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Evaluation & Fitness check of the EU blood legislation - Contribution document from the EDQM

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EDQM

EVALUATION & FITNESS CHECK OF THE EU BLOOD LEGISLATION

**Contribution from the European Directorate for the Quality of Medicines and
Healthcare/Council of Europe**

1 **General Statement**

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Executive summary

- 1 This document provides a non-exhaustive evaluation of the European Union (EU) blood
2 legislation. It was produced based on desk research and scientific evidence collected as part
3 of EDQM's activities.
- 4 The first part of this report describes major current trends in the blood transfusion field as
5 well as a number of challenges that the blood sector is facing nowadays, in particular
6 related to the collection and use of blood components, self-sufficiency, Voluntary Non-
7 Remunerated Blood Donation (VNRBD), blood safety, scientific and technical developments
8 and socio-economic changes. The second part provides an evidence-based evaluation and
9 fitness check of the EU blood legislation in the light of current trends and challenges.
- 10 The report concludes with a number of key messages and recommendations intended to
11 illustrate how future EU blood legislation may help to achieve new regulatory needs.

1. Blood Transfusion – Current trends and challenges

1 With a view to providing a comprehensive evaluation of the current status of the EU
2 legislation on blood and assessing its fitness with regards to the current circumstances, a
3 careful description of current trends and challenges in the sector is deemed necessary.

4 **Current trends in collection and use**

5 Blood transfusion is undeniably a life-saving measure. In 2012, the EU Member States (MSs)
6 reported collection of more than 20 million Whole Blood (WB) and components donations
7 in over 1350 BEs [1]. According to the last published EU report on SARE (2015 data), 26
8 million units are issued per year on average in the EU.

9 According to the last published report of the EDQM/CoE on the collection, testing and use
10 of blood and blood components in Europe (Council of Europe Member States (MSs)), the
11 number of WB collections is on average 35 per 1000 inhabitants [2]. The average use of Red
12 Blood Cells (RBCs) is 34 per 1000 inhabitants [2]. It is worth mentioning that the numbers of
13 WB and components collected and used vary a lot between MSs. Therefore, any
14 interpretation should be made with caution.

15 The variation in the collection and use of WB and components is influenced by many
16 factors. Donor management and donor eligibility criteria may differ from one country to
17 another and transfusion practices in clinical settings may considerably influence the use of
18 components.

19 Although blood transfusion is recognised as essential in treating numerous acute and
20 chronic diseases or conditions, initiatives and ensuing guidelines have recently been
21 developed both in Europe [3], [4] and worldwide with the aim of ensuring an optimal use of
22 blood components and avoiding their over-prescription [5], [6]. These projects have
23 essentially been patient-oriented. Focusing on patient safety, they aimed at avoiding or
24 treating anaemia, and minimising blood loss and bleeding to avoid unnecessary blood
25 transfusions. In addition to this primary objective, these initiatives have helped prevent
26 unnecessary exposure of patients to allogeneic blood components thus reducing adverse
27 effects. As RBCs are the most commonly transfused blood components, a decrease in their
28 use has been observed [2] as a result of these initiatives.

29 Although the use of RBC is declining, additional influencing factors – such as current
30 demographic changes – need to be taken into consideration. Europe is evidently undergoing
31 demographic changes with the decline in birth rates and increasingly ageing population. It is
32 therefore expected that this would lead to an increase in transfusion therapies and thus to
33 growing blood needs which will coincide with a decrease in blood donations [7], [8]. As a
34 consequence, motivation both of young people and of people from all other age groups will
35 become increasingly important.

36 Lastly, a lot of MSs still have a large proportion of first-time donors [2] which may lead to
37 several problems such as generation of extra costs for the recruitment of new donors and
38 difficulties in maintaining an adequate supply of blood.

1 **Blood Safety**

2 Donor selection, blood components' screening for pathogens causing Transfusion
3 Transmitted Infection (TTI) and the introduction of Quality Systems (QS) in Blood
4 Establishments (BEs), have considerably decreased the risk of transfusion-acquired
5 infections and risks associated with the collection, testing, preparation, transport, storage
6 and transfusion of blood components.

7 In particular, the reduction of TTI has essentially been a result of the introduction of Nucleic
8 acid Amplification Technique (NAT) testing in addition to serological screening. Although TTI
9 transmission remains a rare event [9] , new TTI have emerged over recent years such as
10 Hepatitis E Virus, West Nile Virus and ZIKA virus, leading to the need to introduce new
11 preventive and screening measures in affected and potentially affected areas. It is worth
12 mentioning that the enlargement of the EU combined with the increasing movement of
13 people between EU MSs and continents may contribute to spreading newly emerging TTI as
14 well as reducing the number of donors due to their deferrals.

15 The application of modern technologies in the blood supply chain has introduced new
16 categories of risks, for example risks related to Pathogen Reduction technologies (PRT).
17 Although, the introduction of PRT has greatly reduced the risk of TTIs, the residual content
18 of the toxic compounds introduced needs to be measured and their effect on the
19 functionality of platelets or coagulation factors needs to be checked. As a consequence,
20 each PRT needs to be licensed e.g. CE marked and quality control implemented.

21 Among others, bacterial sepsis due to bacterial contamination of blood components, in
22 particular platelets components, also remains an important issue. For the past several years,
23 bacterial contamination of platelets has in fact been the greatest TTI risk – a risk significantly
24 higher than the risk of a viral TTI. The root causes are multiple but have so far often been
25 identified to be related to skin contamination, non-appropriate disinfection of donor arms
26 and contamination of the bags of the components at the time of collection or during
27 processing. As a consequence, many BEs have introduced bacteria detection technologies
28 for platelets.

29 **New technologies and scientific progress**

30 With the expansion of transfusion medicine, numerous new technologies have been
31 introduced into BEs to enhance productivity, ensure better traceability, and provide an
32 adequate supply of components to hospitals.

33 Blood collection has been marked by the introduction of automated aphaeresis procedures.
34 A considerable automation of serological, NAT and immuno-haematological testing has
35 occurred in blood laboratories associated with the introduction of computerised systems for
36 the management of results. This has significantly standardised testing processes, reduces
37 human errors in sample identification and transcription errors while, on the other hand, has
38 required training of personnel in automation and documentation of the validation and
39 qualification process.

