ESC
European Society of Cardiology

BioMed Alliance

Opinion prepared on behalf of the BioMed Alliance concerning

Scientific bodies under the new EU medical device legislative framework

(European Commission Joint Research Centre, Draft technical report, July 2018)

10 September 2018

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1. Background

The Health Technologies group in the Consumer Products Safety Unit of Directorate F (Health, Consumer and Reference Materials) of the Joint Research Centre of the European Commission has asked stakeholders to comment on the implementation of the new scientific advisory structures required by the EU Regulations on Medical Devices and In Vitro Diagnostic Medical Devices that will come into effect from 2020 and 2022 respectively. It requested a combined opinion from all medical specialties and professional associations in Europe, if possible.

There are many medical professional and scientific associations in Europe, but to our knowledge there are only a few bodies that could coordinate advice in this field for regulators in the European Commission.

The **European Union of Medical Specialists** (UEMS) is the doctors' organisation that is recognised officially by the European Union. It represents the interests of physicians from 40 national member organisations, for example concerning medical education and professional qualifications, and it has 43 specialist sections each related to a recognised medical specialty. Its list of officially recognised medical specialties in Europe is available via the following link:

https://www.uems.eu/about-us/medical-specialties

The UEMS is not particularly engaged with scientific matters or regulatory affairs relating to pharmaceutical agents and medical devices but it is the organisation that deals with conflicts of interest, for which it sets the relevant rules. Furthermore, it is the only European legal entity that currently coordinates all medical specialities, so it is able to achieve consensus in medical affairs when more than one medical specialty is involved.

The Scientific Panel for Health is an independent committee of scientific experts each appointed in their personal capacity to advise the European Commission and DG Research about the EU Horizon 2020 programme [https://ec.europa.eu/programmes/horizon2020/en/h2020-section/scientific-panel-health-sph]. The **Federation of European Academies of Medicine** (FEAM) is also concerned primarily with biomedical research; it coordinates scientific advice to the European Commission from its 18 member Academies [https://www.feam.eu/].

The **Alliance for Biomedical Research in Europe** (BioMed Alliance) has 29 members, all of them scientific and professional medical associations which are active in all aspects of their specialties across the whole of Europe. It was created in 2010 to establish a mechanism for biomedical and clinical researchers to provide a collective voice to the European Commission in support of medical research. Its objectives have recently been expanded to include other shared concerns which are relevant for biomedical societies in Europe. ["The Association's principal goals and objectives are to promote the best interests and values of researchers and of healthcare professionals, organised in non-for-profit scientific medical associations and organisations across all medical disciplines in Europe, in those general areas where common interest is identified."]

The **European Society of Cardiology** (ESC) has been engaged with regulators throughout the process of review and revision of the EU medical device directives, leading to the adoption of the new EU Regulations in May 2017. It organised a meeting of medical professional associations with regulators from the European Commission on 21 March 2018, at the ESC Office in Brussels

(the European Heart Agency), in order to expand the number of medical associations engaging in the new structures. A report and slides from the presentations at that meeting are available:

https://www.escardio.org/The-ESC/Advocacy/Shaping-policy-and-regulation/engaging-with-the-new-european-regulatory-landscape-for-medical-devices

2. European Commission / Joint Research Centre consultation on scientific advisory structures

At the request of the Joint Research Centre of the European Commission, this response has been coordinated by the Advocacy Division of the European Society of Cardiology in conjunction with the secretariat of the BioMed Alliance. The EU consultative documents were circulated to all members of the BioMed Alliance and to associations and individuals who attended the meeting in March 2018. Other medical associations were approached by personal contact. The major respondents are listed in Appendix 1; some comments were received from 16 BioMed members.

Many associations stated that the period of consultation, over the summer vacation, made it difficult for them to consult thoroughly with their members and thereby to provide detailed and comprehensive answers. Most associations would welcome further opportunities to develop their responses and to collaborate with regulators in establishing efficient and effective scientific advisory structures for the evaluation of medical devices.

3. Specialisation of expert panels on medical devices (Section 1 of the consultation)

The distribution of panels should reflect the expected workload. An estimate can be based on the experience of the Food and Drug Administration in the USA (personal communication from Dr Jeffrey Shuren, Director of the Center for Devices and Radiological Health, FDA, on 29 June 2018; attached as Appendix 2). There are no data available in the public domain in Europe that would allow us to make a more informed prediction for expert panels in Europe.

