EUROPEAN
BLOOD
ALLIANCE

EBA response to Call for evidence on
EU rules on medical devices and in vitro diagnostics

The European Blood Alliance (EBA), representing public and non-profit blood establishments in 29 countries in Europe, welcomed the MDR and IVDR and their decisive contribution to a more harmonised framework across Europe, which we believe can lead to an improvement in the quality and performance of medical devices and in vitro diagnostic medical devices.

The safety and quality of these devices is absolutely paramount and must remain a priority to any future changes to this legal framework.

However, we stress that the implementation of the current MDR and IVDR raised many challenges and had unintended consequences which impact blood establishments today and are expected to continue doing so in the future. These issues must be addressed as soon as possible.

The need for a simpler and more coherent system

The current CE-marking system, relying on notified bodies, has shown its limits. The transition period was extremely problematic and despite a recent improvement of the situation due to increased capacity, the system remains fragmented, lacks consistency of practice and, in some notified bodies, specific expertise.

Ultimately, the additional complexity and costs the new system introduced is having a considerable impact in the access to MDs and IVDs. Several European blood establishments have already been notified by their suppliers of the cessation of production of several products.

On IVDs in particular, blood establishments are concerned about class D devices, as the future extent of availability of these devices following the transition period remains unclear, amid a slow recertification rate and what seems like a loss of interest from manufacturers of certain IVDs given the complexity of the process. For example, some manufacturers have already announced production stoppages for some solutes and our members fear they will shift investment away from key niche areas like emerging viruses.

Our members are also concerned that this trend will lead to more situations of (quasi) monopoly, with less choice on the market, which could increase the risk of shortages in the absence of alternatives, or force establishments to use less-optimal products with an impact on quality of care.

Finally, the MDR and IVDR exist in a wider legal framework and this raises additional challenges. EBA would highlight in particular the new SoHO Regulation and the ECDC and EDQM guidelines that establishments must comply with to meet the regulation standards. We stress the need for a close coordination between the two systems, to ensure optimal implementation of the rules and that legal complexity and costs are limited as much as possible.

Given this context, and despite the recent increase in the capacity of notified bodies, EBA remains convinced that the EU must work towards the establishment of a pan-EU body for MDs and IVDs, with a role similar to the one played by the European Medicines Agency with regards to medicines.

The specific concern with article 5 of the IVDR

We remain concerned that in some very specific situations of rare blood conditions, the implementation of article 5 of the IVDR will be detrimental to the interests of some patients.

Some niche blood conditions require very particular protocols only available in reference laboratories for immunohaematology. The testing for these conditions occurs only very sporadically, always beyond first- and second-line testing. When confronted with these rare situations, searching the market for the right IVD represents a very unpractical and unreasonable use of the clinicians' time and resources, especially when compared to using in-house devices. It is also important to stress that, when and if identified, the cost of CE-marked solutions for such unique cases often makes them virtually prohibitive, for instance when having to genotype tens of thousands of blood donors.

Should establishments be required to follow the current rules set out in article 5 paragraph 5 (d), (e), (f), (g), (h) and (i), the time required for each very singular and different process, and the additional cost it represents, would effectively mean that the tests would not be carried out. This would also impact rare blood-type patients who develop antibodies against very common erythrocyte antigens and therefore need blood from rare donors who do not have the corresponding antigen. It will also severely impact individuals in need of complex case investigation at reference laboratories for immunohematology. We are annexing to this evidence more information on the process and costs involved in this, which we hope you will find useful.

In addition to this, blood establishments have experience with in-house solutions which are both cost effective and a match for patients' needs in terms of accuracy (both specificity and sensitivity). They also have experience with existing commercial solutions that are lower quality and do not exactly match patients' needs. As rules in article 5 stipulate that the onus to prove that in-house devices are more suitable and effective will fall on blood establishments, we are concerned this will be a complex process that may impact negatively laboratories' capacity to meet the needs of these patients.

