SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

Deliverable 9.6

Devices approval experience report

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Executive summary

This report provides an overview of the regulatory dossier (Pre-Submission) that BIOTRONIK submitted to the *United States Food and Drug Administration* (FDA) to gather feedback on the design of in-silico-clinical-trials for the US regulatory approval of the proprietary PAPS device. To provide insight for both the in-silico community and the specific development aspects of the PAPS device, a set of specific questions were submitted to the FDA. This experience report aims to provide direction for future FDA Pre-Submissions in the field of device-related in-silico-methods and is intended to guide first-time applicants and the in-silico-community. As the value of the FDA's response is strongly connected to the quality of the questions, this report focuses on the process of identification and refinement of suitable and relevant questions. This report also suggests future strategies to increase the impact of in-silico methods to medical device development, including all endpoints to be covered in an in-silico-clinical trial.

Table of contents

List of figures

List of tables

Acronyms

Acronym	Full name
ASME	The American Society of Mechanical Engineers
BIO	BIOTRONIK
CM&S	computer modelling and simulation
CoU	Context of Use
EMA	European Medicines Agency
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
FDA	United States Food and Drug Administration
FOIA	Freedom of Information Act
HF	Heart Failure
PAPS	Pulmonary artery pressure sensor
ISCT	In-silico clinical trials
IST	In-silico trials
HF	Health Failure
QoI	Question of Interest
Q-Sub	Q-Submission Program
Pre-Sub	Pre-Submission
SOP	Standard Operating Procedure

Definitions

Computer modelling and simulation: *computer modelling and simulation* (CM&S) refer to the process of using computer programs and mathematical algorithms to replicate real-world phenomena or systems. It involves creating digital representations of physical objects, processes, or situations to analyse and predict their behaviour.

Virtual patient: a virtual patient is a member of a virtual cohort that mimics the physiology of a real patient as accurately as possible *prior to* and *after* medical intervention.

Virtual cohort: a "set of virtual patients that mimics a cohort of real patients with respect to all reasonably expected patient states, patient dynamics and evolution of patient condition which might occur in practice"[1]

In-silico trials (or) in-silico clinical trials: broadly, *in-silico trials* (IST) or *in-silico clinical trials* (ISCT) are (CM&S)-based clinical and pre-clinical experiments, in a cohort of virtual patients conducted during the development or regulatory evaluation of a medical product[2]. ISCT in particular, replicate various aspects of real clinical trials, device testing, or product evaluations, by using computer models for development of patient-specific models to form virtual cohorts for testing the safety and/or efficacy of new drugs and of new medical devices[3]

Q-sub (or) Q-submission Program: the term "Q-Submission" or "Q-Sub" refers to the system used to track the collection of interactions – namely Pre-submission (Pre-subs), Submission Issue Requests (SIRs), Study Risk Determinations, Informational meetings, Other Q-Submission Types

Pre-sub: (or) Pre-submissions: a Pre-Sub includes a formal written request for feedback from FDA that is provided in the form of a formal written response or, if the requested, formal written feedback followed by a meeting. While the feedback is not binding for FDA, it does include their current thinking on the subject.

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[1] J. G. Chase, J. C. Preiser, J. L. Dickson, A. Pironet, Y. S. Chiew, C. G. Pretty, G. M. Shaw, B. Benyo, K. Moeller, S. Safaei, M. Tawhai, P. Hunter, T. Desaive, Next-generation, personalised, model-based critical care medicine: A state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them. *Biomed. Eng. Online*. **17** (2018), pp. 1–29

[2] Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba Tshinanu F. In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods. 2021 Jan;185:120-127. doi: 10.1016/j.ymeth.2020.01.011.

[3] Pappalardo F, Russo G, Tshinanu FM, Viceconti M. In silico clinical trials: concepts and early adoptions. Brief Bioinform. 2019 Sep 27;20(5):1699-1708. doi: 10.1093/bib/bby043. PMID: 29868882.

Introduction

In the context of regulatory approval of a medical device, validation studies in the form of bench tests, animal experiments, animal and/or human trials are indispensable. The outcomes of such studies are significant, only when the regulatory agencies, such as FDA or conformity assessment bodies, agree on the underlying study design. The validation study should encompass all relevant hypotheses and the input data should be adequate to establish strong evidence of the study endpoints to demonstrate a reasonable assurance of device safety and/or efficacy.

