Dear Sir/Madam

Subject: Comments on the Application for the Addition of Whole Blood and Red Blood Cells to the WHO Model Essential Medicines List and the WHO Model Essential Medicines List for Children

We carefully reviewed the application for the addition of Whole Blood and Red Blood Cells to the WHO Model Essential Medicines List and the WHO Model Essential Medicines List for Children. The enclosed comments are being submitted on behalf of international experts working in the field of Blood Transfusion Medicine. These experts also serve as members on several important international working groups, networks and fora on blood transfusion convened under the International Society of Blood Transfusion, World Health Organization, International Federation of Red Cross and Red Crescent Societies and other international organizations.

We sincerely hope these comments, given in our individual capacity, will be made public and will be considered by the Expert Committee while deliberating on the agenda to include whole blood and red blood cells on the WHO Model Essential Medicines Lists.

Sincerely yours

Dr Che Kit Lin (signed on behalf of the following experts)
Chief Executive and Medical Director
Hong Kong Red Cross Blood Transfusion Service
15 King's Park Rise, Yaumatei
Kowloon
Hong Kong SAR, China

Enc
The attached comments (pages 3 to 10) are provided on behalf of the following international experts in Blood Transfusion Medicine.

1. **Australia**: Mr Peter Carolan, International Consultant, Voluntary non-remunerated Blood Donation (VNRBD), formerly Senior Officer (Blood), Health and Care Dept, IFRC, Geneva, Switzerland; Member, WHO-IFRC task force for 'A global framework for action towards 100 per cent VNRBD'.

2. **Cameroon**: Dr Jean-Baptiste Tapko, former Regional Adviser, Blood Safety and Laboratories, WHO/AFRO; President Elect, African Society of Blood Transfusion, Yaoundé.

3. **Ghana**: Dr. Justina Kordai Ansah, Director, National Blood Service Ghana; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

4. **Honduras**: Dr Elizabeth Vinelli, Medical Director, National Blood Program, Honduras Red Cross, Comayaguela; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

5. **Hong Kong SAR, China**: Dr Che Kit Lin, Chief Executive and Medical Director, Hong Kong Red Cross Blood Transfusion Service; Chair, Asia Pacific Blood Network; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine; Member, Global Advisory Panel on Corporate Governance and Risk Management, International Federation of Red Cross and Red Crescent Societies.

6. **India**: Dr Zarin Bharucha, International Consultant Transfusion Medicine; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

7. **India**: Dr Nabajyoti Choudhury, Additional Director, Department of Transfusion Medicine, Fortis Memorial Research Institute, Haryana; Secretary General, South Asian Association of Transfusion Medicine; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

8. **India**: Dr Sanjay Kumar Jadhav, Assistant Director (Blood Transfusion), Maharashtra State Blood Transfusion Council, Government of Maharashtra, Mumbai; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

9. **Italy**: Dr Giuliano Grazzini, Director, Italian National Blood Centre, Istituto Superiore di Sanità, Rome; Member, European Committee on Blood Transfusion (Partial Agreement) (CD-P-TS), Council of Europe; Italian Representative, Competent Authorities on Blood and Blood Components, European Commission.

10. **Macao SAR, China**: Dr Crystal Ping Hui, Director, Blood Transfusion Service, Macao Health Bureau; Member, Asia Pacific Blood Network.

11. **Malaysia**: Dr Yasmin Ayob, Medical Consultant to the National Blood Centre and National Heart Institute, Kuala Lumpur; President of the Malaysian Blood Transfusion Society; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

12. **Malawi**: Dr Bridon Mbaya, Medical Director, Malawi Blood Transfusion Service, Blantyre; President, African Society for Blood Transfusion.
13. **Mauritius**: Dr Janaki Sonoo, Pathologist, Laboratory and Transfusion Medicine, National Blood Transfusion Service, Quatre Bornes; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

14. **Nigeria**: Prof. Banji Adewuyi, Professor of Haematology, University of Ilorin Teaching Hospital, Kwara; Vice President (ECOWAS), African Society for Blood Transfusion.