Cardiovascular devices are likely to form the single largest group of high-risk medical devices undergoing the new scrutiny procedure, in which case two or more subspecialist cardiovascular panels could be established, to share that workload. Natural groupings would include devices for structural heart interventions, and percutaneous and surgical treatment of heart valve disease; cardiac surgery, cardiopulmonary bypass equipment, extracorporeal membrane oxygenation (ECMO), left ventricular assist devices, and artificial hearts; percutaneous devices for treating vascular disease including stents, bioresorbable scaffolds, intravascular diagnostic devices, and thoracic endovascular aortic repair (TEVAR); and active electronic devices such as pacemakers, resynchronisation therapy, implantable defibrillators, and implantable diagnostic monitoring devices.

This incomplete list of high-risk medical devices within one system illustrates the challenge of composing groups of experts who would have the expertise necessary to review a range of devices. When the call from the European Commission is announced for applications for members of expert panels, the aim should be to recruit a very large pool of experts drawn from basic science and engineering (including materials chemists, electronic engineers, experts in fluid

dynamics, biomedical scientists, etc), informatics and computing, epidemiology and statistics, and from all clinical disciplines. Each panel could then be constituted with the mix of specialists required to review particular application(s). Medical advice should be available to determine the academic expertise needed in each case, or to advise on the selection proposed by regulators.

There has been strong representation from paediatric specialists that there should be a separate expert panel to review applications concerning high-risk medical devices intended for use in babies and children. That would be appropriate if justified by the workload. An alternative model would be for a member to be appointed to each panel who has a background in paediatrics, who could identify particular issues relating to a device with versions intended for use in all age-groups including children. For more details, please refer to Appendix 3.

The configuration of panels could vary as required for the applications under review. They could be composed of specialists within one medical field, or of specialists across all fields but knowledgeable about a particular age-group of patients and users, or of specialists across all clinical fields but expert in using a particular technology. Lay members should be included (see section 5).

3.1 Clinical Evaluation Consultation Procedure ("CECP")

Clinical areas where expert panels will be required for the Medical Device Regulation, include:

- Musculoskeletal system (especially orthopaedic devices; including rehabilitation medicine, and rheumatology)
- Cardiovascular devices
- Respiratory and anaesthetic devices (including intensive care)
- Neurological devices (or central and peripheral nervous system devices; overlap with devices and implants for hearing and vision; includes neurosurgical devices)
- Ophthalmology
- Dental devices, and implants (linked to maxillofacial surgery and implants)
- Endocrinology and diabetes (including insulin delivery systems)
- Obstetrics and gynaecology (including in vitro fertilisation; overlap with urology; depending on the workload this panel could also encompass nephrology/renal devices)
- Gastroenterology including hepatology and parenteral nutrition
- Renal disease (including dialysis systems)
- General surgery (could include laparoscopic and robotic devices; and surgical implants)
- Plastic surgery, and wound care (overlap with infectious agent testing/IVDs)

Note that these recommendations include modified terms and combinations from the list that was proposed, as well as some important systems that had been omitted (especially anaesthetic and respiratory devices). Subject to further consultation it may not be necessary to appoint a specific panel for ear, nose and throat devices (which accounted for 2% of the FDA workload), if high-risk ENT devices could be combined with neurology and/or maxillofacial surgery (or perhaps

with ophthalmology). Advice is needed also about the linkage of plastic surgical devices either with general surgery, or with wound care. A "general hospital" category may be unnecessary; depending on their number, "general" devices could be shared between other panels.

It is difficult to predict the combinations of expertise that may be needed in future to evaluate devices as they become more complex and specialised, and so evolution of the configurations can be expected. It is recommended that the call for experts should include a comprehensive list of all the types of devices for which it can be anticipated that special expertise will be needed.

Not yet included, but strongly recommended for consideration as topics for expert panels under the Medical Device Regulation, are:

- Specialist paediatric devices (see above); the body size of users has marked effects on the relevance and practicability of medical devices and in vitro diagnostics.
- Haematology devices (e.g. cell separation/plasmapheresis, cell therapy, devices for marrow transplantation, etc; some may be hybrid devices); if not allocated a separate panel, then this field will need to be combined with another panel.
- Radiological devices (for diagnostic imaging and radiotherapeutic devices in Class IIb, as well as other devices that emit radiation such as brachytherapy and implanted radiation-emitting devices); their review would need a specific combination of experts including physicists, radiation oncologists, radiation protection experts, and software engineers. This panel could also serve a useful advisory role concerning standards and evaluation for all diagnostic imaging devices.

Expert panels to review non-clinical topics (i.e. not systems-based) should include:

- Software, artificial intelligence, and machine learning (but note that aspects of these are likely to be relevant to most of the clinical systems-based panels too; for example, cybersecurity is relevant especially to cardiac implantable electronic devices). Responsibilities for this panel may need to include the evaluation of apps that are classified as high risk because they are used either to drive clinical management or to diagnose or treat disease, with potentially serious or critical consequences if they do not perform as intended (using the definitions given in the recent IMDRF guidance document [1]).
- Innovative technologies (since some developments may not fit into existing categories).