In reality, there is often a lack of shared criteria that constitutes sufficiency of above device approval studies due to the complexity and wide array of potential medical devices and technologies. This complexity can lead device manufacturers to redesign the study or trials, potentially causing delays in the evaluation and approval of the device. Thus, directly hindering the availability of life-saving technological advancements to patients.

Engagement with regulators

To alleviate above challenges within the regulatory approval process, regulatory agencies (e.g. FDA, *European Medicines Agency* (EMA), *Medicines and Healthcare products Regulatory Agency* (MHRA)), encourage device manufacturers to seek feedback regarding a potential or planned medical device investigations studies. To this end,

- multitude of channels (e.g., written feedback, in-person or online-meetings, etc.) and
- formats (informational meetings, pre-submission, Q-subs, Qualification advice etc.) are offered by regulatory agencies.

Requests for feedback and meeting with FDA
Engagement with regulators through the above channels are common in the medical device industry, especially to collect feedback on specific questions during product development and/or submission preparation. With the fast-evolving complexity and speed of technological innovation, device manufacturers, and regulatory agencies are increasingly in need of the above-described interactions, to mutually understand each other, in support of the innovation process.

At times, medical device manufacturers have limited regulations and standardised guidelines for new technologies like *computer modelling and simulation* (CM&S). In many instances, they may need to go beyond the default regulations and standards. Especially in these circumstances, timely exchanges between technology developers and regulators facilitate faster development of novel devices and support obtaining more efficient regulatory approvals.

Scope

One of the project objectives is to realise the use of in-silico methods for the regulatory evaluation of device safety, efficacy and usability endpoints at the preclinical and clinical trial level. Increasing the level of confidence of regulatory agencies on the in-silico results is paramount to integrating in-silico solutions into the regulatory approval process.

In order to achieve the above objectives, SIMCor requested FDA's feedback on the in-silico models and simulation results generated within the project. This was envisioned for one of the key cardiovascular device applications dealt in SIMCor, namely the *pulmonary artery pressure sensor*

(PAPS). This high-risk implantable medical device is used to infer cardiac filling pressures in *heart failure* (HF) patients, to facilitate their medical management.

Device approval process and expected learnings

Building on the wealth of in-silico models as well as multitude of bench, animal and human experiments conducted within SIMCor, we strive to demonstrate that simulation results complement traditional verification and validation results, for providing evidence of safety, efficacy and usability. With limited precedence and reports of similar in-silico evidence-based pre-submissions, this report includes our first-hand learnings. This document aims to share our approach and strategy, alongside the learning and recommendations as possible best practices for supporting the future regulatory approval process involving in-silico methods.

Procedure for regulatory pre-submission

Part A: Overview of FDA guidelines on Q-submissions

The different steps and structure of a Q-submission are best described in FDA guidance documents. These help the applicant to understand the different kinds of Q-Submissions and provide valuable hints for the preparation of the request.

Briefly, it starts with identifying the motivation for triggering a formal interaction with regulatory authorities, followed by identifying the most appropriate channel of interaction among the various categories. Subsequently, one must refer to the respective official guidance document, as advocated by the regulator.

The applicant needs to duly prepare the regulatory dossier in the prescribed format, style and language, which requires a team of inter-disciplinary professionals who are not only product experts, but also regulatory seasoned liaisons. The regulator often provides a written response to the specific questions being raised, which can then be discussed in a follow-up meeting, if needed.

With respect to the pre-submission process conducted within the project, the motivation, strategy, the key themes of the questions and the decision to follow up with a meeting, were addressed by BIO.

Part B: Using in-silico methods for device approval process

This section presents the aspects pertaining to in-silico methods and their impact on ISCT. To begin with, the general considerations that directly dictate the desired pre-submission process are outlaid. Whenever appropriate, the implementation of these considerations specifically for the PAPS device is briefly indicated, for understanding.