1 With a view to reducing manual operations, semi-automatic equipment is now available for
2 the processing of WB into plasma, RBC and platelets with the use of top and bottom blood
3 bag systems and optipress devices. Outbreaks of HIV and HBV, and reactions in patients
4 have prompted the development of vigilance systems leading BEs to develop software
5 dedicated to that purpose. With the requirements for traceability from the donor to the
6 patients and traceability of critical instruments to each blood unit, the implementation of
7 Information Technology (IT) systems has become systematic.
8 Therefore, continuous scientific progress combined with automation and computerisation
9 has enabled maintaining a high level of quality in BEs while prompting them to train
10 personnel and implement Quality Management (QM) in order to ensure all processes are
11 appropriately implemented.

12 Furthermore, transfusion science has greatly evolved within the past 20 years. Emergence
13 of new specialities has enabled extension of the scope of blood transfusion research. While
14 the initial focus of attention was transfusion safety with the development of screening
15 assays, recent focus has been on the improvement of methodologies and techniques.
16 Efforts are being made to constantly increase the sensitivity of screening assays and
17 towards the development of multiplex NAT assays and assays for new emerging diseases.
18 With the growing relevance of vigilance, behavioural science and epidemiology, recent
19 research topics have focused on donor safety and donor management.

20 **Self-Sufficiency**

21 In its communication dated 25 May 1993, the Commission called for the Community to
22 *'consider undertaking actions in its efforts to promote self-sufficiency in human blood or*
23 *human plasma through voluntary unpaid donations'*. Due to the importance of achieving
24 self-sufficiency in Europe, this objective was enshrined in the EU Mother Directive
25 2002/98/EC [10], in its preamble. Although it can now be stated that almost all MSs have
26 attained national sufficiency for blood components, it is less the case as far as plasma for
27 the production of Plasma Derived Medicinal Products (PDMPs) is concerned.

28 With regards to PDMPs, according to data presented by the Market Research Bureau (MRB)
29 at various stakeholder meetings, Europe holds 26.4 % of the global PDMPs' markets with
30 10.7 % of the world population while North America holds 44% of the market with 5% of the
31 world population. The need for plasma for the production of PDMPs has considerably
32 increased, the main driver being Immunoglobulin. In order to achieve sufficiency in PDMPs,
33 Europe largely depends on plasma imported from the United States (US), mainly collected
34 by aphaeresis (estimated percentage of plasma collected in the US: 65% used for the
35 European market) [11]–[13]. As a consequence, Europe has become extremely dependent
36 on the US for the collection of plasma for fractionation. This dependency may have serious
37 consequences in the event of an interruption of plasma supply that may occur for various
38 reasons e.g. economic crisis, export restriction or a major health issue such as the
39 emergence of a new virus contaminating US donors.

1 It is also worth mentioning that a considerable volume of recovered plasma remains unused
2 in Europe essentially due to non-compliance with quality requirements from the plasma
3 industry [14].

4 In addition, new PDMPs or new indications for PDMPs already on the market (e.g.
5 Immunoglobulin for multiple sclerosis, Alpha-1 antitrypsin for Graft Versus Host Disease
6 (GVHD)) are under investigation. It is therefore likely that the need for plasma for
7 fractionation will increase in the coming years. Despite recombinants plasma proteins
8 coming onto the European Market in 1990s, their access and use are relatively limited in
9 several MSs, due the unequal pricing and reimbursement systems.

10 **VNRBD**

11 Over the past 40 years, special consideration has also had to be given to a guiding principle
12 that was embedded in the EU Mother Directive [10] at the time of its adoption: the
13 Voluntary Non Remunerated Blood Donation (VNRBD) principle also commonly referred as
14 Voluntary Unpaid Donation (VUD). This concept is rooted in the theory of the 'gift
15 relationship' introduced by R. Titmuss, a British sociologist in the early 1970s following the
16 publication of his work in the field [15]. The gift relationship is characterised as the altruistic
17 donation of blood to an anonymous patient-recipient without the expectation of a financial
18 or equivalent reward. Using previous scientific publications [16] Titmuss provided evidence
19 that blood collected in the US, obtained from paid donors, was associated with an increased
20 risk of transmitting Hepatitis C in comparison to blood collected in the UK from voluntary
21 non-paid donors [15]. He came to the conclusion that no financial value should be attached
22 to blood donations.

23 With the HIV crisis the concept was given much more prominence and VNRBD became a
24 principle underpinning national and supranational blood legislation. Besides being a safer
25 approach to blood collection, it has also been recognised as being a more ethical one.
26 Indeed, the prohibition of financial gain arises from the respect of a fundamental value,
27 human dignity, which is also closely related to the principles of non-maleficence and
28 beneficence.

29 A number of organisations have committed to enforcing the VNRBD concept. For example,
30 VNRBD forms one of the pillars of the work carried out by the CoE/EDQM in the field of
31 blood transfusion, tissues and cells and transplantation. Article 2 of the appendix to
32 recommendation No. R (95) 14 of the Committee of Ministers to the MS of the CoE [17]
33 states that: "*A donation is considered voluntary and non-remunerated if the person gives
34 blood, plasma or cellular components of his/her own free will and receives no payment for it,
35 either in the form of cash, or in kind which could be considered a substitute for money. This
36 would include time off work other than that reasonably needed for the donation and travel.
37 Small tokens, refreshments and reimbursements of direct travel costs are compatible with
38 voluntary, non-remunerated donations.*

39 The 1997 Oviedo Convention of the CoE [18] on Human Rights and Biomedicine established
40 an overarching convention applicable to SoHO, which explicitly prohibits any financial gain
41 from the human body and its parts. Other organisations such as the World Health

1 Organization (WHO) have committed to promoting VNRBD [18] at the international level. In
2 EU blood legislation, VNRBD is known as Voluntary Unpaid Donations (VUD), and is
3 recognised as the preferred method for supplying the Community with blood.
4 Although current data [14], [19], demonstrate that EU MSs moved towards VNRBD, and the
5 principle is well recognised, it is enforced to different degrees. Divergence is observed with
6 regards to its legal enforcement and with regards to practices. A broad range of incentives
7 are used ranging from small tokens, refreshments, time-off, food vouchers, free physical
8 check-up, reimbursement of medical costs, compensation linked to loss of earnings or
9 travel, and fixed sums of money, some of which – such as the fixed sum of money or time-
10 off – strictly speaking deviate from the VNRBD principle. Main arguments put forward to
11 justify such practices are the importance of keeping continuity in the blood supply and
12 improvement of safety through the introduction of testing of transfusion- transmitted
13 disease.

