators and professional organizations
6. Encourage the adoption of globally unique donation identification and an international coding and labeling system for all MPHO to enhance the traceability, quality, and safety of MPHO	ICCBBA, regulators, accreditation and standard-setting organizations, professional organizations
7. Improve systems and skills to ensure recognition of potential adverse outcomes attributable to MPHO and develop consistent reporting mechanisms that include patients and donor adverse events	Professional organizations
8. Establish a global system for adverse events reporting	WHO, governments, professional organizations
9. Improve biovigilance by enhancing adverse events reporting (also by patients) and systematic analysis of these events	WHO, regulators, professional and patient organizations
10. Build a global biovigilance system using new information technologies, while safeguarding privacy, for MPHO starting from collection to clinical application	ICCBBA, WHO/CNT, regulators and professional organizations
11. Improve dissemination of information on MPHO-based therapies by rapid communication of reliable scientific results, encourage replication studies and the publication of clinical trials with negative results	WHO, regulators and professional organizations
12. Define the safety and efficacy parameters for MPHO-based therapies to accelerate the use in patients	WHO, regulators, professional and patient organizations
13. Assure the safety and efficacy of existing MPHO-based therapies and evaluate clinical trials prior to acceptance of new or unproven MPHO-based applications	Regulators and professional organizations
14. Discuss and communicate the ethical challenges of new emerging technologies	WHO, regulators and professional organizations
15. Reach international consensus on quality, efficacy and ethical standards for MPHO	Governments, standard-setting and professional organizations
16. Ensure that all traceability data related to an MPHO-based therapy is incorporated into the electronic patient record in a consistent searchable manner.	ICCBBA, IT specialists and professional organizations

Introduction

Blood transfusion has been essential and critical to healthcare for at least a century, while organ transplantation has developed over the past fifty years to become a mainstay of the therapy for end stage organ failure with more than 120,000 transplants performed each year. Tissue (excluding blood and organs) and cell therapies also are increasing in numbers and applications. The need for these products to be donated, while maintaining quality and safety, have harmonized some of the approaches for MPHO safety and efficacy. Availability of MPHO has been a constant challenge, with some products being scarcer than others. Patients are dying on waiting lists for organ transplantation, women are crossing national boundaries to gain access to assisted reproductive therapy with donors' oocytes, and corneas are sent often to other continents where eye banks have not been developed. Wherever severe shortages of life-saving MPHO exist (as with human organs in many parts of the world) exploitation and human trafficking have occurred. The transplant community rejects such activity and has joined to formulate the Declaration of Istanbul delineating the fundamental principles for ethical organ donation and transplantation[2]. There are multiple quality, safety, availability and ethical issues associated with the retrieval and use of MPHO.

Donation is a recognized civic gesture and national organizations are striving towards an equitable burden of donation to achieve self-sufficiency. MPHO donation as a voluntary activity, free of coercion and exploitation is a recognized objective for WHO. The definition of self-sufficiency is not strict and can vary from local to national, regional, or even global needs. It depends on MPHO-specific criteria, including preservation limits, extent of processing, compatibility constraints, emergency needs, and other responsibilities. Throughout the expansion of MPHO availability and use, governments maintain responsibility to the public that the MPHO are safe and effective. Despite the universal recognition that coercion and exploitation of people is best avoided through voluntary donation, MPHO availability practices continue to vary across the globe, some even using compensation. During the early expansion of MPHO development, a tradition to compensate live donors (including blood and reproductive tissue) was commonplace. Despite the recognition that compensation introduces ethical and product safety concerns, payment for some plasma products and semen is still permitted to ensure availability.

[2] https://declarationofistanbul.org/

However, irrespective of source and whether the donation was truly voluntary, national governments are responsible for ensuring that the MPHO product for clinical application meets quality and safety standards through effective oversight.

There are significant concerns for effective governmental oversight of MPHO. All MPHO start with a donation, but the diversity of living or deceased donation events, and the volume of products resulting from processing or manipulation, creates complexities for governmental agencies. The public needs assurance that an adverse event for a specific recipient was not the result of quality or safety errors in the retrieval and release of the MPHO, or that if there is a safety concern, others receiving a MPHO from the same donor can be quickly identified and, where necessary, treated. The challenges across the spectrum of MPHO are prodigious.

