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Toward A Regulatory Pathway for the Use of in Silico Trials in the CE Marking of Medical Devices

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I. INTRODUCTION

Abstract—In Silico Trials methodologies will play a growing and fundamental role in the development and de-risking of new medical devices in the future. While the regulatory pathway for Digital Patient and Personal Health Forecasting solutions is clear, it is more complex for In Silico Trials solutions, and therefore deserves a deeper analysis. In this position paper, we investigate the current state of the art towards the regulatory system for in silico trials applied to medical devices while exploring the European regulatory system toward this topic. We suggest that the European regulatory system should start a process of innovation: in principle to limit distorted quality by different internal processes within notified bodies, hence avoiding that the more innovative and competitive companies focus their attention on the needs of other large markets, like the USA, where the use of such radical innovations is already rapidly developing.

Index Terms—Medical devices, in Silico Trials, regulatory system, notified bodies.

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THE In Silico Medicine refers to the exploitation of modelling and simulation technologies in healthcare. Of the many possible taxonomies, a particularly popular one divides In Silico Medicine solutions in three categories depending on who is the user: Digital Patient solutions, where the model predictions operate as clinical decision support systems; In Silico Trials, where computer models and simulations enable the evaluation of the safety and efficacy of new medical products, and Personal Health Forecasting solutions, where the end users are the patients themselves [1], [2], [3].

The regulatory pathway for Digital Patient and Personal Health Forecasting solutions is clear. There is now consensus among most national regulatory authorities to acknowledge the

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category Software as Medical Device (SaMD) as a medical device class in its own right. According to the International Medical Device Regulators Forum (IMDRF), the term “Software as a Medical Device” (SaMD) is defined as a software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device [4]. When the safety of a SaMD relates to its ability to accurately predict an endpoint, its certification must include evidence to support the expectation of its predictive accuracy. This clearly applies to Digital Patient solutions and to all digital health solutions with a clear medical purpose, including Personal Health Forecasting solutions.

The regulatory landscape is more complex for In Silico Trials solutions, and therefore worth a deeper analysis. In Silico technologies are widely used in the development of medical products. For example, medical devices are designed using computer aided engineering tools, such as finite element analysis of computational fluid dynamics [5], [6]. Systems biology models are used to identify druggable targets [7], [8]. Molecular dynamics models are used to optimise the potency of new molecular entities [9], [10]. However, the integration of In Silico Trials based on modelling and simulation to inform regulatory decisions presents distinct features and challenges. Firstly, the regulatory target is not the In Silico technology itself; rather it is the new medical product for which the In Silico Trials solution is expected to provide evidence on a par with, or in lieu of, benchtop testing, preclinical studies, or human clinical studies. Secondly, it is important to note that In Silico evidence does not rely solely on the output from a computational or mechanistic model. Instead, it is a framework that comprises both traditional evidence generation methods with modelling and simulation. In many cases the evidence provided to support the validity of the computational model would serve as primary evidence were the computational model not used. In the remaining cases the evidence supporting the validation of the model enables the use of the model to provide complimentary evidence that is difficult or impossible to measure on the bench, in animals, or in humans. Finally, there is a rigid separation between medical devices, medicinal products, and Advanced Therapy Medicinal Products (ATMPs) in terms of regulatory processes. The three classes of medical products follow quite different regulatory pathways to fulfil patients’ needs, and in some countries their marketing authorisation is provided by distinct authorities.

For medical devices, the use of In Silico Trials in submissions to the US Food and Drugs Administration (FDA) is clearly regulated. The Center for Devices and Radiological Health (CDRH), in charge of the evaluation of medical devices, provides a guideline for reporting modelling studies in medical device submissions [11], and recommends the use of a technical standard, the ASME VV-40:2018, to assess the credibility of computer models used for this purpose [12]. Some details on an early submission by Medtronic are provided here [13], [14].

Within the European Union (EU), the marketing authorisation for medical devices is based on the new European Medical Device Regulation (EU-MDR, entered into application on 26 May 2021) [15]. The EU-MDR considers a new medical device safe and performant as far as it satisfies the general safety and performance requirements listed in the Annex I of the regulation. Authorised entities, called notified bodies, present in the various member states of the European Union, evaluate if

such requirements are met, in which case they provide for the new medical device a Conformité Européenne mark (CE mark). While this distributed model is effective and agile, the lack of a centralised authority makes more difficult the adoption of the type of radical innovation that In Silico Trials represents, even if in principle the EU-MDR allows evidence from modelling and simulation in the regulatory process.