14 **Restructuring of the blood transfusion system, globalisation, internationalisation, and** 15 **socio-economic changes**

16 Following the introduction of the EU legislation in early 2000, many countries decided to
17 reorganise their blood systems with the objective of becoming more efficient and meeting
18 new regulatory provisions. Centralisation of testing and/or processing sites has been
19 observed in many MSs as well as outsourcing of activities – for instance related to
20 maintenance and qualification of equipment or testing.

21 In addition, BEs have started to introduce Quality Systems (QS). The implementation of QS
22 started quite recently, essentially due to a shortage of public funding, compounded by poor
23 access to training in the field and a lack of interaction with the pharmaceutical industry.

24 At present, BEs are also continually required to meet current corporate management
25 practices such as strategic planning, human resources management, accountability and cost
26 accounting. The blood sector is evolving, becoming more professional and is undergoing
27 globalisation and is thus more internationally exposed.

28 Collaboration between BEs, networking and exchange of information and the development
29 of collaborative projects between BEs and CAs have been enhanced.

30 Through globalisation and movement of persons and services, BEs are nowadays operating
31 in a competitive environment and are also facing increasing economic pressures. Blood
32 transfusion is very often one of the most costly sectors in the field of public health, thus BEs
33 are constantly requested to reduce their costs while being asked to improve quality and
34 safety of blood components through the implementation of new measures and introduction
35 of new technologies. Safety interventions have accumulated over recent years due to an
36 over-adherence to the precautionary principle rather than being evidence- or risk-based. As
37 a result, costs tend to accumulate at the expense of no real increase in safety accompanied
38 by a significant loss of donors.

39 Lastly, the establishment of the EU internal market has facilitated the movements of goods
40 and persons creating a competitive market in the field of blood.

For instance, competition with regards both to the sale of labile components and to donor recruitment have been observed over recent years. Such unregulated competition in the blood sector may place the blood supply at risk e.g. by donor shortage, components wastage. Competition in the field of blood thus deserves increased attention.

- 1 In section 2 of the present document, the EU blood legislation is evaluated in the light of the
- 2 major trends and challenges described above.

2. Evaluation of the current European blood legal framework

2.1. Relevance, effectiveness and efficiency of the EU blood legislation

2.1.1. Objective(s) of the EU blood legislation

1 The EU Mother Blood Directive, namely 2002/98/EC [10], was developed in 2002 and
2 entered into force on 8 February 2003, at a time where the EU was composed of 15
3 Member States (MSs). This was followed by the development of 3 implementing technical
4 Directives which entered into force in 2004 and 2005. These Directives have their root in
5 Article 168 (4 & 7) of the Treaty on the Functioning of the European Union (TFEU) (former
6 article 152 (4) of the Amsterdam Treaty).

7 The main objective of the EU blood legislation was to develop high standards in the EU MSs
8 and thus to provide minimum requirements. In addition, the EU blood legislation was set up
9 in such a way that it does not affect the organisation of the blood services nor the national
10 provisions on the donation or medical use of organs and blood with respect to article 167
11 (7) of the treaty.

12 From the audits performed by the EDQM as part of the B-QM activity and as also
13 demonstrated in the EC implementation survey [20] it can be concluded that the objective
14 of the EU blood legislation has been achieved to some extent resulting in the improvement
15 of the level of safety and quality in blood transfusion across EU MSs. The EU blood
16 legislation has thus been effective.

17 In addition to this primary objective, the EU legislation has also enabled export/import of
18 labile components across Europe in emergencies and has stimulated MSs to share
19 information and initiate EU projects.

20 However, since the adoption of the legislation in 2003, the EU expanded to 25 MSs in 2004
21 and to 27 EU MSs in 2007. It is likely that other candidate countries will join the EU in the
22 coming years. The further enlargement of the EU would necessarily increase the free
23 circulation of goods and persons, combined with potential health threats related to the
24 movement of people and health concerns related to migration issues. This situation may
25 also call for further export/import of blood components, although this practice is not yet
26 widespread [1]. More importantly this would call the plasma industry to seek plasma from
27 these potential new MSs to produce PDMPs, considering the growing demand and needs for
28 PDMPs. In addition, as mentioned in section 1 of this document, a number of scientific and
29 technical developments have taken place and a number of new technologies have been
30 introduced since the adoption of the blood legislation. Thought should thus be given to the
31 harmonisation of requirements across Europe, especially on the basis of equal treatment as
32 laid down in the Cross border healthcare Directive 2011/24/EU [21].

33 It is worth noting that a recent initiative towards harmonisation of quality requirements has
34 been the publication of the Good Practice Guidelines (the GPG) in 2016, which was jointly
35 developed by the EDQM and EC.

1 The GPG have their roots in Good Manufacturing practices (GMP), lay down requirements
2 which are applicable to BEs and enable the harmonisation of practices.
3 The relevance of the objective of the blood legislation needs to be reviewed in the light of
4 current public health challenges and as to meeting current and upcoming scientific and
5 regulatory needs. A possible switch to harmonisation is to be explored to lay the
6 groundwork to achieve an EU-based self-sufficiency and equal treatment. Still, MSs need to
7 be given some leeway with regards to the organisation of their blood services.

2.1.2. Scope of the Directives

8 The Mother Directive covers different aspects and activities of the blood supply chain as
9 well as related professionals and authorities involved. Its scope is summarised below:

- 10 ○ Overseeing duties such as authorisation, inspection, traceability and
11 vigilance. In this context the Directive regulates National Competent
12 Authorities (NCAs).
- 13 ○ The collection, testing of blood and its components whatever their intended
14 purpose and to the processing, storage and transport/distribution of blood
15 (hereinafter referred as core activities) and its components when intended
16 for transfusion. It also lays down requirements related to personnel, Quality
17 System, documentation, traceability, notification of SARE and data
18 protection.