In the same way that blood transfusions have progressively become regulated and standardized through testing and quality oversight, effective use of all MPHO will require the same approach for their acquisition, use and distribution. It may be perceived that all MPHO are of high quality and safely provide the purported benefit, but that is not universally verifiable nor demonstrably true. ICCBBA thus convened a forum with global stakeholders, regulators and providers to discuss the diverse uses of MPHO and the real and potential gaps in safety, quality and availability. A summary of the topics covered is provided in this paper together with a table of recommended actions.

Safety of MPHO

While disease transmission through transfusion and transplantation of MPHO had been known to occur, the mass transmission of HCV and HIV through blood transfusion after lack of effective testing processes and other means of donor screening in the 1980s and 1990s resulted in justifiable public scrutiny and outrage. Public health officials were chastised for failing to establish a "safe" system. Blood and plasma products were exchanged across national borders and raised questions of where jurisdiction and responsibility resided (the procurer, processor or organization delivering the product). In 2004, the issue was discussed at the World Health Organization and resulted in resolution WHA57.18[3] Human organ and tissue transplantation which urged member states "to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring

[3] https://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf?ua=1

accountability for human material for transplantation and its traceability". In 2005, the resolution WHA58.13[4] on Blood Safety proposed to establish World Blood Donor Day, and encouraged member states "to establish a quality process for policy- and decision-making for blood safety and availability based on ethical considerations, transparency, assessment of national needs, scientific evidence and risk/benefit analysis".

MPHO's source is a human donation and a single donation can yield a host of products (see fig.1)

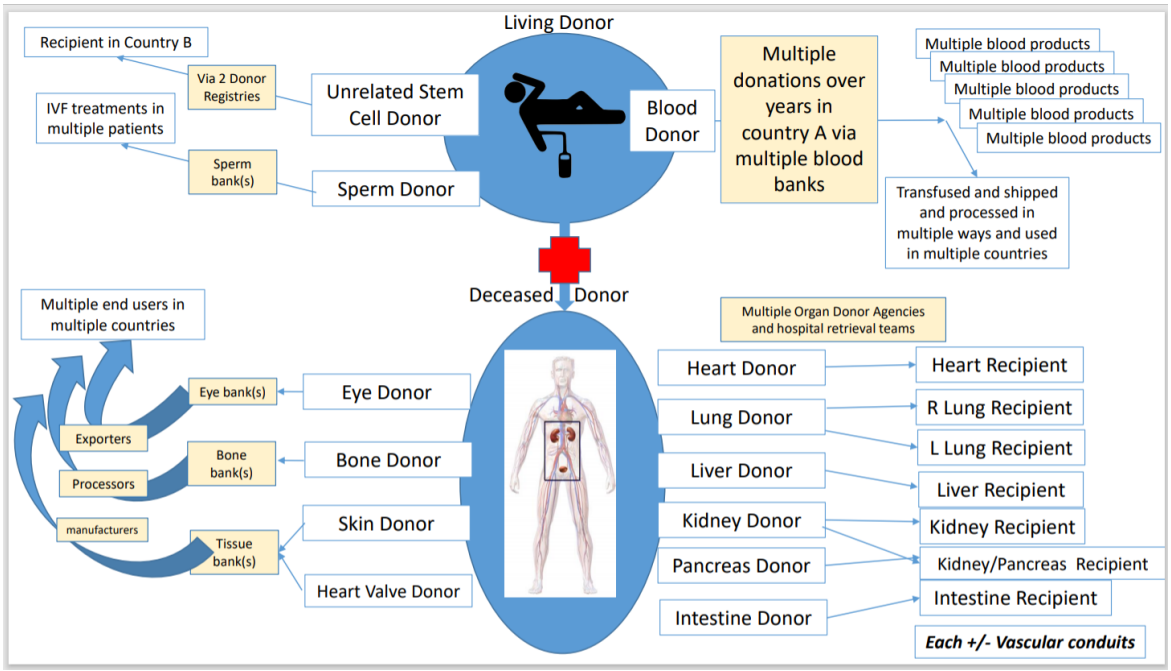

Figure 1: MPHO donation, processing and application involves many organizations and can result in multiple products for many patients worldwide.