At the outset, few critical factors impact the consideration of in-silico methods for device approval:

1. Despite valuable insights and alternate evidence generated using in-silico methods through ISCT, the current device approval regulations do not recommend or address their use. On the contrary, real-world clinical trials are still the gold standard for any device approval.

2. To define the scope of in-silico methods within the regulatory process, one needs to critically evaluate whether the in-silico method and related experiments/trials contribute to the device development phase and/or into the device approval phase. Only if they would support and benefit the approval process, these methods can be used in the Pre-submission exercise.

3. Incorporating in-silico methods into the device approval process necessitates substantial proof (validation) of the credibility of the model. The efforts needed to establish this credibility may outweigh any simplifications that in-silico methods bring compared to traditional preclinical and clinical studies. This is relevant not just from an economic standpoint, but also from an ethical perspective. For instance, additional animal trials may be necessary to demonstrate the credibility of the model.

4. Adherence to modelling and simulation-related standards and guidelines from ASME[4], NASA[5] or the FDA[6] are generally accepted. Given that they leave room for interpretation, any deviations from published standards and guidelines are accepted within the regulatory process, as long as

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[4] ASME V&V40: Assessing Credibility of Computational Modelling Through Verification and Validation: Application to Medical Devices, 2018

[5] NASA-STD-7009A NASA Handbook for Models and Simulations: an Implementation Guide, 2019

[6] FDA Assessing the Credibility of Computational Modelling and Simulation in Medical Device Submissions, 2023

they can be well reasoned with regulatory authority. The interaction platform facilitated by a Q-submission is an opportunity to discuss such critical aspects with FDA, in anticipation to the premarket submission of the product under consideration.

Formulating the scope of in-silico-methods: PAPS device

A good starting point to inquire about the benefits of in-silico methods is the classical device approval pathway. For the development and approval of the PAPS, BIO has already developed a clinical study plan, including preclinical studies, with identification of all relevant endpoints, the statistical description and inclusion/exclusion criteria. This pathway has been discussed for the PAPS device in a previous Q-Submission, which did not include any specific questions on the use of in-silico methods within the approval procedure.

There are a variety of parameters and endpoints of the study that can, in theory, be influenced using in-silico-methods. Table 1 provides an overview of typical device approval study designs and their critical parameters. For each study type (animal, early feasibility or pivotal), the table highlights the possible benefit or insight gained from a prospective or a simultaneous in-silico study. This is detailed for each study state, namely:

1. Preparation phase, that deals with patient/animal selection;

2. Implementation phase, that facilitates implantation procedure and monitoring of patient/animal as well as data concerning the implanted device itself, and finally

3. Evaluation phase, that investigates the outcome or effects.

Study type	Study design		Possible study aspects influenced by in-silico-methods for each phase of the study		
	Parameters	Endpoints	Preparation	Implementation	Evaluation
Animal study	Number of animals, time	Safety (e.g., absence of device caused embolism)	Ethical considerations (refine animal experiments to maximise insights provided by the animals experiments), Identify relevant species	Procedure planning (e.g., implant positioning)	Determine results relevance to human use
Early feasibility	Number of patients, time	Safety (e.g., absence of device caused embolism)	Proof of patient safety to physicians by prediction of freedom of adverse events	Procedure planning (e.g., implant positioning)	Refined insights of study results (e.g., Thrombosis risk assessment)
Pivotal study	Number of patients, time	Efficacy (e.g., hospitalisation rate) and safety	Inclusion criteria, inclusion rate	No impact at the time being. Future work should include in-silico-clinical trial that consider interactions between sensor data, monitoring by the physicians, patient characteristics, and therapeutic effects	Support evidence of effectiveness

Table 1: List of device approval studies and corresponding parameters and endpoints that are likely to impact in-silico-clinical-trial outcomes, across the different phases.

Strategy for regulatory process

In a general ISCT for device approval, the ISCT or a combination of an ISCT with a (simplified) classical approval study, must cover the same endpoints and provide the same or higher level of validation strength (e.g., the same statistical power) as a conventional clinical trial would. For instance, based on the evidence from ISCT covering the relevant safety endpoints, the number of animals or number of patients can potentially be reduced within the animal study or the early feasibility study (first in-human study). On the contrary, reducing the number of actual patients in a pivotal study (real-world study) based on ISCT is currently not possible, if not all the study endpoints can be simulated.