15. **Norway**: Dr Hans Erik Heier, Professor Emeritus (Transfusion Medicine), Institute of Clinical Medicine, University of Oslo.

16. **Oman**: Dr Shahnaz Al-Balushi, Director, Department of Blood Services, Ministry of Health.

17. **Pakistan**: Prof. Hasan Abbas Zaheer, Project Director, Safe Blood Transfusion Services Programme, Pakistan; Founding President, Pakistan Society of Blood Transfusion; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

18. **Singapore**: Dr Diana Teo, Senior Director, Blood Services Group, Health Sciences Authority.

19. **United Arab Emirates**: Dr Amin Hussain Al Amiri, Assistant Undersecretary, Medical Practice and License; Chairman of Supreme National Blood Transfusion Committee, Ministry of Health, Sharjah; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.

20. **United Arab Emirates**: Dr May Raouf, Medical Director, Sharjah Blood Transfusion and Research Centre, Ministry of Health, Sharjah; WHO Expert Advisory Panel on Blood Transfusion Medicine.

21. **United Kingdom**: Dr Alan Kitchen, Head, National Health Service Blood and Transplant, National Transfusion Microbiology Reference Laboratory, London; Member, WHO Expert Advisory Panel on Blood Transfusion Medicine.
Comments on Application for the Placement of Whole Blood and Red Blood Cells on the WHO Model Essential Medicines List (EML) and the WHO Model Essential Medicines List for Children (EMLc)

1 Whole blood and red blood cells, essential for health care

- The essential role of whole blood and red blood cells for patient care in every health system is universally accepted. It has been specifically addressed in a number of World Health Assembly (WHA) resolutions and declarations, notably resolutions WHA28.72: Utilization and Supply of Human Blood and Blood Products (1975), WHA58.13: Blood Safety: Proposal to establish World Blood Donor Day (2005) and WHA63.12: Availability, Safety and Quality of Blood Products (2010) and the Melbourne Declaration on 100% Voluntary Non-remunerated Donation of Blood and Blood Components (2009).

- These resolutions have also identified the guiding principles, and policy and technical requirements for the development of sustainable national blood systems that can ensure access to safe blood and blood products as part of universal health coverage.

- World Blood Donor Day, held annually on 14 June, is one of eight health days mandated by the World Health Assembly that WHO observes in collaboration with governments, national blood services, international organizations, national Red Cross and Red Crescent societies, patient and blood donor organizations and other stakeholders and partners. World Blood Donor Day was established to promote voluntary non-remunerated blood donation as the foundation of a safe, stable and sustainable blood supply and provide high level advocacy to governments on the essential role of blood in the delivery of key services and interventions of public health significance.

- Furthermore, access to safe blood and blood products is integral to global strategies for the prevention of HIV and hepatitis infections and to the achievement of Millennium Development Goals 4, 5 and 6.


- Essential Interventions, Commodities and Guidelines for Reproductive, Maternal, Newborn and Child Health published by the Partnership for Maternal, Newborn & Child Health (2011) recognize access to safe blood transfusion as an essential intervention for improving maternal and child health.

2 Application to place whole blood and red blood cells on the Essential Medicines Lists

- The application to add whole blood and red blood cells to the EML and EMLc is designed to underscore the essential role of these therapeutic substances in the health-care system in every country. While it aims to promote higher quality of care for patients, better management and more cost-effective use of health resources, it has raised major concerns among policy makers and professionals working within blood systems at national and international levels.
• The application states that one purpose in requesting the placement of whole blood and red blood cells on the EMLs is to standardize the processes followed to "make and use this medicine" so that the product itself becomes more standardized and safer. We suggest that the classification of blood as a medicine that can be "made" is inappropriate.