19 Thus, the Directive regulates the following establishments:

- 20 ▪ BEs;
- 21 ▪ Plasma facilities (when responsible for the collection and testing of
22 blood components intended for the manufacture of PDMPs);
- 23 ▪ Hospital Blood Banks (HBB) when it comes to requirements related to
24 personnel, QS, documentation, traceability, notification of SARE.

25 Very few changes have occurred in the distribution of duties and responsibilities among
26 stakeholders operating in the blood field. The scope of the Directives is still relevant and
27 effective.

28 In the future, minor changes could be expected with the expansion of subcontracted
29 activities; thus subcontracted activities would need to be better regulated.

30 All intermediate products, whatever their intended purpose, need to be covered by
31 common legislation to avoid diverging safety and quality requirements, and thus to ensure
32 that citizens are equally treated whatever the type of component received (labile
33 components or PDMPs).

34 Lastly, some products such as serum eye drops and in particular platelets-rich plasma, which
35 are increasingly used, are currently not properly regulated as they do not fall under any of
36 the Blood or Tissue and Cells legislation. To avoid diverging practices in the EU MSs, this
37 shortcoming should be taken on board.

- 1 With this exception, the scope of the directives is still relevant and appropriate. Thought
- 2 could be given to the establishment of general provisions to regulate competition when
- 3 competition may have a direct impact on access to blood components.

2.1.3. Content of the Directive and its implementation

2.1.3.1. Provisions for Competent Authorities (CAs)

◆ Accreditation, designation, authorisation or licensing of BEs

According to article 5(1) of Directive 2002/98/EC, MSs shall ensure that activities are undertaken only by BEs which have been designated, authorised, accredited or licensed by the competent Authorities for that purpose.

The last report from the EC on the application of Directive 2002/98/EC indicates that all establishments have effectively received a designation, authorisation, accreditation or licence from the NCAs in 25 MSs, though there are still MSs encountering difficulties in meeting this requirement for various reasons. It is worth mentioning that the accreditation, designation, authorisation or licensing procedure is not standardised and varies from one country to another. This has also been observed as part of the B-QM activity run by the EDQM, and highlighted in the last EC implementation survey [20]. During audits performed by the B-QM, the auditors were often requested to provide their opinion on the extent to which a BE should be accredited/licensed/authorised thus demonstrating that there was still ambiguity with regard to the broad range of terminology used. Whereas in some countries accreditation is understood as an ISO 9001 certification, it may be understood as a health authority accreditation in another country.

This issue showcases a clear shortcoming in the effectiveness of the provision. Although the provision is relevant, the lack of a clear definition and lack of standardised procedure to achieve it has prevented its effective implementation. This has resulted in a lack of mutual trust between MSs. In any future revision of the legislation, this issue would need to be addressed.

◆ Inspection and control measures

According to article 8 on inspections and control measures, MSs shall ensure that the CAs organise inspections and appropriate control measures in BEs to ensure that the requirements of Directive 2002/98/EC are complied with. Implementation reports [20] and EDQM audit reports show that while inspection bodies are in place in almost all MSs, the conduct of inspection and control measures still remains an issue. The 2-year inspection interval is difficult to achieve and in some MSs, some BEs have never been inspected according to audit reports. This situation is essentially due to staffing problems and lack of financial resources, and in some cases due the lack of appropriate training of inspectors. Although it is commonly agreed that inspections require an on-site visit, desk-based inspection has also been observed.

This provision can be considered relevant – control measures have been introduced by MSs with few exceptions – but the provision is not entirely effective and needs to be reviewed. The legislation should allow risk-based inspections. Clarification is also necessary on the degree of inspection required (paper-based and/or on-site inspection).

2.1.3.2. Provisions for BEs

1 The technical content of the EU Blood Directives, in particular Directives 2002/98/EC [10]
2 2005/62/EC and 2004/33/EC [22] have their roots in the *Guide to the preparation, use and*
3 *Quality Assurance of blood components of the Council of Europe, 8th Edition*, hereinafter
4 referred as the *CoE Blood Guide*. Since their adoption, the EU Blood Directives have been
5 subject to a limited number of amendments which have only been possible through the
6 adoption of Commission Directives but whose scope is quite restricted.

7 As a result a great number of technical provisions are:

- 8 ○ no longer up-to-date;
- 9 ○ subject to interpretation;
- 10 ○ or missing.

11 Examples are provided below:

12 ◆ **Responsible person**

13 Article 9 of the Directive 2002/98/EC requires the designation of a responsible person. This
14 provision also needs to be read in conjunction with annex 2.2 of Directive 2005/62/EC which
15 requires the processing and quality assurance functions to be independent, as also required
16 in the GPG. During EDQM audits, it has been observed that many BEs have had difficulties
17 in complying with these requirements as the 'responsible person' function has frequently
18 been equated with the quality manager or the production manager. In addition, due to
19 resource constraints, the quality manager was also very often also the production manager.
20 This demonstrates that those provisions are ambiguous and require further guidance.
21 Although the recent version of the GPG has further delineated these functions, it remains
22 ambiguous as to whether or not these functions may be held by the same person and to
23 what extent independence is necessary. This is especially relevant in countries which are
24 facing resource shortages. In addition, BEs operate under GMP in several EU MSs and the
25 definitions laid down in the GMP are not fully aligned with the above ones. Should a new
26 legislation be developed, the rationale underpinning such provisions should be considered
27 in order to facilitate their implementation and to remain compatible with other legislation.
28 The reference to a unique set of quality requirements such as the GPG and the removal of
29 QS requirements from the EU blood legislation, in particular Directive 2005/62/EC [23]
30 would also be deemed appropriate.

1 ◆ Donor Selection Criteria

2 Directive 2004/33/EC, Annex III lays down eligibility criteria with regard to donor selection.
3 There is little evidence on the scientific soundness of some of these criteria. The application
4 of scientifically outdated criteria may hence result in unduly high deferral rates. Examples
5 are provided below:

6 • For instance, the directive requires donors to weigh at least 50 kg to donate blood.
7 However, the volume to be collected should be based on the blood volume of the
8 prospective donor rather than the weight in order to prevent risk of adverse
9 reactions as a consequence of over-collection. The blood volume of each donor for
10 example may be calculated from their weight, height and gender using a validated
11 formula as prescribed in the CoE Blood Guide.