A single blood donation can result in multiple products that are potentially given to multiple individuals (red cells, platelets, many plasma products and leukocytes). A deceased donor can provide an overwhelming number of products (up to 7 organs, hundreds of bone products, skin, blood vessels, heart valves, cartilage, ocular tissues, cells and bone growth potentiating products). A very large number of people can benefit from the use of MPHO given by a single donor and through the efforts of a substantial number of involved organizations. Most governmental oversight has evolved to address new products and the oversight responsibility is often assigned to varying offices/agencies.

[4] https://www.who.int/worldblooddonorday/resources/WHA58_13-en.pdf?ua=1

Fragmentation of governmental MPHO oversight is commonplace and will require special attention to address the increasing diversity of MPHO products. Additionally, the assurance of donor safety, respect and privacy are also inherent with the acquisition of MPHO, including those used as starting material for advanced therapies in Europe. Governments must find means to implement overarching principles, ethics and guidance within specific jurisdictions with differing cultures. However, the requirement that each government is charged to provide systems assuring the quality and safety of administered MPHO remains paramount. In an era of hope that biologic treatments will become available to (globally) treat a broadening spectrum of diseases, the challenge to combine simplicity, international integration and system performance is becoming increasingly important.

Regulation

Representatives from the US and European regulatory communities discussed the regulatory challenges of oversight associated with MPHO safety and quality. While the overall goals of traceability, quality, and safety of MPHO are relatively consistent for all governmental bodies, the mechanisms employed and the tools available differ between the two regions. For example, the US Department of Health and Human Services is charged with overseeing all MPHO quality and safety. The Food and Drug Administration Center for Biologics Evaluation and Research (CBER) oversees blood, tissues and cells (and other products). Within CBER, the Office of Blood Research and Review (OBRR) is charged with overseeing the nation's blood supply; and cells and tissues are within the purview of Office of Tissues and Advanced Therapies (OTAT). However, cells and tissues regulated as medical devices are overseen by the Center for Devices and Radiological Health (CDRH), also at FDA. Solid organ donation and transplantation is overseen outside the FDA by the Health Resources and Services Administration (HRSA). Breast milk does not currently fall under federal regulation and the only controls on quality and safety are some State regulations and the voluntary standards of the Human Milk Bank Association of North America. Therefore, while the "rules" and implications for donation screening and processes are associated with the use of each MPHO, the requirements are not routinely integrated with other regulatory efforts leading to divergences in regulatory enforcement and oversight.

European systems have an additional element of complexity beyond specific national regulatory issues in that national processes must be integrated within European conventions. MPHO in the European Union fall within the scope of a number of different directives (which are transposed in national

legislation of the EU member states) and regulations (which enter directly into force without the need to be transposed in national legislation) including 2002/98/EC (blood and blood components), 2004/23/EC (tissues and cells), 2010/53/EC (organs) and 2001/83/EC as amended by Regulation (EC) 1394/2007 (advanced therapy medicinal products). Breast milk does not fall under any of these regulations.

The regulatory challenges identified by these two examples are common across regulatory systems worldwide. While the intent of all systems is to meet the needs of society, dictated by legal mandates and mission statements, the gaps in processes associated with information transfer and regulatory structure are not hard to identify. Many countries with developing oversight systems can avoid the similar "gaps" by awareness of broad goals and analysis of established systems as specific areas of oversight evolve. The gaps in US and European oversight were discussed during the meeting and actions formulated.