In the specific consideration within the PAPS use case, the efficacy endpoints have not been simulated. However, when ISCT are used for the reduction of sample size within the above-mentioned studies, the model risk assessment of the in-silico study is affected. The decision consequence of the simulation studies can be rated low or middle, as long as the successive real-world studies provide the proof of safety. Otherwise, the decision consequence would have to be rated as high, if no support of real-world studies is available. It is also possible that if the data from both an animal study and a

human study correlate well, the regulatory agency may be able to approve the changes in the device, based on the data only from an in-silico-study.

Brüning et al.[7] present that in-silico methods could offer **additional insights on device-related alterations**, like the influence on patients' hemodynamic. They propose that a real-world-study covering the minimum requirements regarding statistical power, is enhanced by in-silico methods. This can improve patient safety and, therefore, address possible concerns of regulatory authorities regarding safety of an approval candidate device like PAPS. Furthermore, this additional information might allow identifying device failure modes in case of non-successful clinical trials, facilitating and informing specific device updates rather than omitting the device altogether due to insufficient clinical results.

Another device approval aspect that needs careful consideration are **inclusion and exclusion criteria, for each clinical study**. These criteria can directly affect the outcome of the study, thereby risking the intended approval process. At the same time, they can also lead to the exclusion of more patients than necessary. This can eventually limit the number of patients that can profit from the new device, once it gets approved. In the case of the *PAPS approval process*, in-silico methods could be deployed to examine the severity of heart failure and the frequent comorbidities. Thus, they can help make **informed decisions about the inclusion of certain patient groups**.

Furthermore, the inclusion rate is also crucial for the time elapsing until the study results are available and the next step of approval process can be explored. The physicians carrying out device approval studies, among others, are at the forefront of making decisions on the inclusion rate. In the case of a new device like PAPS, physicians will be cautious about the inclusion rate, in order to be responsible towards their patients. To mitigate such challenges, an ISCT on the safety of the device can **increase the confidence of physicians and patients, much before the start of the real-world study** and thus support a stronger inclusion rate.

Regulatory approval plan

When the above steps and process are thoughtfully evaluated for the given in-silico methods and medical device under consideration, a broad sketch of **a device approval plan** starts to surface. Thereby, one would identify:

● How are the in-silico studies planned to be implemented?
● What contribution in-silico-methods are meant to have?
● How is its credibility planned to be proven?

These questions are always device-specific.

With regard to the current **regulatory approval plan of PAPS device,** a set of 7 questions included the following themes:
● Proposal of two ISCT, and the corresponding
    o Virtual cohorts used for the ISCT,
    o Related model risk assessment consideration, in terms of model influence and decision consequence, and
    o Model validation strategy.

Collectively, they demonstrate the model credibility and are presented for discussion through this pre-submission process with the regulator.

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[7] Brüning, Jan et al. "In-silico enhanced animal study of pulmonary artery pressure sensors: assessing hemodynamics using computational fluid dynamics." Frontiers in cardiovascular medicine vol. 10 1193209. 7 Sep. 2023, doi:10.3389/fcvm.2023.1193209 https://pubmed.ncbi.nlm.nih.gov/37745132/

Part C: Example Q-submission process with in-silico methods: PAPS device

This section presents a high-level overview of how the entire Pre-submission process was handled for PAPS. For the ease of readability, the technical details are avoided, rather the practical aspects like structure of the pre-submission document, the need to assemble a multi-disciplinary team, the extent of time and resources to foresee and finally the dependencies on pre-submission are highlighted.

Goal

Briefly, the goal of the Pre-Submission on PAPS device was defined as follows: "The purpose of this pre-submission was to receive FDA feedback with regards to the proposed simulation studies, in-silico clinical trials and validation concept for the PAPS device."

Sample questions

Three representative questions from the actual Pre-submission dossier are provided here. Owing to confidentiality reasons, only representative questions are listed.