• The special character of therapeutic substances such as blood, kidneys or gametes is their human origin. Blood donated by humans is a precious national resource that is, and will remain, limited by nature. It is not produced or manufactured in the same way as medicines and should not be regarded as a mere commodity. Blood is a living human tissue similar to cells and organs for transplant; the donation of blood is comparable to organ donation rather than to the procurement of raw materials for the production and manufacture of medicines.

• Attempts to harmonize standards for the production of whole blood and red blood cells as medicines will have major policy, legal, regulatory, financial, ethical and societal implications that may weaken the foundations of national blood systems in many countries. Contrary to the stated intent of the application, this may have a serious negative impact on the accessibility and safety of whole blood and red blood cells currently provided by national blood transfusion services, based on voluntary non-remunerated blood donation. In this respect, developing countries will be particularly vulnerable.

• We also consider the increased commodification and commercialization of the collection, processing and supply of whole blood and red blood cells to be a likely consequence, as has been the case with plasma for fractionation. This will undermine systems of voluntary non-remunerated blood donation, which are accepted as the cornerstone of safe and sufficient blood supplies and the first line of defence against the transmission of infectious diseases through transfusion, and will pose a grave threat to the capacity of resource-limited countries to make these therapeutic substances available to all patients in need.

3 Legislation and regulation of whole blood and red cells as medicines

• While some countries already regulate blood as a "medicine", many others apply different regulatory requirements to blood and medicines. Globally, close to 100 countries, including countries in the European Union, have separate legislative and regulatory frameworks for whole blood and red blood cells due to the specialized nature of these therapeutic substances of human origin and the risk of transmission of HIV, hepatitis B, hepatitis C and other life-threatening infections through transfusion.

• The adoption of different regulatory frameworks for blood and medicine in so many countries reflects the differences between blood and medicine. These differences are recognized even in countries which regulate medicine and blood similarly. The
Swiss Federal Law on Therapeutic Products, for example, contains a separate section on special provisions that apply only to blood and blood products.

- The classification of blood as a medicine would require legislative changes in many countries to ensure compliance with regulatory requirements, notably good manufacturing practices (GMP), for the production and manufacturing of medicines. This will have serious financial, infrastructure, logistics and ethical implications and may threaten national capacity for self-sufficiency in safe blood and blood products and for the security of the supply.

4 Quality systems and GMP requirements

- All medicines used for patient care, whether produced domestically or imported, should be manufactured in compliance with internationally recognized standards and, specifically, with GMP. If whole blood and red blood cells are classified as medicines, they will be required to comply with GMP. This raises three important issues.

- Firstly, much of the blood chain lies outside the scope of GMP. As a human-derived biological material, blood has unique characteristics that differentiate it from the raw materials used in medicines. GMP covers the technical aspects of production to ensure that products are consistently produced and controlled in accordance with defined quality standards. It cannot address the inherent biological variations in the source material – human blood donors – nor such factors as the incidence and prevalence of infection in the blood donor population or the quality of clinical transfusion practice.

- Quality systems designed to ensure the quality and safety of whole blood and red blood cells should not be limited to production but should encompass the entire blood chain, from blood donors to the follow-up of recipients of transfusion, including assessment of the suitability of individuals to donate blood, testing for transfusion-transmissible infections and blood group serology, appropriate prescribing and safe administration of blood, and haemovigilance, which is not synonymous with pharmacovigilance.

- Secondly, GMP compliance requires the full implementation of a standard. It does not accommodate a stepwise implementation process or opportunities for improvement. Developing nations which are still struggling to establish basic quality systems and which are unable to comply with GMP standards will be left with even more limited access to a safe blood supply.

- Thirdly, in the foreseeable future many countries, particularly developing nations, will be unable to provide whole blood and red blood cells that meet GMP requirements in sufficient quantities to meet the transfusion needs of their populations. The outcome will be less – rather than more – access to these components. This may force countries into purchasing them on the global market or make them susceptible to pressure from the for-profit sector to permit the commercial production and supply of whole blood and red blood cells obtained from paid donors.