Global Distribution and Traceability

MPHO are distributed and used across the globe, making common tools and coordination of reporting an international responsibility, requiring coordination and collaboration across different countries. However, there are few, if any, available international MPHO safety and quality mechanisms. This need is similar to the transnational standardization required within the airline and communications industries after activity grew beyond internal/national businesses. Fundamental to the use of any MPHO must be the recognition that each MPHO is the gift from a specific person, whether that donor is living or deceased. Traceability back to that person is the start of the accountability process. However, regulation has developed around products and each organization responsible for a specific product has typically evolved its own way to identify the donor. In the USA, for MPHO gifted from a single donor, multiple unique donor identification numbers are assigned, one by the Organ Procurement and Transplant Network (OPTN) associated with each organ donor; many tissue banks assign a donor ID unique to their institution for the tissues processed (bone, skin, vessels/valves, orthopedic and marrow may all have different tissue banks), and eye banks have a separate code for their products. Any one donor can have multiple identifying codes that describe the same donor, each corresponding to the various processing organizations. At the Forum, an example was given of a serious advance event that occurred, when a glioblastoma was identified in an organ recipient 2 years after donation. Tracking all the donated tissues, cells and eyes gifted from that donor was cumbersome and inefficient. Traceability is a matter of good

medicine and public safety. In 2013, in an attempt to address the growing complexity associated with MPHO quality and safety and to help MPHO users understand associated risks and notify competent authorities in a prompt fashion for the safety of others, the WHO initiated an effort with three global governance goals: 1) develop governance principles for countries inherent to the acquisition and use of MPHO, 2) the universal use of ISBT 128 as the best available, universal tool to link all MPHO to the donation event, and 3) establish global vigilance and surveillance tools.

Simple in concept, implementation of these goals has proven difficult. Most countries will readily agree that the principles of MPHO processes should be equitable, transparent and ethical; that donor approach and authorization must be non-coercive; and that safety and quality measures must be established and maintained for both donors and recipients. Fundamental to this process is the uniform linkage of MPHO and donation. The inefficiencies associated with multiple donor identification codes within a single country are magnified when global distribution of MPHO occurs. To address this difficulty, the WHO recommended the universal use of the ISBT 128 coding system (including its common global products nomenclature) for all MPHO, as it is already a global coding system for blood and blood products and has the capacity is designed specifically for traceability of products derived from a human donor, and has the capacity to link a single (living or deceased) donation with a wide spectrum of products, that is essential for tracking and traceability. The key safety element that was stressed during the Forum was the benefit associated with the creation of a global, standard link from a human donation event to all products obtained from that event/donation. The universal adoption of ISBT 128 has been constrained by legal restraints on governmental proscription of specific systems, although voluntary adoption of the standard continues to increase. Yet the role of governments is crucial as the field of MPHO relies on them. There is fragmentation and little or no coordination between entities operating nationally and internationally. Most of the operations are not-for-profit entities, which lack the resources. This contrasts with the capacity of the profit-making pharmaceutical industry to invest resources to develop global collaborative ventures such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH is playing an important role in the global safety of drugs. Each MPHO entity is required to assure tracing ability within their organization. The complex challenges of traceability, safety, and quality specific to all MPHO deserves a similar effort.

The adoption of ISBT 128 is a step towards achieving reliability, trustworthiness, and transparency, which are key to the public's motivation to donate components of the human body for MPHO. Quality and safety requirements of uniform MPHO labelling, if a product is to be made available for transfusion or transplantation, is certainly feasible.

Vigilance and Surveillance of MPHO- the NOTIFY Project and other International Initiatives

The risk of disease transmission through MPHO is real. Prevention/minimization of adverse events through the establishment of protocols for donor selection and testing is a fundamental role for regulatory agencies. These processes have to be reviewed and regularly assessed to be adapted to evolving applications and the actual risk/benefit balance.

Since the emergence of HIV in the United States, the US Public Health Service has provided recommendations for the prevention of HIV transmission through organ and tissue transplantation. In 1994, guidelines were released that recommended that donors who engaged in certain behaviors should be identified as "high risk" donors, irrespective of testing results. Despite both recommendations for behavioral screening and laboratory testing, organ donor-derived HIV transmissions continued to occur, and other bloodborne pathogen transmissions were increasingly recognized, and the guidelines were revised in 2013. Risk criteria were modified and those identified were reclassified as "increased risk" donors, and testing recommendations were expanded to include HCV and HBV. The implementation of nucleic acid testing in addition to serology greatly improved the sensitivity of donor screening. However, patient and healthcare providers associated the terminology of high or increased risk with lower quality organs and therefore less likely to accept organs from donors with that label. This led to significant discussion between the transplant community and government about the intent and practice of the guidelines. As a result of these discussions, advances in solid organ transplantation, including improved donor screening and improvements in treatment for HIV, HBV, and HCV, have led some government entities to consider the revision of recommendations to reflect recent, organ transplant-specific evidence and thereby increase the utilization of organs while continuing to maintain transplant recipient safety.