There are commercial serological reagents available for typing of about 25 antigens and (uncomplicated) determinations of antibodies directed to them, and blood establishments have expressed concerns about the increasing prices of some of these commercial serological reagents (e.g. anti-Coa). Additionally, blood establishments are concerned that many manufacturers have stopped producing antisera because they rely on human sources which can be unreliable, and it seems this is no longer economically attractive. There are 393 known antigens on red cells giving rise to many different antibody specificities, beside autoantibodies and other conditions interfering with standard serology, and there are no commercial solutions for the majority of these problems. It is the community of scientists, serologists and physicians in these

reference laboratories that exchanges samples and in-house devices, that have red cells with rare blood group phenotypes, rare antibodies or other substances useful for the investigation of complex serological problems, saving lives in the process. The current rules in article 5 paragraph 5 (a) of IVDR will simply make some of this joint work impossible in Europe. More generally, it would stifle the innovation developed inside and between these reference laboratories for immunohaematology when these extremely rare cases present themselves.

In conclusion, it is not in the benefit of patients with these rare conditions, or the public interest, for establishments to follow the current IVDR rules and we call for letters (a) and (d) through to (i) of article 5 paragraph 5 to be removed from the IVD Regulation at the next possible opportunity.

Annex – Process and costs of selected in-house IVDs at risk under current IVD rules
Examples from the Austrian Red Cross
1. Rare blood
Before the introduction of a cost-efficient high throughput genotyping project (testing 20,000 donors for 36 antigens), the laboratory had to type donors on demand on a 24/7 basis every time a patient with either antibodies to a High Frequency Antigen (HFA = a patient who needs a rare blood type), or with a combination of several (usual) antibodies to polymorphic antigens was referred to the reference laboratory. The process to type the laboratory's red cell unit inventory for suitable units required hours, sometimes even up to a day, and it was not possible to predict if or when it would be successful.

Presently, with the data of 20,000 donors, the equivalent of 0.75 million antigen types, the laboratory only needs to perform a database query to produce suggestions for suitable red cell units in less than one minute. The specific antigens are being confirmed using CE-marked reagents (if available).

The total reagent costs for the project (0.75 million results) was about 80,000 Euro. Commercial typing for less than 36 antigens would have costed 1.6 million Euro.
If the same laboratory is forced to use only CE-marked IVDs, the same budget of 80,000 Euro will only be sufficient to commercially type 1,000 donors instead of 20,000, far too few for it to be effective.

It is also very important to remember that this project is absolutely indispensable for around 20 patients per year. Commercial solutions would therefore raise reagent costs to about 10,000 Euro per case. Needless to say, no cost bearer would reimburse such costs and certainly not pre-finance a 1.6 million Euro typing project for such a small number of patients.

2. Complex case investigations in reference laboratories for immunohematology
have to safely differentiate potentially between mixed allo-antibody specificities to 393 known red cell antigens, autoantibodies, and other conditions which affect serological reactions. To do this they use a great variety of patient or donor cells (many of which are acquired by international rare cell

and fluid exchange programs), methods, protocols, enzymes and chemical modifiers. In total a reference laboratory may store and use thousands of cells and sera, hundreds of reagents and protocols.

For each complex case only a handful of suitable cells and protocols are identified and used. Most of these are not on the market or if they are, they do not meet all specific requirements.

Even with the current existence of some reagents in the market, these would always only be a small part of a complex investigation, which is unique for each patient. Because the laboratory only finds out what each patient needs at presentation, there is no time to go through the purchase process on demand. Such additional complexity and constraints mean that, should the new IVDR rules remain in place, laboratories might not be able to provide the necessary testing in these situations.

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About EBA

Created in 1998, EBA represents public and non-profit blood establishments in 29 countries in the EU, EFTA and the UK, who work together in the interests of donors and patients to:

- contribute to the availability, quality, safety and cost-effectiveness of the blood and tissue supply for the citizens of Europe by developing and maintaining an efficient and strong collaboration amongst European blood and tissue services;

- increase public and professional awareness of voluntary and non-remunerated donation (VNRD) of blood and blood components, and of preparation of blood components as an indispensable therapeutic means to help patients;

- assist European blood establishments to continuously improve their performance, based on scientific and ethical principles for the benefit of patients.

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