5 Commodification of whole blood and red blood cells, undermining of voluntary non-remunerated blood donation and risk to public health

- The Oviedo Convention on Human Rights and Biomedicine of 1997 explicitly prohibits any financial gain from the human body and its parts. In 2000, this was echoed in the Charter of Fundamental Rights of the European Union, in which article
3, Right to the Integrity of the Person, states that "In the fields of medicine and biology, the following must be respected in particular: the prohibition on making the human body and its parts as such a source of financial gain". As such, it would be inappropriate to include any such specialized substances of human origin on the EMLs.

- The proposed addition to the EMLs would enable the pharmaceutical industry to exert pressure on countries to open their markets to whole blood and red blood cells and to trade in their procurement, processing and distribution. The operation of parallel, commercial systems will jeopardize the continued existence of national blood systems based on voluntary non-remunerated blood donation.

- Increased commercial interest in the production of whole blood and red cells will almost inevitably lead to significant increases in the purchase of blood by profit-driven companies as "raw material" for the manufacturing process. It is uncertain that appropriate safeguards for blood donor health and safety can be maintained in countries with inadequate regulatory systems.

- The provision of financial incentives or payment to obtain blood for the manufacturing process seriously undermines the efforts of national blood services to provide safe blood and blood products. National blood systems based on voluntary non-remunerated blood donation, which is associated with the lowest risk of transfusion-transmitted infections, will be directly threatened by parallel systems of paid donation. Once donors are paid for their blood, fewer will be motivated to donate without receiving payment, particularly in low-income countries. Voluntarism and the concept of the "gift" relationship will be weakened.

- We believe that there would be significant international public health risks if whole blood and red blood cells were to be traded internationally in the same way as medicines. The global export of whole blood and red blood cells on an industrial scale would facilitate cross-border movement of transfusion-transmissible infections. The HIV epidemic and the outbreak of vCJD have demonstrated that global distributions could increase the risk of global spread in the event of a new emerging transfusion-transmissible infection.

- Many developing countries are still struggling to reform fragmented blood supply systems with multiple players, including small commercial blood banks which operate outside government control. In such fragmented systems, where regulatory authorities are likely to be weak, opening up commercial markets in blood may serve to protect or strengthen their status as commercial suppliers of blood and make any necessary structural reforms even more difficult. An unregulated private sector has been identified as one of the key challenges to the achievement of universal health coverage.

- The commodification and commercialization of blood is entirely contrary to World Health Assembly resolutions, global policies and international treaties that identify voluntary non-remunerated blood donation as the foundation of a safe and sufficient blood supply and preclude substances of human origin from becoming marketable commodities. Concerns about the commodification of whole blood and red blood cells extend to other substances of human origin, including cord blood, stem cells and organs.
6 What has been learned from the placement of plasma derivatives on the EMLs?

- Concerns about the potential negative outcomes of the placement of whole blood and red blood cells on the EMLs in part derive from the case of plasma-derived medicinal products (Factors VIII and IX, and Immunoglobulin). Their inclusion on the EMLs has not brought the desired results of increased global availability and access. Few governments have invested in infrastructures and systems for the provision of plasma for fractionation and regulatory authorities remain weak in this area in many countries.

- Large volumes of plasma recovered from whole blood donations by voluntary non-remunerated donors are currently discarded, mainly in low- and middle-income countries, because regulatory requirements for the manufacture of plasma-derived medicinal products cannot be met. Most countries remain dependent on the importation of these products and often face critical shortages and limited patient access because of their high cost on the international market.