"Bioinformatics" could be reviewed in other panels as appropriate, for example if it refers to diagnostic software integrated with drug delivery, or with estimating prognosis; this topic may not be necessary as a separate expert panel.

3.2 Performance Evaluation Consultation Procedure ("PECP")

Expert panels for in vitro diagnostic medical devices in Class D, should include:

[1] International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Clinical Evaluation. 21 September 2017. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf

- Blood groups and tissue typing (could encompass other haematological tests, such as devices for home anticoagulation testing)
- Microbiological in vitro diagnostic tests / infectious agent testing (could include devices for infection control)
- Immunological tests (could be combined with haematology)
- Clinical chemistry and toxicology (including biomarkers) (including home blood glucose monitoring)
- Cytology and pathology (overlap with biomarkers, genetic tests, and future overlap with computer vision and machine learning)
- Molecular and clinical genetic tests
- Companion diagnostics (to predict individual responses to treatment, for the future practice of personalised medicine, especially for cancers) (overlap with genetic tests and biomarkers)

3.3 ***Priorities for the designation of expert panels***

The grading of relative priorities (0 – 10, see question 1a) is impossible; in each field and for any individual patient requiring a particular high-risk medical device or needing a class D diagnostic test, the priority for expert advice to be available will always be 10.

4. Workload of panels, and time commitment of experts (Sections 2 and 3)

The letter from the FDA indicates that expert reviewers are given 1 month to read material in preparation for a panel meeting, requiring an estimated total of 10 – 15 hours. They then attend a meeting for 10 hours, once or twice per year.

Responses from European medical associations suggest that a maximal realistic commitment from reviewers would be 2 days/month (one day to review material, one day for an internet-based or face-to-face meeting) (i.e. 5% of working time, rather than 10% as proposed). For some panels, a meeting 1-2 times per year would be sufficient. A 3-year term of office was suggested.

These figures imply that the timescales for responses to manufacturers and/or notified bodies given in the E.U. Regulations may be unrealistic, possibly unattainable. It will be impossible for panels to meet face-to-face to consider each request for scrutiny, within 3 weeks; some system of shared electronic scrutiny will be needed, with review by selected members acting on behalf of the full panel. Revision of the system, perhaps even legal amendments, may be required as experience accumulates of how the system is functioning. Much will depend on the professional expertise and manpower available for the central coordination of the whole process.

5. Composition and size of expert panels (Section 4)

It is difficult to give one single answer since the composition of each expert panel may vary according to its tasks designated for consideration at a specific meeting.

There should be an appointed chairperson/coordinator, and an alternate/deputy, for each designated panel. Either could chair a meeting.

There may be a core of permanent members of each panel, which can be supplemented by specific expert advisors on an *ad hoc* basis, depending on the devices under review. Some flexibility of membership for each meeting may be essential if the time limits for response that are set in the Regulations are to be met.

Expert panels may meet to review specific requests for advice from manufacturers, and to scrutinise dossiers submitted by notified bodies. Panels meeting to fulfil these tasks should include a wide range of experts (see also paragraph 3 of section 3 above), including basic scientists/engineers, clinical experts, and a statistician. Members of the public/patients/users should be included. A typical panel might have 10 – 15 members.

Expert panels may also meet to provide advice to regulators, concerning standards and device-specific guidance, and for horizon-scanning. One meeting each year for each panel could be allocated for these and other more general tasks. The need for EU standards cannot be assessed until the panels have been established and gaps in regulatory guidance are identified. Reviewing dossiers and Clinical Evaluation Assessment Reports from notified bodies will highlight which ISO standards are being used for reference; those should be available also to the expert panels for consultation. The landscape may change if more global standards are developed by the International Medical Device Regulators Forum (IMDRF).

It would be helpful if the chairpersons of all panels could meet together with regulators and with representatives from notified bodies, perhaps once per year, to benchmark workloads, audit performance, and review the decision-making process, in order to advise about the optimal structures and working methods of the system of Expert Panels.

Finally, it is recommended that there should be designated capacity within existing structures, or else at a special forum, for all scientific and medical professional associations to advise the European Commission and EU national regulatory agencies on strategic issues relating to the evaluation of medical devices.