- *Does FDA have any concerns with the approach for translating preclinical to predicted human data?*
- *Does FDA have any concerns with the proposed simulation validation strategy?*
- *Does FDA have any concerns with the risk assessment proposed in SIMCor Standard Operating Procedure for validation of in-silico models?*

Structure of Pre-submission

Due to confidentiality reasons, only a brief overview of the Table of Contents (see Figure 1) of the actual Pre-submission is provided below. The document details the questions and substantiates these questions with the *context of use* (CoU), the actual *question of interest* (QoI) and proposed rationale of generating and using the evidence in the regulatory process. Each specific question is linked to a dedicated sub-section that outlines the necessary background and depth of scientific evidence for the regulatory advisor to evaluate.

Table of Contents

Figure 1: Table of contents of the PAPS ISCT Q-Submission.

Standard operating procedure (SOP)

One unique addition to the Pre-submission document drafted by the SIMCor consortium, is an extensive Annex (see Figure 2) document on the '*standard operative procedure* (SOP) on in-silico validation'. This was a project deliverable that details the rationale behind tailoring the existing ASME V&V40 standard[9] and FDA guidance document to establish the credibility goals for the in-silico methods[11].

This SOP document was used to explain how the verification and validation exercise for PAPS was extensively addressed by tiered low-fidelity and high-fidelity validation schemes. More importantly, it demonstrates with detailed documentation the rationale and depth of the chosen approach in a transparent manner. Thus, it is expected to bring credibility to the Pre-sub, which may support mutually transparent exchanges during the future regulatory approval processes.

Appendix 1

SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

Call: H2020-SC1-DTH-2018-2020 (*Digital transformation in Health and Care*)

Topic: SC1-DTH-06-2020 (*Accelerating the uptake of computer simulations for testing medicines and medical indevices*)

Grant agreement No: 101017578

Deliverable 4.6
SOPs for validation of in silico models

Due date of delivery: 31 December 2023
Actual submission date: 27 December 2023

Start of the project: 1 January 2021
End date: 30 June 2024

Figure 2: Appendix 1 of the PAPS ISCT Q-Submission – Standard Operating Procedure for validation of in-silico models.

Practical considerations

The preparation of the pre-submission dossier involved a multi-disciplinary team effort, which included consultations from scientific colleagues from SIMCor, as well as product experts and regulatory professionals in the organisation. Moreover, effort with respect to person months of work to prepare the submission, needed to be carefully planned in consultation with various stakeholders.

Dependencies: priorities and timeline

While the Q-Submission guidance includes timelines as prescribed by FDA[8] , with a process that is well-known and straightforward, we encountered few dependencies both in the leadup and downstream phases of the Q-submission. First of all, the timelines directly impact the manufacturer's process streams and planning. This may influence immediate validation studies or related forthcoming decisions. Our experiences are that such processes and timelines are straightforward to plan, and the preparatory work can be started well ahead of time. But in practice, it is often not the case as the **necessary resources may be bound to other activities.**

In our case, we had to delay the preparations as not all of the necessary internal resources could be secured at the desired moment. Ideally, the timing of a Q-submission would need **to match the product development process and the resources to handle the submission**.

Reflecting back on the whole preparatory phase, we noted that **priorities within the organisations** are an important factor to consider. Often regulatory processes of privileged products in a mature stage of development may be given priority over early phase development projects. Therefore, it is important to anticipate such dynamics, when considering the planning for a pre-submission.

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[8] FDA (U.S. Department of Health and Human Service - Food and Drug Administration): Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, 2023

Learnings from regulatory pre-submission

Part A: Key observations from regulator

First of all, the Q-Submission is not to be seen as a test submission but is an early communication process during the device development phase. The objective is to gather feedback from the regulatory body. It is device specific, and likely related to a future regulatory submission. Therefore, the responses from the regulator, FDA in this case, went beyond answering to the specific questions raised in the submission. Thus, the response provides insight as to what the regulator often expects a regulatory submission to address.

Observations

Replacement of GLP animal and/or clinical studies

Broadly, the regulator raised concerns that only 3 safety aspects and no effectiveness aspects were used in the proposed simulation studies. Especially, considerations on sensor accuracy and long-term effects were deemed critical. Therefore, our proposed ISCTs that targeted the safety aspects alone were considered not to be substantial enough to replace GLP animal studies or clinical studies.