The EU-MDR does not exclude the use of evidence produced using computer modelling & simulation; vice versa, in annex VII it explicitly acknowledges computer modelling as one possible source of evidence. The regulation specifies that, where appropriate, “the results of biophysical or modelling research the validity of which has been demonstrated beforehand” may be considered in relation to the device requirements regarding design and manufacture [16]. The authors have no knowledge whether any EU notified body has accepted In Silico evidence in recent regulatory submissions for medical devices; anecdotal reports suggest that Finite Element Method (FEM) models and Computational Fluid Dynamics (CFD) models have been used to reduce the number of bench experiments. However, there is currently no technical standard harmonised in the EU regulatory system that one can use to demonstrate the credibility of an In Silico Trials solution, which the American Society of Mechanical Engineers Verification & Validation 40 (ASME VV-40) provides. The development of new harmonised standards is a complex and time-consuming process.

Another issue is the lack in the EU regulatory system for medical devices of a process equivalent to the qualification advice procedure provided by the European Medicine Agency for new methodologies used in the development and derisking of new medicinal products. The FDA has similar programs for both drugs (Drug Development Tools programme) and medical devices (Medical Device Development Tools programme). Such programmes make it easier to separate the evaluation of the In Silico Trials technology from the specific request for marketing authorisation of the medical device where such technology is used to provide evidence of safety and efficacy.

The aim of this position paper is to propose a possible trajectory for a wider adoption of In Silico Trials solutions in the CE Marking system for medical devices.

II. BENEFITS TO STAKEHOLDERS

A wider adoption of In Silico Trials solutions in the CE marking of new medical devices would significantly benefit all stakeholders of the regulatory process. The general framing we are proposing is that In Silico Trials methodologies are used to replace, reduce, and refine experimental studies used to produce regulatory evidence as depicted in Fig. 1 [17]. This applies to all kinds of experimental studies used in the regulatory process, including in vitro/ex vivo/bench studies (hereinafter simply called bench studies), animal studies and clinical studies. The EU Medical Device Regulation (MDR) does require a clinical investigation for all implantable and high-risk (Class III) medical devices. There are some exemptions in Art. 61.4, 61.5 and 61.6 but there are no exemptions based on data obtained by in-silico trials. For non-implantable, low-risk devices per Art. 61.10, the demonstration of conformity with the General Safety and Performance Requirements (GSPRs) in Annex I without clinical data might be appropriate.

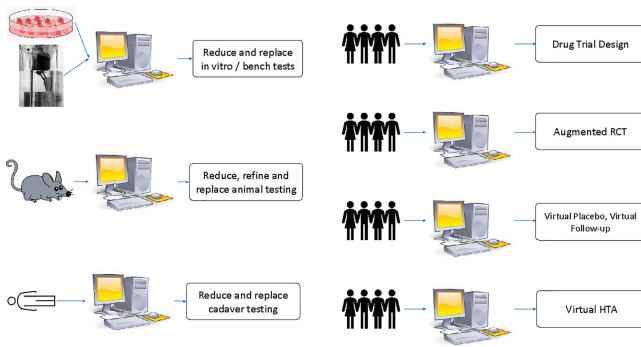


Fig. 1. The proposed general framing of In Silico Trials solutions in the CE marking of new medical devices.

Replace means to avoid an experimental study, partially or totally, with an In Silico Trial solution, while reduce means to minimise the number of animals used in an experimental study. The fundamental idea here is that experimental studies in animals and humans involve financial and ethical costs, and present significant inter-species and disease-specific differences impairing in-market, real life clinical translation. Animal studies are expensive [18], and clinical studies even more so [19], [20], with the costs proportional to the number of animals or humans involved and to the duration of the study. Any method that reduces the number of animals or humans to be enrolled in the study, and/or shortens the duration of such study, will drastically reduce the cost of that study. The discussion on the ethical costs is complex and beyond the aim of this position paper. Here, it is enough to say that there is a growing consensus in society that *ceteris paribus* (everything else being the same) animal experimentation should be reduced as much as possible [21], [22]. For clinical experimentation the argument is also very complex, but again the principle that for any clinical study one should enrol the smallest possible number of patients / volunteers applies [23].