6. Managing potential conflicts of interest (section 5)

It has been argued that some conflicts of interest in medicine are difficult to recognise and unavoidable and that all sources of possible bias cannot be abolished by disclosure.[2] These may include personal academic interests as well as formal links with industry, so 'competing interests' may be a more helpful and inclusive indicator of potential bias than 'conflicts of interest'.[3] Many scientists and clinicians with the expertise necessary to provide an authoritative review of a new medical device, will have worked with manufacturers or may have experience of evaluating

[2] Gelberman RH, et al. Orthopaedic surgeons and the medical device industry: the threat to scientific integrity and the public trust. J Bone Joint Surg Am. 2010;92:765-7. https://doi.org/10.2106/JBJS.I.01164

[3] Bruyere O, et al. The need for a transparent, ethical, and successful relationship between academic scientists and the pharmaceutical industry: a view of the Group for the Respect of Ethics and Excellence in Science (GREES). Osteoporos Int. 2010;21:713-22. https://doi.org/10.1007/s00198-010-1190-9

competing products. It is the collective opinion of the medical professional associations that a blanket ban on reviewers with any such links will be unwise; in some very new or very restricted fields, it may be very difficult to find reviewers with the necessary technical expertise who are not also involved in the development and early clinical evaluation of those devices.

European drug regulatory agencies have determined that conflicts of interest cannot all be eliminated but the risk of bias can be managed.[4] In general, the medical professional associations endorse the policies of the European Medicines Agency (EMA).[5,6] For chairmen of scientific advisory committees, no financial interests within the previous 5 years have been allowed; for committee members and experts, some links are allowed but with restrictions on the contributions that potentially conflicted advisors can make to the decisions of a committee. The general "cooling off period" for previous conflicts to lapse, has been set at 3 years.

The primary requirement must be full disclosure and transparency of any academic or clinical activities and/or links with companies and/or other relationships that could be perceived to influence decisions. These disclosures should be available in the public domain. Individuals with major links (such as patent holders) and/or major financial interests (using the definitions developed by EMA) should not serve as members of an expert panel, but if essential they could be consulted for advice on specific questions. Individuals with less strong or previous links, could serve as members of an expert panel, but those links should be disclosed to all other members. In the case of disagreement and the need for a vote, those with any interests relevant to the device under review should not participate. Permitting financially conflicted individuals to participate would be a basic flaw in the review procedure and a possible major limitation to achieving fair, independent and ethical review of new devices.

Most medical professional guidance in the management of competing interests has been developed in the context of continuing medical education [7] but similar principles would apply for the selection of experts to participate in the new advisory roles envisaged by the medical device regulations.

7. Qualifications and competences of experts, and selection criteria (sections 6 & 7)

Experts should be appointed because of their specialised knowledge. A balance of countries and parity of genders would be good but these should not be used as criteria to select members of expert panels. Some experience in regulatory affairs and/or the evaluation of devices would be an advantage (at least for some members) but it should not be an essential requirement; the only essential qualification is academic or technical experience in the relevant discipline.

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[4] Lexchin J, O'Donovan O. Prohibiting or 'managing' conflict of interest? A review of policies and procedures in three European drug regulation agencies, Soc Sci Med. 2010;70:643-7. https://doi.org/10.1016/j.socscimed.2009.09.002

[5] European Medicines Agency (16 June 2016). The European Medicines Agency Code of Conduct. EMA/385894/2012 rev.1. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004924.pdf

[6] European Medicines Agency policy on the handling of competing interests of scientific committees' members and experts. European Medicines Agency, 6 October 2016. EMA/626261/2014, Rev. 1. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216190.pdf

[7] Griebenow R, et al. Proposal for a graded approach to disclosure of interests in accredited CME/CPD. Journal of European CME 2015; 4:1. https://www.tandfonline.com/doi/full/10.3402/jecme.v4.29894

It is appropriate for the Joint Research Centre to consider the medical specialties listed in Annex V of Directive 2005/36/EC concerning the mutual recognition of professional qualifications. [8]

For the criterion of "scientific impact", the advice of the relevant professional associations should be sought, as they will often be best placed to judge the scientific impact of an individual's contributions. Only publications relevant to the topic or type of device should be considered. The support of scientific associations should be enlisted also to ensure that calls by the European Commission for applications to become experts are widely advertised.

The percentage representation of various disciplines in any particular panel will vary according to the type of device that is being evaluated. It is therefore impossible to predict in general terms which proportions of specialists will be needed in expert panels for all medical devices; that will be defined by experience.

The European Commission should offer a training programme for experts appointed to panels.

8. Decision criteria of expert panels (section 8)

Expert panels should determine if the application under review relates to a new device that is first-in-class, or if it is a new device where there are already alternative devices on the market. The panel should identify if the device meets a genuine unmet need, if it is an orphan device, and if its design includes new substances or constituents in contact with blood and/or tissues.