- Meanwhile, there has been an exponential increase in paid plasma collection, Source plasma collections have risen by around 15% per annum over the last decade and account for approximately 75% of the global plasma supply. Source plasma is collected almost entirely by the private sector from paid donors in a small number of countries, with an increasing volume of paid plasma being collected from students and poor populations. In the long term, it will not be feasible for this small number of countries to continue collecting sufficient plasma to meet global demands for plasma-derived medicinal products.

- Despite being on the EMLs for several years, the international distribution of plasma-derived medicinal products is inequitable, with disproportionately high consumption in countries with high GDPs. “Off-label use” of intravenous immunoglobulin in some countries has further enhanced this trend, in spite of the inherent limits of availability of substances of human origin. High prices and extensive use in high-income countries have resulted in poor access to these blood products in countries with limited purchasing power.

7 The EMLs and blood safety and availability. More harm than good?

- The EMLs serve as important tools at national level to assist in the purchasing of medicines to meet the basic health-care needs of the population. One of the purposes of the EMLs is to aid governments in identifying the treatment of first choice and selecting the most efficacious, safe and cost-effective medicines from the range available. In the case of whole blood and red blood cells, no alternatives exist.

- If blood is classified as an essential medicine in the EMLs, procurement policies in some countries would require it to be subject to a formal tendering process in which bids would have to be sought from rival suppliers, even if blood and blood products are currently supplied by a single provider, such as the national blood transfusion service. This may force governments to seek tenders from blood providers in other

---


countries in order to meet this requirement. It may also prove to be an important opening for the commercial sector to enter the market in these countries.

- In developing countries today, medicines account for 25–70% of total health expenditure compared to less than 10% in most high-income countries. If blood were to be included on the EMLs, countries may face pressure to purchase “safer”, more expensive blood products than those available locally.

- The application makes a somewhat simplistic correlation between the inclusion of whole blood and red blood cells on the EMLs and improved access to safe blood. It does not address the complex interactions between national blood services, other health-care institutions, civil society and individuals who donate blood, nor the changes at the systemic level that are required for improved access to safe blood.

- WHO has published extensive policy and technical guidance on strategies for blood safety and availability and the requirements for national blood systems that can ensure universal and timely access to safe blood and blood products. These requirements include:
  - development and implementation of a national blood policy
  - legislative and regulatory framework
  - national coordination of blood transfusion systems
  - collection of blood from voluntary non-remunerated blood donors at low risk for transfusion-transmissible infections, the phasing out of family/replacement blood donation and elimination of paid donation
  - quality-assured screening of all donated blood for transfusion-transmissible-infections, blood grouping, compatibility testing, and preparation of blood components
  - rational use of blood to reduce unnecessary transfusions and minimize the risks associated with transfusion, the use of alternatives to transfusion, where possible, and safe clinical transfusion procedures
  - effective quality systems, including quality management, documentation, training of all staff and assessment
  - haemovigilance systems for the monitoring, investigation and reporting of adverse effects of blood donation and transfusion, and appropriate corrective and preventive actions.

- These strategies of proven effectiveness have been implemented in many countries, including those in which PEPFAR has supported the strengthening of national blood transfusion services as a means of limiting and ultimately halting the transmission of HIV and hepatitis infections through blood transfusion. Published literature and global data demonstrate significant, sustained improvements in the safety, availability, accessibility and appropriate clinical use of blood and blood products.

- Medicines which have proven value in reducing bleeding and surgical blood loss and which can significantly reduce the need for blood in the clinical setting should be considered for inclusion on the EMLs.

- Equipment, reagents and devices, including blood collection bags and blood screening assays, required for the collection, testing, processing, storage and use of donated blood are regulated, marketed and procured in a similar way to medicines. It would be appropriate for such commodities to be placed on an “essential
commodities or devices list” with the aim of securing price reductions for developing countries and limiting the costs of patent claims for such countries.