Refine means to minimise the suffering in animal experimentation and the risks in human experimentation, but also to improve the predictive accuracy of the evidence. In the regulatory process, the preclinical evidence is used to infer the safety and efficacy observed in the clinical experimentation, and clinical experimentation is used to infer the safety and effectiveness of the new medical device when used in normal clinical practice. In Silico Trials can refine experimental studies in the sense that they better predict the result of the next step in the regulatory process. The key advantage is that we are closer to the clinical scenario than animal experiments. Here, the expectation is that the In Silico Trials methodology, in addition to or combined with experimental methods, will reduce the so-called attrition rates, e.g., the decision to abandon the development of a new medical device at some point during its regulatory evaluation. Attrition rates are quite high for medicinal products, and in fact they represent one of the main factors of the high costs of development of medical products [24]. To our best knowledge, there are no studies on the attrition rates for medical devices, but it is possible that the introduction of the new EU-MDR will increase them, considering clinical trials are now almost always mandatory for class III devices.

This considered, we can identify, for each group of stakeholders, specific benefits associated with a wider adoption of In Silico

Trials. There are no extensive studies on the benefits provided on the In Silico Trials because their adoption is very recent and very few use cases have been yet reported so far. However, we conducted a consultation in In Silico World Community of Practice and the expectation of the main benefits of the various stakeholders are listed below.

Manufacturers

- Statement that technology is accommodated by US and EU legislation.
- Benchmark competing solutions.
- Demonstrate value to payers by predicting the real-life solution related benefit and the optimal target population.
- More efficient, less expensive development approaches.
- Help better understand biology.
- Increase chances of success.
- Accelerate market access.
- Products bearing the CE marking can be traded in the European Economic Area (EEA) without restrictions.

Health systems and policy makers

- Demonstrate value to payers by predicting the real-life solution related benefit and the optimal target population.
- Accelerate access to value-adding technologies.
- Flexible strategy that can play into emerging needs (e.g., pandemic).

Patients

- De-risk trials.
- Accelerate access to beneficial technologies.
- Same level of health and safety protection throughout the EEA [25].

III. NEED FOR GLOBALLY ACCEPTED STANDARDS

As other industrial sectors have already demonstrated, the advent of modelling and simulation is inevitable. The risk in such a situation is that of an adoption denial, where the slow and resisted adoption of In Silico Trials creates a patchwork of practices of limited confidence, distorted quality levels and differences between Member States and between types of products. The best way to avoid this is to pursue globally accepted standards that provide to each regulator the necessary technical level upon which to evaluate the credibility of the In Silico Trials used in producing regulatory evidence.

It is thus necessary, to develop an International Organization for Standardization (ISO) standard that is recognised by FDA and harmonised in the EU regulatory system, to evaluate the credibility of In Silico Trials technologies. The basis for such an ISO recognised standard exists, provided by the ASME VV-40, which may provide a more globally consistent credibility assessment across countries and across medical products.

IV. EXISTING FDA REGULATORY PATHWAY

The existing FDA regulatory pathway for qualifying IST for medical devices is quite clear. While the qualification of a Medical Device Development Tool (MDDT) is not mandatory, the case of complex methodologies such as IST it is highly recommended. Essentially, an applicant requests to FDA the qualification of a MDDT by producing evidence that such a method is accurate and effective in supporting the regulatory decision process. In the case of ISTs this is done primarily

by demonstrating the credibility of an in-silico methodology following the ASME VV-40. Once the in-silico methodology is qualified, it can be used in any subsequent regulatory submission without any further scrutiny on the methodology itself.

V. A CE MARKING PATHWAY

Time is ripe to pursue a well-coordinated strategy toward the adoption of In Silico Trials methodologies in the production of evidence toward the CE marking of medical devices. We propose that such a strategy is composed of five steps:

1. Transitional adoption of VV-40
2. Development of an EU harmonised standard
3. Tailored training and re-training programs
4. Global harmonisation via the International Medical Device Regulators Forum (IMDRF)
5. EU qualification programme for Medical Device Development tools

A. Transitional Adoption of VV-40

To avoid a major difference between the USA and EU regulatory pathways, it is important to allow companies applying for the CE marking for new medical devices to produce evidence using In Silico Trials methodologies. To ensure the credibility of such methodologies, EU notified bodies should request, in the absence of a harmonised standard, to be provided with evidence of credibility according to the ASME VV-40.