12 • Another example relates to risk-behaviours. Permanent deferral of persons whose
13 sexual behaviour puts them at high risk of acquiring severe infectious diseases that
14 can be transmitted by blood is required according to Annex II point 2.1 of the
15 Directive. This requirement has led to discrepancies with regards to its
16 implementation and has been subject to differing interpretations for years. With a
17 view to clarifying the extent to which this requirement is to be implemented, the
18 EDQM/CoE created an *ad hoc* experts Working Group, whose objectives was to
19 monitor current practices, evaluate scientific data and define a harmonised
20 approach for donor deferral, linked to the risks attributable to sexual behaviour. The
21 work of the group resulted in the elaboration of a CoE resolution. In March 2013,
22 *Resolution CM/Res(2013)3 on sexual behaviours of blood donors that have an impact*
23 *on transfusion safety* was adopted. This example does not only show the room for
24 improvement of Directive 2004/33/EC but also the value of the CoE work in further
25 supporting MSs to implement requirements in an appropriate way and based on
26 evidence. Of particular importance, recommendation N° 5 of *Resolution*
27 *CM/Res(2013)3* calls for standardised, ongoing data collection on the incidence and
28 prevalence of sexually transmitted infections in the general population, in blood
29 donors and among individuals with risky sexual behaviours for use as a scientific
30 basis for amendments to donor-deferral policy. It is also worth noting that overall
31 the donor selection criteria are more nuanced in the CoE Blood Guide.

32 • Lastly, donors with a history of malignant diseases are permanently deferred.
33 However, considering the improvement of oncological therapies and using a risk-
34 based approach, more permissible criteria could be applied and thus allow cured
35 cancer patients to donate blood, as is currently prescribed in the CoE Blood Guide.

36 The approach to donor selection should be risk-based. Individual risk rather than
37 collective risk should be considered. This is especially topical in risk behaviour deferral
38 but also holds true for other issues. Thus, the Directive should specify more on proper
39 documented and evidence bas risk assessments.

◆ Donor Safety

Scientific studies on blood donor safety have increased over recent years. In addition, the voluntary reporting on Serious Adverse Reactions (SAR) for donors since 2012, as part of the annual EC SARE reporting exercise, has highlighted donor safety as an issue.

Several scientific articles [24], [25] have highlighted that vasovagal reactions were quite commonly observed to be putting donors at risk. In addition, iron deficiency [26] and protein depletion might be observed in frequent donors [27],[28]. Current provisions laid down in the Directives do not require MSs to report such reactions and to take preventive measures.

Reporting of SAR in blood donors should become a requirement as a way to raise awareness about the need to consider those reactions and take necessary measures to prevent them. In addition, donor selection criteria should be regularly updated in the light of new acceptable risks. Hence, with a view to protecting donors, evidence-based data will be collected in the near future to support the revision of the text of the recommendations to be published in the 20th edition of the CoE Blood Guide concerning donor selection, donor protection, donor management and plasmapheresis.

Donor protection is of increasing importance considering that first-time donors represent a large proportion of the donor pool in many MSs and that blood supply needs to be maintained. In addition, the issue of pre-qualification of donors should be risk-based depending on multiple factors e.g. epidemiology, testing strategy.

◆ Components monographs

Directive 2004/33/EC annex V, though it lays down product-oriented provisions, offers a limited number of provisions with regards to quality control of blood components; in contrast the CoE blood guide gives more nuanced provisions with regard to quality control. In addition, the guide provides for additional categories of components which are not listed in the EU Directive such as the *red cell, washed*, a component which is in use in EU MSs.

In the light of the above-mentioned issues, it can be said that the technical content of EU blood legislation has not kept pace with technical and scientific developments and is not sufficiently adapted to, adaptable to and up-to-date with scientific, technical and epidemiological developments.

With a view to harmonising technical requirements, avoiding duplication and non-coherent provisions, thought needs to be given to the adoption of the CoE Blood Guide, in particular its monographs and minimum requirements (Standards section) as technical references in the new legislation, much as the European Pharmacopoeia is mentioned in the EU pharmaceutical legislation. Indeed, technical and scientific advances are constantly evolving and thus a flexible approach needs to be found to allow the legislation to continuously provide evidence- and risk-based provisions.

The CoE Blood Guide provides a support mechanism – already in place, appropriate and easy to use – to allow rapid and regular updates of technical and scientific provisions.

1 The CoE Blood Guide is a technical annex to Recommendation No R (95) 15. It contains a
2 compendium of measures designed to ensure safety, efficacy and quality of blood
3 components and is particularly intended for those working in blood transfusion services. It
4 provides users with a set of standards and principles that cover many aspects of blood
5 collection from donor criteria and component processing, to blood testing. It is updated
6 every two years, and is currently in its 19th edition. The process of updating the Guide
7 ensures a continuous assessment of scientific issues and contributes to ongoing
8 harmonisation. This document has been crucial for setting technical standards for blood
9 safety and quality in Europe. Today it is the basis for a large number of national regulations
10 besides the EU legislation. Indeed, EDQM survey results [14] show that the CoE Blood Guide
11 was as often implemented as the EU legislation in the responding countries. Besides its wide
12 use, it is worth mentioning that several countries such as Greece, Portugal, Romania, Serbia,
13 Spain, Serbia have adopted the Guide or part of it in their national legislation.

◆ Safety provisions

Testing requirements are laid down in Annex IV of Directive 2002/98/EC and 2004/33/EC (ABO Group, Rhesus D, Hepatitis B virus surface antigen (HBsAg), Hepatitis C Virus antibodies (anti-HCV antibodies) and Human Immunodeficiency Virus 1 and 2 antibodies (Anti-HIV 1/2). In addition, other tests considered as being of paramount importance for the protection of both the donors and recipients are also performed by most of EU MSs. This includes NAT testing for HCV RNA, HBV DNA and HIV RNA (HCV-NAT, HBV-NAT, HIV-NAT), HIV antigen (p24), HBV core antibodies (Anti-HBc), Treponema pallidum antibodies (anti-Treponema), erythrocytes antigens phenotyping (Rhesus C, c, E, e, Kell, Duffy, Kidd, MNSs) and irregular antibodies screening and identification. Indeed, as clearly depicted in the exercise entitled 'Mapping of more stringent blood donor testing requirements' carried out by DG-SANTE in 2015, the most frequently reported additional tests performed in EU 28 are NAT testing for HIV, HBV, HCV, anti-Treponema and extended blood grouping [30], [31].