These preliminary judgements will determine the level of clinical evidence that should be available for expert review. They will help to determine if a device can be considered on the basis of equivalence to previous products, or if it must be reviewed *de novo* with new clinical evidence.

In the case of *in vitro* diagnostic medical devices, the expert panel should review the classification of the diagnostic test under consideration. Concerning medical software, the panel should review its functions and consider any risks to patients if the software does not operate as intended; it should then determine if it agrees with the manufacturer and notified body on the IMDRF risk category of the software.

All these judgements will determine the balance between benefit and risk that should be considered by the Expert Panel when it evaluates the clinical evidence that is presented. These steps will be essential in order to determine if a scientific opinion should be given concerning a particular dossier, and then again when the panel recommends to the notified body if an application for conformity assessment should be approved or if more evidence is needed before approval.

Expert panels must have the fullest information possible on the safety, performance and effectiveness data of the device, including the number of patients studied, the precise nature of the trial, the methods of follow-up, the length of follow-up, the number of patients lost to

[8] Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0036&from=EN

follow-up, the percentage completeness of follow-up and the number of follow-up years to permit calculation of adverse event rates. Expert panels should also be given all details of preclinical data, including animal studies if performed, all field experience adverse event data reported to the manufacturer, and all explant and autopsy data.

In practice, unless the expert panel can devote the same amount of time, personnel, experience and expertise to the evaluation of a new device that a competent and scrupulous Notified Body does, they will not be able to provide worthwhile scientific advice. Rigorous scientific evaluation of a potentially dangerous product is much more important than a rapid decision. It will be essential to audit this process carefully, so that the system can be revised if it becomes necessary to ensure that the public health is appropriately protected.

An expert panel may be asked to adjudicate on adverse events and serious incidents on the basis of few cases or relatively limited experience of a new device. It should therefore have authority to recommend to the notified body that it should require the manufacturer to collect additional clinical evidence (especially concerning safety) as an essential part of its agreed programme for post-market clinical follow-up; and it should be able to specify when those data should be presented to the notified body.

It is possible that there will be a difference of opinion between Expert Panel members and the experts already employed by notified bodies, either in-house in the case of larger notified bodies, or externally. It is not clear how any difference of opinion would be resolved.

9. Expert laboratories

The **European Federation of National Associations of Orthopaedics and Traumatology** (EFORT) reports that 160 per million inhabitants receive a total hip or knee replacement, and an equivalent number receive an implant during surgery for trauma, annually. This equates to > 3 million European citizens who receive a high-risk orthopaedic device every year. Currently, any failed implants that are retrieved, are analysed by manufacturers. EFORT strongly advises that retrieved and failed orthopaedic implants should be evaluated independently in an Expert Laboratory, without the participation of industry. It would help to establish such a Laboratory, with the support of experts from the orthopaedic and traumatology community.

The **European Society of Cardiology** recommends that a similar laboratory is needed for the independent examination and analysis of explanted cardiovascular devices, particularly heart valve repair and replacement devices, and cardiac implantable electronic devices and their leads. After independent investigation, devices should also be made available to the manufacturers.

The **European Society of Human Reproduction and Embryology** (ESHRE) advises that the composition of culture media that are used during the process of in vitro fertilisation (IVF) to maintain human embryos before they are transferred in utero, is unknown, since the commercial companies which produce them do not disclose this information. These culture media have the potential to cause epigenetic consequences, which therefore remain an unknown potential hazard. ESHRE recommends that its working group that is concerned with this problem (for contact details, see page 14) could help to establish a central laboratory to address it.

Thus the initial recommendations of the BioMed Alliance members for the fields of expertise of Expert Laboratories include:

- Orthopaedic devices: for the independent analysis of failed or explanted devices.
- Cardiovascular devices: for the independent analysis of explanted heart valves, heart valve repair devices, intravascular devices (such as stents), cardiac electronic devices and their leads, and other high-risk devices.
- Prosthetic heart valves: for accelerated testing of haemodynamic performance and endurance, using pulse duplicators. This is currently performed by all manufacturers, so an independent reference laboratory might not be necessary if the results of preclinical bench testing of new heart valve devices were made publicly available. This expert laboratory might also offer expertise in computational fluid dynamics so that manufacturers could submit the design of their new devices for an *in silico* evaluation of their flow characteristics.
- In vitro fertilisation (depending on the classification of the devices and procedures involved, this might either be a Reference Laboratory or an Expert Laboratory).
- Diagnostic imaging devices, in class IIb and class III, for issues such as radiation protection and safety, independent evaluation of physicochemical effects on biological tissues, and evaluation of performance using standard physical imaging phantoms. Ideally, an Expert Laboratory could also offer similar assessments to the manufacturers of class IIa medical imaging devices. Synthetic datasets have been developed by some medical associations in order to compare and report the performance of image processing algorithms used by different manufacturers.
- Computing and informatics: an expert laboratory should be designated for the independent scrutiny of software programs, from apps that are designated as medical devices to high-risk devices that use integrated software to control drug delivery. This laboratory would provide expert evaluation of the risk of software bugs that might influence the performance of a device, and an impartial review of issues such as encryption and cybersecurity.