However, in order to develop evidenced-based policies, there is a need for systematic assessment of adverse outcomes. The dialogue about organ transmission risk was greatly enhanced because of a

mechanism for donor-derived disease reporting within the US organ donation and transplantation system. Biovigilance, the process of monitoring adverse events and errors across the breadth of MPHO, is a daunting project. In the US with millions of MPHO transfused, implanted or transplanted every year, a comprehensive, independent biovigilance system of every unit would be difficult (if not impossible) and prohibitively expensive to implement given the current regulatory patchwork and limitation of electronic health records. Rather, provider-reported adverse events form the backbone of the system to assess the risks associated with the use of MPHO. The biovigilance systems in the US and Europe are now mature but are structured quite differently with respect to authority and systems implementation. In the US, annually there are millions of units of blood products transfused, hundreds of thousands of tissues implanted and tens of thousands of organs transplanted. The systems to assess the safety of MPHO are not uniform. The National Healthcare Safety Network Hemovigilance module collects information from over 300 hospitals (<10% of all US hospitals) but has several strengths. Its users are trained, and standardized definitions are used for reporting adverse events. Users report the number of adverse events and total number of transfusions by type of blood product, enabling calculation of adverse event rates. The FDA only requires reporting of transfusion-related deaths and product deviations. The remainder of non-network system data comes from access to state or institution-specific reports, but these are not nationally consistent and there is no mandate for healthcare facilities to report adverse event data to CDC. This is a similar process in Europe for dealing with suspected adverse reactions associated with the use of MPHO. Europe depends on an upward reporting of adverse reactions from a hospital/facility to the blood establishment, which reports to the national competent authority that finally provides the information to the European Commission. Tissues and cells are different from organs and blood products and the regulation of their use is not necessarily as well-established. In Europe, the process for dealing with suspected adverse reactions/events associated with the use of MPHO is similar for that of blood and blood products. The FDA is involved with assuring that MPHO manufacturing standards are maintained, but because most products are “minimally manipulated”, any adverse outcomes are predicated upon recognition by providers who often consider that MPHO are similar to devices. In the US, a suspected tissue donor-derived adverse event is not required to be reported to an oversight body, but voluntarily to the tissue processor/bank. The tissue bank is then responsible for investigating the event and, depending on the type of adverse event (i.e., infections), may be required to report conclusions to the FDA. Organ safety and quality issues in the US are handled differently from blood and tissue. Oversight of organ transplantation, including establishing

policies to maintain safety is the responsibility of the OPTN, composed of member organ procurement organizations and transplant centers, with the federal government (HRSA) providing oversight. Suspected donor-derived transmission events (e.g. infection or malignancy) are reported to the Disease Transmission ad hoc Committee (DTAC), which includes ex-officio representation from CDC. The query is shared with other centers that transplanted organs from the same donor as a risk alert and to discern if similar events occurred in other recipients of organs from the donor. DTAC conducts investigations and produces reports to determine the likelihood that the donor was the source of the disease. There are mechanisms in place to provide prompt feedback for other recipients at risk and system process evaluations. Even in the established systems of Europe and the US, very different system structures are used to assess safety among MPHO with variable ability to efficiently trace back to a common source and track other products from the same donor. Each specific MPHO is relatively stable in potential to function within its domain, but crosstalk is quite limited.

Reporting of events is dependent on providers being suspicious of an adverse event. Attribution of a MPHO as the cause of an adverse reaction is difficult without the consistent ability to recognize and define the event. Clinical medicine is not always precise, and systems should probably over-report potential adverse events in order to increase the likelihood of identification/capture of events (not dissimilar to the airline industry reporting of risky operations and deviations).