8 Implications for national goals of self-sufficiency and security

- In 2010, the World Health Assembly deliberated on challenges to the availability, safety and quality of blood products. Resolution WHA63.12 defined self-sufficiency in the supply of safe blood and blood components based on voluntary non-remunerated blood donation, and the security of that supply, as important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. The definition of blood as a medicine through its inclusion on the EMLs will undermine the efforts of many countries to achieve or maintain self-sufficiency in a sustainable supply of whole blood, red blood cells and other blood products. In some cases, it may cause a reverse in progress towards this goal and threaten the security of blood supplies.

9 Need for assessment, review of evidence and further consultation

- We acknowledge that the rationale for the application is to encourage governments to ensure sustainable funding and support for safe and adequate national blood supplies that are accessible to all patients in need. On review of the application and support letters, however, it appears that there has been relatively limited consultation on this issue, particularly with countries which may be most impacted if the application is approved.

- We submit that the proposal to place whole blood and red blood cells on the EMLs does not reflect the realities in developing countries, with blood systems and health systems that are at varying stages of development, nor does it address their priorities, needs and resources.

- In accordance with the requirements for the addition of any medicine to the EMLs, the applicants cite evidence on the comparative effectiveness, safety and cost-effectiveness of whole blood and red blood. The benefits and importance of improved access to whole blood and red blood cells, as cited in this application, are already universally recognized. However, because of the intrinsic differences between medicines and whole blood and red blood cells, the application form does not provide an opportunity for the wider implications to be addressed.

- For this reason, we propose that a systematic assessment and review of evidence should be conducted on the potential impact of the inclusion of whole blood and red blood cells on the EMLs, with particular reference to the capacity of countries to ensure universal access and safe and appropriate use. We propose that such an assessment and review of evidence should focus particularly, but not exclusively, on the possible consequences, in both the short and long term, for countries with limited resources, fragmented blood supply systems, poor legislative and regulatory frameworks, weak infrastructures, insufficient trained personnel, lack of standards and quality systems, inadequate procurement and supply systems, and poor clinical transfusion practice. Universal health coverage has become a priority objective of WHO and it is incumbent on the organization to ensure that its decisions do not undermine countries working towards universal access to safe blood transfusion as part of this goal.

- The application states that “Placement on the WHO EML underscores the government’s responsibility for ensuring financially sustainable funding and support
for a safe and adequate supply of blood that is accessible to patients in need...". Since it thus presumes the willingness of governments to "invest in infrastructure, systems and governance for blood establishments", far wider consultation with governments themselves is required, perhaps through the World Health Assembly, before any decision is taken by the Expert Committee on the Selection and Use of Essential Medicines.

- The consultation process should ensure the full participation of developing countries and extend to national blood services, regulatory authorities and other stakeholders, including inter-governmental organizations, international non-governmental organizations, international and national blood donor and patient associations, members of professional societies and individual experts in blood transfusion medicine/science and blood programme management, using all possible mechanisms, networks and fora convened by the International Federation of Red Cross and Red Crescent Societies and International Society of Blood Transfusion, and WHO, including the WHO Expert Advisory Panel on Blood Transfusion Medicine and WHO Global Blood Safety Network.

10 Summary

In our capacity as international experts in blood transfusion medicine and science, we do not support the application to place whole blood and red blood cells on the WHO Model Essential Medicine Lists at this time because of serious concerns about the potential outcomes, particularly for developing countries. We therefore urge the Expert Committee to:

- Give careful consideration to the issues we have set out in this document
- Provide sufficient time for a full consultative process with governments, national blood services and other stakeholders
- Defer a decision on whether to place whole blood and red blood cells on the EMLs until a systematic assessment, evidence review and analysis of the possible consequences have been completed.

Melbourne Declaration on 100% Voluntary Non-remunerated Donation of Blood and Blood Components, 2009.
DOI: 10.1111/j.1423-0410.2012.01630.x
Federal Assembly of the Swiss Confederation. Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, PA) of 15 December 2000 (Status as of 1 January 2013).