Further proposals may be received once other medical professional associations have considered this question in detail.

10. In vitro diagnostic medical devices, and EU Reference Laboratories

The responses relating specifically to the Regulation on In Vitro Diagnostic Medical Devices have been fewer, so relevant medical associations were also contacted personally. All expressed interest in interacting with the Commission but need more time to develop detailed responses. For example, the BioMed Alliance member, the Federation of European Biochemical Societies (FEBS), is primarily a scientific society for biomedical researchers; the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has also been approached and its advice is awaited.

Biomarker assays are used increasingly to guide the personalised treatment of diseases. Using diagnostic tests to improve the selection of treatments tailored to individual patient profiles can improve outcomes and reduce side-effects. Incorrect results could lead to the administration of ineffective therapies or harm for the patient, so the tests must be accurate and highly reliable.

The **European Society of Pathology** (ESP) has listed the special diagnostic techniques that its members use, as electron microscopy, immunofluorescence, immunohistochemistry, molecular pathology, morphometry, enzyme histochemistry, tissue microarrays, and digital microscopy. The ESP has established an external quality assurance program for testing biomarker mutations in cancers such as colorectal cancer and non-small cell lung carcinoma, with the aim of ensuring optimal accuracy and proficiency in cancer biomarker testing across all countries.

This example illustrates that there may be substantial overlap of topics between expert panels established to evaluate in vitro diagnostic medical devices (see section 3.2 above), and that there may be many programs that could be relevant for an EU Reference Laboratory for class D tests. The optimal configuration of panels for the IVD regulation, and the best choice for reference laboratories, need to be developed during more detailed interactions with the relevant specialist associations. The implementation date of 2022 for the IVD Regulation should allow that.

The initial recommendation is that there should be (at least) one European Union Reference Laboratory in each of the fields for which there will be an Expert Panel (see section 3.2). This would allow for constructive interaction concerning standards, quality control, testing, and approval of Class D in vitro diagnostic tests.

The **European Haematology Association** (EHA) has identified the following fields as emerging technologies in haematological laboratory practice, which it considers should all be covered by Expert Panels and/or EU Reference Laboratories for IVD Medical Devices:

- next generation flow cytometry: multicolour flow, and automated non-supervised analysis software (i.e. machine learning)
- next generation sequencing (NGS) technology for oncogenic and immunogenetic markers, including markers used to monitor the effectiveness of treatment
- integrative diagnostic laboratory haematology (i.e. cytology with immunohistochemistry and conventional cytogenetics); fluorescence in situ hybridization (FISH) with genetic analysis of single nucleotide polymorphisms (SNP) and NGS, all integrated with artificial intelligence and automated computational diagnostic algorithms; and
- the development of cellular immunotherapeutic products (for example, immune monitoring of immunotherapies).

The EHA further recommends that the following combinations of fields of expertise in IVDs would be suitable for Reference Laboratories:

- blood grouping and tissue typing, linked with immunology
- human genetic testing, including companion diagnostics; screening, diagnosis or staging of cancer; screening for congenital disorders in the embryo or foetus.

11. Conclusions

The consultation initiated by the Joint Research Centre has triggered considerable interest amongst medical professional associations in Europe. The replies that have been received at short notice have been summarised here in order to provide initial feedback, but more considered responses from a larger number of medical specialties could be provided. We

recommend that the Joint Research Centre should organise a meeting for medical associations to review their conclusions and proposals following this consultation; the BioMed Alliance could help to ensure that invitations are sent to associations representing all medical specialties.

The scientific advisory structures for medical devices and in vitro diagnostic medical devices in Europe are a new venture. It will be important to conduct pilot exercises to test how they work, and then to adapt and develop the structures as experience is accumulated. While experts will be appointed in their personal capacity, European medical professional associations would like to be involved as advisers to regulators, so that they can identify and recommend qualified individuals from their networks of experts.

For these new structures to be successful, it is essential that the European Commission invests adequate resources.