Concerning cells, in the area of stem cell donation there is a global system for reporting serious adverse events and reactions, developed by the World Marrow Donor Association (WMDA). Their aim is to gain insight into the occurrence of serious events and adverse effects in relation to blood stem cell donation by unrelated donors and blood stem cell collection/processing from unrelated donors.

Project NOTIFY was started through the joint effort of WHO and CNT (Centro Nazionale Trapianti, the Italian National Transplant Centre) to raise the consciousness within the MPHO community of the spectrum of potential adverse events. The Notify Library[5], the global vigilance and surveillance database for MPHO transplantation, infusion and assisted reproduction was established to provide a resource for MPHO users. On the site, global experts shared didactic information on documented adverse outcomes

[5] https://www.notifylibrary.org/

associated with clinical use of MPHO. Education and knowledge are key to accurate recognition of a possible MPHO transmission that other centers/patients should be observed for a risk of similar disease.

An important observer who should consistently be included in the reporting network/system is the recipient of the MPHO and the live donor. There is a growing sentiment (at least in the US) that patients should have direct access to adverse event reporting systems. There is rarely an avenue for patient involvement today. While many patients report symptoms to their providers, the latter do not provide system input or receive direct feedback. Without a comprehensive MPHO biovigilance system, there is an opportunity for the professional and regulatory communities to join efforts and establish mutual goals, find means to begin closing gaps in biovigilance and to improve communications between systems that are not yet well-established. Changing technology and innovation in addition to the globalization of MPHO use should encourage national systems/competent authorities to rethink the integration of the aggregate oversight of the MPHO reporting systems.

Implications of Unregulated Activities for Patient Safety

Not all use of MPHO is regulated by governments. Well intended, as well as opportunist providers have established clinics in virtually every country offering “unique” and non-evidence-based therapies for cancer, arthritis, chronic wounds, neurologic diseases and sundry maladies. Often these clinics use unregulated autologous or allogenic “stem cells”, platelet enriched plasma or other biologic products to treat the myriad of diseases and conditions. As these treatments may fall outside the oversight of governmental agencies, no independent data is collected to discern the risks, while any benefits cannot be quantified. Additionally, with a global organ shortage, it is estimated that 10% of all organ transplants are performed outside governmental oversight, typically through illegal, for-profit organizations that use organ trafficking as an organ source. The risk to the recipient of disease acquisition (HIV, HCV, HBV, tuberculosis, etc.) through this activity is unquantified, but well recognized by the transplant community that ultimately ends up caring for these individuals.

The promise of unproven therapy, but hope in the face of futility, is difficult to combat in unregulated clinics. The benefit (if any) of cellular treatment for the disease is not publicly or uniformly measured, but the anecdotal risk to the patient has been heartbreakingly real. However, as demonstrated by the development of chimeric antigen receptor T cells (CAR-T), cell therapy can be remarkably beneficial and

give hope to people without any other options. Yet, the pathway to prove and develop accepted cellular therapeutics is arduous and very expensive. This probably impairs the development of effective treatments. There is a consensus that governments have the responsibility to create safety and efficacy parameters for the changing world of MPHO therapeutics. Whether the risk/benefit thresholds and measures should be altered for "minimal, moderate or significant" modifications of an MPHO may allow more timely development of new products that could give patients and donors significant benefit with an acceptable level of risk. Consensus and dialogue between professional societies and regulatory agencies is required as the field expands.

Scientific and Ethical Practice: Future Challenges

The source of, and the beneficiaries of, MPHO are people. This fact mandates that there be concern that broad ethical principles permeate the acquisition, distribution and use of these products. The acquisition and use of MPHO occur within diverse regions of the world, where people have unique local traditions and values. Failure of a local culture to accept how MPHO are obtained and used will adversely affect the process and preclude benefit for the recipients. The WHO has worked to harmonize local values across the member states and articulate principles and processes that permit the efficient use of MPHO within a framework of values/ethics embraced by the global community. Agreements by the World Health Assembly started with WHA28.72 (1975), "Utilization and supply of human blood and blood products" and continue through today. The statements and agreements have stressed the consensus human values of respect, autonomy, equity, efficacy and value as they relate to donation and use of MPHO. More so, as the products diversify, the WHO has recognized the need to reduce fragmentation of oversight and strive for consistency in order to retain core values and approaches.