Testing measures combined with the additional interventions, in particular donor selection, leucodepletion and PI/PRT have definitely played an important role in improving the safety of blood components. However, as mentioned in section 1, over recent years the interventions have multiplied. Several cost analysis studies [29], [33], demonstrate that each additional intervention implies adding significant cost to blood components not always with an additional safety value. It has to be noted that this may vary depending on the epidemiological situation of the country and the infectious profile of the studied pathogen.

Policy makers and society are willing to accept additional costs to achieve greater blood safety. This is greatly influenced by the precautionary measures, perceived risks and the HIV episodes that affected Europe in the 1980s.

Also, emphasis is placed on TTI; it has also been observed in audits performed by the EDQM, that many BEs still continue performing ABO, Rhesus testing on all donors and Irregular antibodies screening on donors with no history of pregnancy and transfusion.

In view of this, it can be concluded that although the Directives have increased the safety of blood components, the precautionary principle remains very much predominant in today's interventions. Reflection should take place on the acceptability of multiple safety measures and their cost-effectiveness while considering the regional epidemiology with regard to each TTI. New legislation should allow permissible measures that would be proportionate to the risk. Cost-effectiveness- and risk-based safety interventions should underpin the new blood legislation. On this basis for example, a screening strategy in combination with PI/PRT may be considered in an area at high risk whereas screening strategy alone would be acceptable in less risky areas. The decision to opt for a given intervention should be supported by scientific data and demonstrate that the end result leads to equivalent safety measures across Europe.

The EDQM proficiency testing programme has demonstrated that blood screening laboratories have an overall good performance. Although they remain very rare, failures in proficiency testing are often related to the sensitivity of the assays used and to the inappropriate validation of the assay (preliminary data).

1 These observations will be further investigated but provisions could be laid down to ensure
2 BEs use sensitive techniques and use minipool/Individual Donation NAT testing in the light
3 of the regional epidemiology of a given TTI. In addition to general provisions, actions need
4 to be taken to develop guidelines on process validation and qualification of
5 premises/equipment. This shortcoming is currently tackled as part of the EDQM B-QM
6 programme, in which a certain amount of training and the development of guidelines about
7 these subjects are planned, in a very similar way to what EMA is doing in the
8 pharmaceutical field.

9 Lastly, other safety issues such as bacterial contamination require attention. Currently, no
10 provision with regards to bacterial testing exists in the legislation whereas the CoE Blood
11 Guide lays down requirements on bacterial testing, highlighting again the need to consider
12 referring to the Guide in the legislation.

13 ♦ **New Technologies**

14 Reviewing testing methods used in the EDQM proficiency testing scheme shows that over
15 recent years a considerable automation of blood serological, NAT and immune-
16 haematological testing has taken place associated with computerising systems for the
17 management of results. The same has occurred in other areas of activity e.g. collection,
18 processing, storage and distribution with the introduction of PRT or cold chain equipment as
19 highlighted in section 1 of this document. These significant developments are currently not
20 reflected in the EU legislation while they are addressed to some extent in the CoE Blood
21 Guide.

22 ♦ **Quality Systems (QSs) provisions**

23 Implementation of a QS is required by the EU legislation and is prescribed in the CoE Blood
24 Guide. The objective of a QS is to ensure that all processes performed consistently in an
25 organisation, are under control and continuously improved. When applied in a BE, a QS
26 should be regarded as a set of interacting processes and actions intended to direct and
27 control an organisation towards quality. It should encompass quality, Quality Control (QC),
28 Quality Assurance (QA) and Continuous Improvement [34]. It should cover the following
29 processes: Donor Selection, Blood Collection/Testing/Processing/Issuing/Distribution;
30 General Quality Management & Organisation; Management of Personnel; Contract
31 Management; Management of Quality Documents; Equipment/Material/Premises; Change
32 Control; Non-conformance (NC)/Corrective and Preventative Actions (CAPAs); Management
33 Review; Internal auditing and Risk Management.

34 However, the concept of QM has only been applied in BEs very recently due to a shortage of
35 public funding, compounded by poor access to training in the field and a lack of interaction
36 with the pharmaceutical industry. Data obtained in 2012 [35] shows that QS is often
37 regarded as a burden and has not been widely implemented among BEs.

1 The concept of quality has evolved greatly over the last decade, which might partly explain
2 the situation. BEs are still working in a reactive environment which is driven by the
3 implementation of a Quality Assurance (QA) based system, whereas nowadays the
4 implementation of Quality Management (QM) has become the standard.

5 To implement QS, until recently European BEs were most commonly using the following
6 standards and guidelines [35]:

- 7 • The CoE Blood Guide;
- 8 • ISO 9001;
- 9 • ISO 15189;
- 10 • EU Good Manufacturing Practice (GMP).

11 While all these standards are useful for the implementation of a QS, they are very different
12 in their content and scope. In addition, with the exception of the CoE Blood Guide, they do
13 not specifically target BEs. Approaches taken in this field also vary from one country to
14 another and even within the same country. It has been observed that many European BEs
15 focus only on the quality of their product, i.e. defining quality purely as the degree to which
16 component characteristics fulfil requirements. The lack of a harmonised European approach
17 renders the implementation of a QS a tremendous challenge and in particular for those BEs
18 that provide plasma to the industry.