Alliance for Biomedical Research in Europe

Appendix 1: Contact details for associations responding to JRC Consultation, August 2018

Medical devices

Organisation	Name	E-mail contacts
EASD European Association for the Study of Diabetes	Lutz Heinemann	Lutz.Heinemann@profil.com
EAU European Association of Urology	Jens Rassweiler	Jens.Rassweiler@slk-kliniken.de
ECTS European Calcified Tissue Society	Roberta Mugnai	roberta.mugnai@ectsoc.org
EFORT * European Federation of National Associations of Orthopaedics and Traumatology	Per Kjærsgaard-Andersen Rob GHH Nelissen	pka@dadlnet.dk R.G.H.H.Nelissen@lumc.nl
EORTC European Organisation for Research and Treatment of Cancer	Françoise Meunier	francoise.meunier@eortc.org
ESC European Society of Cardiology	Alan Fraser Eric Butchart Ilaria Leggeri Eric Bienefeld	fraserag@cf.ac.uk egbutchart@aol.com ileggeri@escardio.org ebienefeld@escardio.org
ESHRE European Society of Human Reproduction and Embryology	Roy Farquharson Arne Sunde	rgfarquharson@yahoo.com trondheimivf@gmail.com

Paediatrics † NIHR Children's Clinical Research Network and NIHR Children & Young People MedTech Cooperative (National Institute of Health Research, U.K.)	Paul Dimitri	Paul.Dimitri@sch.nhs.uk
European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)	Mark Turner	Mark.Turner@liverpool.ac.uk
European Network of Excellence for Paediatric Clinical Research (TEDDY)	Adriana Ceci	adriceci.uni@gmail.com

* EFORT has applied to join the BioMed Alliance

In vitro diagnostic medical devices

Organisation	Name	E-mail contact
EHA European Haematology Association	Elizabeth Macintyre BioMed Alliance Delegate Robin Doeswijk EU Affairs	elizabeth.macintyre@aphp.fr R.Doeswijk@ehaweb.org
FEBS Federation of European Biochemical Societies	Emmanuel Fragkoulis Chair of the Science and Society Committee	mfragoul@biol.uoa.gr
EFLM † European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)	Silvia Cattaneo	eflm@eflm.eu
ESP European Society of Pathology	Dina Tiniakos Raed Al Dieri	dtiniak@med.uoa.gr r.aldieri@esp-pathology.org

† not a current member of the Biomed Alliance (as of September 2018)

BIOMED ALLIANCE contacts

Position	Name	E-mail contact
President, Alliance for Biomedical Research in Europe	Axel R Pries Professor of Physiology and Dean of the Medical School, Charité Hospital, Berlin	axel.pries@charite.de
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EUROPEAN SOCIETY OF CARDIOLOGY contacts

Position	Name	E-mail contact
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BIOMED ALLIANCE MEMBERS (at 1.9.2018)

	BioMed Member
1	European Academy of Allergy and Clinical Immunology (EAACI)
2	European Academy of Neurology (EAN)
3	European Association for the Study of Diabetes (EASD)
4	European Association for the Study of Obesity (EASO)
5	European Association for the Study of the Liver (EASL)
6	European Association of Nuclear Medicine (EANM)
7	European Association of Urology (EAU)
8	European Atherosclerosis Society (EAS)
9	European CanCer Organisation (ECCO)
10	European College of Neuropsychopharmacology (ECNP)
11	European Crohn's and Colitis Organisation (ECCO-IBD)
12	European Federation of Immunological Societies (EFIS)
13	European Forum for Research & Education in Allergy & Airway Diseases (EUFOREA)
14	European Hematology Association (EHA)
15	European League Against Rheumatism (EULAR)
16	European Organisation for Research and Treatment of Cancer (EORTC)
17	European Respiratory Society (ERS)
18	European Society for Molecular Imaging (ESMI)
19	European Society for Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN)
20	European Society for Paediatric Research (ESPR)
21	European Society of Anaesthesiology (ESA)
22	European Society of Cardiology (ESC)
23	European Society of Endocrinology (ESE)
24	European Society of Human Reproduction and Embryology (ESHRE)
25	Federation of European Biochemical Societies (FEBS)
26	European Society of Pathology (ESP)
27	United European Gastroenterology (UEG)
28	European Calcified Tissue Society (ECTS)
29	European Association for Cardio-Thoracic Surgery (EACTS)

Appendix 2:

Estimated Workload of Medical Device Expert Panels

Experience from the Food and Drug Administration, U.S.A.

(1) What is the relative workload for an advisory panel for class III devices (e.g., how many people on a panel, how many reviews do they do annually, and how much time do members spend on each review)?

Panels generally meet 1-2 times per year and panels have on average 18 members. The panelists receive the panel materials 1 month prior to the panel and we estimate it takes 10-15 hours to review the materials prior to the meeting. The meeting is 10 hours.

(2) What proportion of new class III devices, for example, are cardiological or neurological or orthopaedic?