The ethical challenges of MPHO oversight expand with advances in scientific and medical knowledge. Current technology offers the extraordinary opportunity to manipulate cells ex vivo. Gamete acquisition, storage and fertilization has evolved into a mature reproductive medicine specialty but has also opened the pathway for ex vivo manipulation of cells to prevent genetic diseases in offspring. This came to fruition with the birth of the "three-parent" baby, a child without the manifestation of Leigh Syndrome, a genetic mitochondrial disease, after ex vivo zygote manipulation. In contrast, DNA editing using CRISPR was used to inactivate the CCR5 genes of an embryo to make resistance to HIV acquisition. The birth of twins with this genetic manipulation was reported at a scientific meeting, to the disdain of

the community for failing to follow “generally accepted” ethical and scientific practices. These two examples helped clarify problems and concerns with manipulations that led to modifications of the genetic core of human life. The processes used for the “three-parent baby” is continuing under the supervision of the Human Fertilisation and Embryology Authority of the United Kingdom, especially for patients with homoplastic mitochondrial diseases. The technique of nuclear transfer can make it possible for these patients to fulfill their wish for a genetically related and healthy child. On the other hand, the inactivation of CCR5 by using CrispCas technology in embryos has been universally chastised for falling outside of scientific and ethical norms and is banned. It is possible to modify human DNA, perform genetic transfer and manipulation of all types of cells. It is even feasible to acquire cells in one location, ship them across borders to another location for manipulation and then transfer somewhere else for implantation. These experiences have prompted professional societies and governmental agencies to consider the impact of how supposed MPHO enhancements should be overseen and regulated. Geographic location is not a barrier to the manipulation of MPHO and hence requires international consensus of quality, efficacy and ethical standards and the establishment.

Healthcare Informatics and the Role of New Technologies

Creation of a comprehensive system that permits biovigilance of MPHO and is consistent with the efficient collection of information on MPHO acquisition, processing and distribution will require technology that is currently being developed. Expansions in electronic identification and product tracking, cloud-based computing, secure data storage, and interoperability are rapidly being developed in accordance with internationally agreed standards. Application of these capacities to healthcare is happening and inevitable. MPHO use is expanding and is not projected to diminish. There is an opportunity for MPHO acquisition and use to avail itself of the expanding informatics capacity to close some of the gaps in current biovigilance systems, consistent with recognized needs. Systems should be designed to meet the processors needs within the supply chain and also those charged with the assessment of safety and quality of that chain. Information on the application of MPHO should be routinely recorded in the (electronic) patient record, for traceability and so that outcomes can be monitored. At the present time, ISBT 128, through its basis in specifically tracing products that are derived from a human donor, is uniquely positioned to provide existing MPHO elements and capable of modification to accommodate a changing MPHO world.

The internet and globalization of information transfer provides opportunities and challenges for MPHO use and oversight. The General Data Protection Regulation (GDPR) in Europe governs how identifiable data about people may be stored, processed, and used. Adherence to the GDPR is a requirement for any system that uses data for a purpose. In the USA, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) rules also need to be incorporated. One should assume that other large national/regional authorities in collaboration with professional societies will also develop particular stipulations relating to personal protection and data use. As machine learning increases the capacity to use "big data" in more meaningful ways, incorporation of more and more data will be necessary to improve function and efficiency. These systems must incorporate regulation and ethical boundaries into their design that protect the rights of the individual.

Acknowledgements.

The organizing committee wants to thank the congress organizers Babette Schmidt and Eveline Koeman from "Your conference support" for organizing the meeting in Lisbon, Portugal. The authors of this summary also want to thank the 16 distinguished speakers, regulators, and all representatives from professional organizations around the world that took part in the lively discussions, ultimately resulting in the 16 action points on how to improve the safety and quality of MPHO.