19 In a more recent survey [14] the EDQM examined the current level of implementation of QS
20 in European BEs. From this survey it can be concluded that the EU legislation has been
21 effective in levelling off/improving the QS of EU and non-EU countries using the EU blood
22 legislation. However, harmonisation is still required in various areas. In addition, other data
23 from the same survey have highlighted that BEs were predominantly encountering
24 problems in implementing management and continuous improvement processes. This
25 situation can be attributed to the fact that the EU legislation is essentially quality and
26 product- oriented rather than QM oriented. This was also confirmed through the audits
27 performed by the EDQM. The majority of the non-conformities found were indeed related
28 to management and continuous improvement requirements which shows that systems are
29 still QA based. More specifically, non-conformities related very often to the disinfection of
30 the venepuncture site, management of the cold chain, validation/qualification of
31 assays/equipment, risk management, thus underlying shortcomings with regards to the
32 implementation of certain quality provisions laid down in the legislation. The extent to
33 which requirements are implemented and technologies and processes validated, vary
34 considerably from one BE to another. These shortcomings cannot be addressed in the EU
35 legislation. The development of high-level guidance and training, as EDQM is doing, is thus
36 needed and is to be given the same status as is given to EMA guidance.

37 In addition, it is likely that the implementation of the recently developed GPG within Europe
38 will help BEs to better implement management and continuous processes and switch from
39 QA to a QM oriented system. For this reason, the GPG should substitute Directive
40 2005/62/EC and QS requirements laid down in the Mother Directive.

1 Given the increasing relevance of QMS, the complexity of the activities undertaken and the
2 difficulties in implementing all standards applicable in this field, the extent to which QS
3 requirements are to be applied is to be tackled in specific guidelines – such as the EDQM is
4 currently doing within the B-QM activity.

2.1.4. Underpinning principles and their implementation

2.1.4.1. Self Sufficiency

5 As highlighted in the first part of this report, plasma self-sufficiency is currently becoming a
6 growing concern. Although the EU legislation is calling for plasma self-sufficiency in its
7 preamble, there is ongoing concern about the dependency on US plasma obtained from
8 paid donors for the production of PDMPs, and its potential consequences. The provision laid
9 down in the legislation had indeed led to negative unintended effects due to its
10 incompatibility with the EU internal market and procurement prerogatives. Indeed, PDMPs
11 are considered as goods and on this basis, the provisions of the TFUE with regard to the
12 internal market are superseding the prerogative of achieving a high level of public health
13 safety.

14 As highlighted in a EDQM survey [14], a large volume of recovered plasma is discarded. BEs
15 reported that often plasma does not meet the quality or the safety requirements (for
16 instance, the requirement imposed by fractionators in the Plasma Master File (PMF), as a
17 result of non-compliant epidemiological data) and as a consequence is not suitable for
18 manufacture. This information matches the information collected from BEs during audits
19 performed by the EDQM. There is thus the need to pursue operational quality programmes
20 such as the B-QM programme to help BEs raise standards to allow recovered plasma to be
21 used for fractionation and increase access to fractionation facilities.

22 Additional reflection is needed, and actions are required in order to explore ways to achieve
23 EU self-sufficiency; e.g. the legal status of Substances of Human Origin (SoHo) should be
24 revisited, and domestic fractionation for national use, currently hindered by the EU
25 procurement law, should be allowed on public health grounds.

2.1.4.2. VNRBD

26 From the various surveys performed within the EU countries [14], [19], it can be concluded
27 that MSs have widely endorsed the VNRBD concept. Despite this, a broad range of
28 incentives are in use in the EU and provisions in place to regulate VNRBD are not fully
29 harmonised. The VNRBD concept is promoted by a plethora of organisations, in particular
30 the CoE and the World Health Organisation (WHO). Its scientific and ethical relevance has
31 been well established. Nonetheless, clarification of the concept as well as defining
32 incentives that are scientifically and ethically acceptable and compatible with altruistic
33 behaviour is urgently needed. Recent studies have demonstrated that some incentives may
34 be considered ethically acceptable [36], [37].

1 Furthermore, the effect of each type of incentive is also to be scrutinised in the light of
 2 current and potential, new epidemiological situations and safety measures adopted by MS.
 3 Besides patient safety and ethical considerations, the risk for the donor (e.g. high frequency
 4 donation due to inappropriate incentive) and the socio-economic situation of the country
 5 should be evaluated so that donors are not exploited. Finally, over-cautious measures
 6 should be avoided to prevent the supply of blood components being impacted, especially in
 7 a time where the attitude of donors towards donation is changing – blood donation tends to
 8 be perceived as a right rather than an altruistic behaviour.

9 With a view to joining efforts and having a convergent approach, consideration should be
 10 given to the current work performed by the CoE Committee on Bioethics (DH-BIO).

11 It is worth mentioning that for instance VNRBD is formulated as a non-legally binding
 12 statement in the recitals of the Directive. In the substantive part of the Directive under
 13 article 20(1) MSs are only ‘encouraged’ rather than required to ‘take all necessary
 14 measures’ to ensure that ‘blood and blood components are as far as possible provided
 15 from’ VNRBD. In preparation for a possible revision of the Directive, the proposal to adopt
 16 VNRBD as a legally binding requirement should receive careful consideration.

2.2.Coherence with other legislation

17 Besides the need to clarify the legal status of SoHO (i.e. good versus public health resource),
 18 better coherence between the blood legislation and the legislation listed below is needed.

19 A brief gap analysis is provided below:

20 Tissue and Cells Directives

21 **Structure**

- 22 • The structure is slightly different;

23 **Definitions**

- 24 • Additional terms are defined;

25 **Regulatory borderlines**

- 26 • Absence of regulation for borderline products (e.g. PRP, eye drop)

27 **Oversight provisions –inspections and authorisation**

- 28 • Tests are to be performed by ‘qualified laboratories accredited,
 29 designated, authorised or licensed by the competent authority’ in
 30 contrast to blood laboratories;
- 31 • Provision of information on results of inspections and control measures
 32 upon request of a MS or the Commission is possible;
- 33 • Guidelines are to be established concerning the conditions of the
 34 inspections and control measures, and on the training and qualification
 35 of the officials involved in order to reach a consistent level of
 36 competence and performance;

37 **Donor selection provisions**

- 38 • Donor selection provisions are diverging;

1 **Blood establishment or hospital blood bank provisions**

- 2 • Provisions for quality are more quality management oriented whereas
3 they are more quality assurance oriented in the blood legislation;
4 • Manufacturing standards are diverging;

5 **Other**

- 6 • Donor consent and export/import of TC is addressed whereas this is not
7 the case in the Blood legislation;
8 • VNRBD is addressed in a different manner;

9 **Pharmaceutical legislation**

10 There are some inconsistencies between the Blood and pharmaceutical EU legislation with
11 regards to the regulation of plasma processing and the definition of an industrial process.