% of new devices*	**Discipline (based on panel name)**
2	Anesthesiology & Respiratory
40	Circulatory (Cardiovascular)
5	Neurological
6	Orthopedic
6	Ophthalmic or Ear, Nose, and Throat (reviewed in same division)
6	Obstetrics & Gynecology or Gastroenterology & Urology (reviewed in same division)
6	General and Plastic Surgery
9	Clinical Chemistry & Clinical Toxicology
6	Microbiology
11	Molecular & Clinical Genetics
3	Radiological

*Based on PMAs & Panel Track Supplements received 2013-2017 (data came from MDUFA reports, which doesn't separate PMAs from PTSs at the division/discipline level)
Total number of PMAs and Panel Track Supplements received 2013-2017 = 290

(3) What percentage of new class III devices undergo a panel review?
11% (based on PMAs & Panel Track Supplements, 2013-2017)

Since 2008, this is the distribution of panel meetings that have been about a high-risk device (i.e., a Class III device requiring premarket approval):

Anesthesiology and Respiratory	**7%**
Circulatory System	**32%**
Clinical Chemistry and Clinical Toxicology	**1%**
Ear, Nose and Throat	**2%**

Gastroenterology and Urology	**11%**
General and Plastic Surgery	**7%**
Microbiology	**1%**
Molecular and Clinical Genetics	**2%**
Neurological	**7%**
Obstetrics and Gynecology	**4%**
Ophthalmic	**9%**
Orthopedic	**13%**
Radiological	**4%**

Total number of meetings since 1/1/2008 = 85

More information about the FDA panel process is available in their guidance document Procedures for Meetings of the Medical Devices Advisory Committee and on this website.

29 June 2018 (by email to Alan Fraser)

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Appendix 3:

Overview of the European paediatric perspective on medical devices

Devices for neonates, children and young people pose specific challenges that need specific assessment.

Option 1: Each panel that reviews a device that could be used in neonates, children or young people includes at least one person with paediatric expertise who gives an opinion

Option 2: Each panel that reviews a device that could be used in neonates, children or young people includes at least one person with paediatric expertise who uses contact with research networks to bring the experience of the paediatric community to the decision-making process

Option 3: There is a specific paediatric panel

Option 4: The people who contribute to Options 1 or 2 meet regularly to share experiences

This response was developed by Mark Turner, University of Liverpool, UK, mark.turner@liverpool.ac.uk in collaboration with:

1. NIHR Children's Clinical Research Network and the NIHR Children & Young People MedTech Cooperative (NIHR = National Institute of Health Research)
2. TEDDY – European Network of Excellence for Paediatric Clinical Research
3. Stichting Katholieke Universiteit Nijmegen (RUMC), on behalf of PEDMED-NL, the Dutch national paediatric research network
4. First Faculty of Medicine Charles University, on behalf of the Czech national paediatric research network

Justification of the paediatric perspective

There are specific issues about the science, usability, and research of devices and in vitro diagnostic devices in neonates, children and young people.

Science: Many conditions are unique to neonates, children and young people. Illnesses present differently in these age groups. The natural history of many illnesses differs between age-groups. There is variation in physiology and anatomy through growth. Devices that are to be used for children will need to take into consideration age, and stage of development. Puberty may also pose some challenges and so this also needs to be taken into consideration.

Usability: the size of individuals varies 100-fold between neonates and adolescents (from 500 g to 50 kg). The size of users has marked effects on the relevance and practicability of devices and in vitro diagnostic devices. Disabilities also have age-specific effects on how devices are used.

Research and development. Neonates, children and young people cannot give consent and may have extra vulnerabilities compared to other populations.

In order to address the needs for age-specific regulatory decisions, it is particularly important to have paediatric expertise concerning medical devices for all age groups available in expert panels, including advice on devices to administer and/or to remove a medicinal product.

Paediatric expertise is well coordinated across Europe through Conect4Children (c4c) (IMI2 JU #777389) [https://conect4children.org/about-conect4children/] and the European Paediatric Translational Research Infrastructure [EPTRI, H2020 INFRADEV-1 # 777554, https://eptri.eu] which are developing coordinated expert groups for methodology, national and specialty interests.

For example, subspecialists in paediatrics in the UK are very well connected through the NIHR Clinical Research Network for Children, NIHR Children & Young People MedTech Cooperative [www.cypmedtech.org.uk], and the National Technology Innovation Transforming Child Health Network [www.titch.org.uk]. Similar groups can be developed in the 19 other countries involved in c4c.

User voices

The user voice should also be included in regulatory decision-making, applying Options 1 – 4 above. The European Network of Young People's Advisory Groups (eYPAGnet) is well-placed to provide the voice of young people with experience in regulatory processes.