B. Development of an EU Harmonised Standard

The In Silico Trials community of practice should drive the creation of a new standard. Through the In Silico World Community of Practice online (ISW_CoP) [26], we propose to organise this emerging industrial sector in speaking with one voice to ISO and to the national standardisation bodies that compose its membership.

A first step would be the identification of the most suitable technical committee. One possible option is the International Organization for Standardization's (ISO) Technical Committee (TC) 215 (ISO/TC 215): Health informatics, but other options might exist. Then, an ad hoc Working Group (WG) should be established, entitled In Silico Trials Working Group. A representational organisation, the Avicenna Alliance [27] should recommend to ISO the inclusion in such a new Working Group (WG) of a pool of experts from academia and industry; additional members could be recommended by national standardisation bodies.

The WG should start to work, using the VV-40 as a starting point. Using the ISW_CoP, the experts in this WG could liaise with those in the ASME VV-40 committee, to ensure that the two standards evolve harmoniously.

The main steps of the proposed strategy toward the adoption of In Silico Trials methodologies in the production of evidence toward the CE marking of medical devices, in comparison to the already adopted FDA qualification program, is sketched in Fig. 2.

C. Tailored Training and Re-Training Programs

Generally speaking, in order to lower the lack of trained workforce barrier, it is needed to develop specific resources for

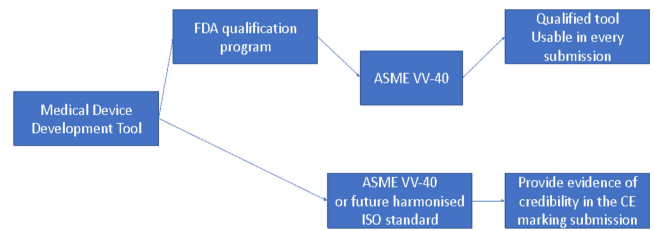


Fig. 2. Comparison between the FDA qualification program for medical devices and the one we propose for EU context.

the education and re-training of specialists in In Silico Trials. This also applies to the notified bodies and regulatory agencies (National, European, private and public) for the development and regulatory evaluation of In Silico Trials for medical devices.

Any educational effort will also need to address medical professionals, both medical doctors and allied professionals. Last, but not least, it is also needed to train groups of technical professionals (bioengineers, medical physicists, computer scientists) to become developers and providers of In Silico Trials technologies and services.

D. IMDRF Global Harmonisation

In addition to an informal alignment among experts, and in parallel to the development of the ISO standard, we recommend the creation under the International Medical Device Regulators Forum (IMDRF) of an In Silico Trials working group that would ensure that the ISO and ASME standards, and possibly other regional standards, evolve harmoniously and consistently and in step.

E. Toward an EU Qualification Program for Medical Device Development Tools

The last step requires the creation of a qualification program for medical device development tools along the lines of those provided by the European Medicine Agency (EMA) for drug development tools, and by US FDA for both drugs and medical devices.

If an innovative methodology is used to produce evidence of safety in support of the request for the CE marking of a new medical device, the notified body must evaluate not only the evidence provided, but also the appropriateness of the new methodology used to produce such evidence. If the methodology refers to a technical standard to document its credibility, this makes the work simpler, but still considerable. Qualification programs evaluate methodologies, and when these are found appropriate for a given context of use in the regulatory process, they qualify them. After that for any regulatory submission that uses a qualified methodology, the notified body can focus on the evidence, trusting that the methodology used to produce it is appropriate.

The existence of a qualification program for Medical Device Development tools would also support the further development of a new thriving European industrial sector that develops In Silico Trials solutions. Once a methodology is qualified, the medical device company can buy with confidence this solution knowing the regulator considers it suitable for that context of use.

Considering that initially the number of requests for qualification would be limited, a single organisation could provide

such a qualification program. Possible candidates are European organisations such as the EMA itself, but also independent non-governmental organisations such as the VPH Institute [28].

VI. CONCLUSION

In Silico Trials methodologies will play a growing and fundamental role in the development and de-risking of new medical devices in the future. The European regulatory system must embrace and guide this revolution, in order to limit distorted quality by different internal processes within notified bodies and also avoid that the more innovative and competitive companies focus their attention on the needs of other large markets, like the USA, where the use of such radical innovations is already rapidly developing.

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