12

13 **Communicable disease**

14 Absence of reference to the communicable disease legislation in the SoHO legislation and to
15 what extent the communicable disease legislation is applicable in the field of SoHO;

16 Definitions for new TTI based on the communicable legislation are not foreseen.

17 **Data Protection legislation**

18 Absence of reference to the new data protection legislation and to what extent the new
19 data protection legislation is applicable in the field of SoHO;

20 **Medical devices legislation**

21 Absence of reference to the new medical devices legislation and to what extent the
22 legislation is applicable in the field, especially when it comes to a medical device vigilance
23 alert applicable to the SoHO field and its reporting.

24 **Cross-border healthcare Directive**

25 Absence of reference to the cross-border directive and to what extent the legislation is
26 applicable in the field;

27 **EU charter on fundamental rights**

28 The prohibition on making the human body and its parts as such a source of financial gain, as
29 laid down in article 3 of the EU charter, is not coherent with article 20 of the Mother
30 Directive, which only encourages voluntary unpaid donations.

31

32 With a view to avoiding litigation cases and facilitating the ruling of court cases, better
33 coherence is needed and a better delineation of the scope of the above-mentioned
34 legislation in the field of SoHO is also needed.

2.3. EU Added Value

35 The EU blood legislation has undeniably created added value. The EU legislation stimulated
36 work sharing, networking and the creation of EU projects and thus has accelerated what
37 would not have been achieved at national level.

- 1 Work sharing and networking has at the same time led to a lack of convergence of projects.
- 2 In this respect a better definition of the governance of key stakeholders in the field of blood
- 3 would be welcome to avoid duplication and to make best use of resources.

3. Conclusions

- 1 The results obtained from EDQM activities combined with desk research demonstrate that
2 the current legislation in the field of blood transfusion requires careful scrutiny as this
3 sector is currently facing many socio-economic, ethical, scientific and technical challenges.
4 The implementation of the EU blood legislation has definitely contributed to improving the
5 safety and quality of blood components within the EU and beyond, and consequently met
6 its initial objective. Its scope remains valid, even though it is still not clear under which legal
7 framework some so far qualified borderline products fall.
- 8 The evaluation of the effectiveness of the technical provisions of blood legislation shows
9 that these provisions have been very much patient- and product-oriented and have not kept
10 pace with latest developments in the field. As a consequence, over time some aspects such
11 as donor safety have been overlooked, which has negatively affected donor management.
12 In addition, a number of provisions are subject to interpretation or their extent is not
13 adequately delineated, preventing their adequate implementation.
- 14 Safety measures have multiplied based around the precautionary principle without any
15 thought on their cost-effectiveness and their degree of impact on the risks.
- 16 Qs have been implemented although they remain quality- rather than QM- oriented.
- 17 The EU internal market prerogatives have hindered the achievement of an EU self-
18 sufficiency – in particular for plasma used for the production PDMPs – making the EU largely
19 dependent on US plasma. While the VNRBD or VUD concept is well endorsed by almost all
20 EU MSs, its practical endorsement greatly varies between MSs
- 21 Finally, due to its rigid framework, the EU blood legislation has not been able to keep pace
22 with the latest scientific and technical developments.
- 23 The evaluation thus reveals that a reshaping of the EU legislation in the light of current and
24 upcoming trends and challenges in the blood sector is needed:
- 25 - First of all, a switch of the objective of the legislation towards harmonisation should
26 be considered with a view to implementing an equivalent level of safety across the
27 EU;
 - 28 - The terminology or wording employed should become unambiguous in order to
29 reach a common understanding. Harmonisation of definitions across key
30 stakeholders is also recommended;
 - 31 - Evidence-based donor eligibility criteria combined with donor protection would
32 prevent unnecessary deferrals and ensure appropriate donor management;
 - 33 - A risk-based and cost-effective approach rather than a precautionary based
34 approach should form the basis of a new legislation.
 - 35 - With the objective of ensuring that EU legislation remains evidence-based and
36 continuously reflects latest scientific and technical developments, the adoption of
37 the CoE Blood Guide, as a dynamic reference in the legislation, is proposed.

- 1 - To ensure a proper delineation of the extent to which technical requirements are to
2 be implemented and to standardise their implementation, development of high-
3 level guidelines is needed; for example those developed under the EDQM B-QM
4 programme could be recognised;
- 5 - Conduct of operational projects such the EDQM B-PTS and B-QM programmes with a
6 view to harmonising practices and developing evidence- and risk-based guidelines
7 should be continued;
- 8 - The incorporation of the CoE Blood Guide together with the development of high-
9 level guidelines would have beneficial impact on the sharing of uniform good
10 practices, and could help to increase the plasma supply and decrease plasma
11 wastage.
- 12 - The inspection procedures should be harmonised in MSs to instil greater confidence
13 in BEs and facilitate cross-border exchanges;
- 14 - Barriers that prevent EU self-sufficiency should be identified and ways to achieve it
15 enforced. Scrutiny of the real need in PDMPs through 'Patient PDMPs Management'
16 projects, such as the EDQM Wildbad Kreuth initiatives, could be explored together
17 with the development of strategic independence and diversification of the supply
18 chain;
- 19 - VNRBD should continue to be an underpinning concept but its practical
20 implementation requires better delineation in the light of current ethical,
21 epidemiological and societal challenges.
- 22 - Cost-effectiveness analysis and risk-based approaches should underpin the new
23 legislation to facilitate and encourage MSs to opt for the most adequate safety
24 measures.
 - 25 ○ Diverging policies should not necessarily result in diverging component
26 quality but to equivalent residual risk.
 - 27 ○ Thus the concept of 'equivalent measures' should underpin the new blood
28 legislation to facilitate import/export of components and following the cross-
29 border directive.
- 30 - Better coherence and delineation of the scope of EU transversal legislation within
31 the SoHO legislation is required;
- 32 - Convergence of projects undertaken by key stakeholders and delineation of their
33 responsibilities and governance would avoid duplication and allow best use of
34 resources.

35 A satisfactory, safe supply of blood components and plasma for the production of PDMPs
36 needs to be guaranteed through an evidence-based, risk-based and flexible EU legislation.

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