The regulator describes that a combination of bench tests, animal trials and the proposed computational modelling data are needed for device approval in the preclinical phase. It was also underlined that the computational models require in-vivo validation. Aspects that need to be investigated in order to demonstrate device performance and safety, were summarised in the written feedback. This included generic requirements like sterilisation as well as product-specific requirements like device interaction within side branches of a blood vessel.

Pre-clinical studies vs. in-silico studies

While the clinical approval strategy has been already discussed in a previous regulatory interaction, the current submission focussed on the preclinical investigation that concerns only fatigue testing. Given that the ISCTs discussed in this Q-Submission are likely to affect other preclinical tests as well, the regulator advised to draw the whole picture of preclinical testing.

The questions of the Q-Submission imagined possible simplifications in the conductance of the animal tests. On that note, the regulator gave many recommendations on the animal tests like specifics on the study procedures, duration of the animal study and the need for usability tests. In addition, for novel devices like the PAPS, a chronic large animal study was recommended.

On the question if the approach of an ISCT for device positioning of the PAPS raises concerns, the FDA responded that the general approach seems reasonable, but the CoU needs a revision, and additional tests would be required. Moreover, the generalizability of the geometries of Berlin-based patients to the US population was deemed important to investigate.

Methodology

From the perspective of the regulator, a difference in reliability of simulations based on computational fluid dynamics and structural mechanics could be noted. Likewise, the use of only virtual cohorts to capture the device performance in reducing heart failure events seemed less convincing for the reviewer. Further, it is pointed out that the proposed engineering metrics like wall shear stress and oscillatory shear index may not be the only reliable markers for assessing the risk of thrombosis.

Regarding the reporting of simulation results, it was recommended to explain all simplifications in detail. Emphasis was made to report what has been, for instance aspects like geometry or mesh discretization but also the mechanical loading modes.

Validation

Although the validation strategy was deemed to be reasonable, emphasis was laid on the need for separate training and validation data. A concern was raised on the validation strategy for wall shear stress using 4D *magnetic resonance imaging* (MRI), as wall shear stress measurements are known to be prone to large uncertainties.

Inconsistencies around the rationale and reasoning were diligently sought out by the regulator. For instance, our categorization that impact of simulation would be low, given there will be a follow-up animal trial, while the animal trial design by itself was based on simulation, were rightly identified.

Part B: Key reflections and learnings

Reflections

The regulator is open for in-silico methods in the context of a medical device submission for regulatory approval, yet there are a number of concerns on different aspects, as currently a combination of bench, animal, and potentially CM&S data are used to evaluate the strength and generation of evidence.

Not every comment, concern or recommendation from the regulator seems entirely new. Still, the meta-information that this specific aspect has relevance to the FDA is valuable and underlines the FDA's approach to give the best possible support even when not everything is entirely clear at this early stage of device development. For example, FDA recommended sample sizes in tests that allow for reliable findings. The FDA is even willing to give reasonable answers to open questions despite specific questions being preferred. To our questions on simplifications in in-vivo tests, the FDA stated that the path to reach this is to provide evidence on how computational modelling could address all critical safety and effectiveness endpoints associated with a traditional human clinical trial, and how it can be combined with additional supporting evidence.

The FDA further recommended additional research, for example exploring more data sources on relevant patient populations.

Learnings

Different stakeholder-perspectives need to be taken into account

As a research project, the consortium's objective was to present the innovation and developments achieved and to discuss future impact of the findings with authorities. Therefore, additional tests that are often necessary for approval but those that do not pertain to the project topic were not foreseen to be in the scope of the Q-Submission.

On the contrary, this created an impression that any tests and device safety or performance aspects not covered in this submission were also not going to be considered by the manufacturer. Therefore, the scope and non-scope with regard to the stakeholder's interest need to be clearly stated in the dossier.

Specificity of the regulatory dossier

The regulator responds to the questions based on the information/material delivered along with the questions. The choice of what and how comprehensive the delivered material needs careful consideration. At the same time, if the provided information is not relevant to the device approval or the relevance is not sufficiently clarified, it does create confusion.

For this Q-Submission, it would have been advantageous to provide another supplement showing the preclinical study plan in its entirety. Likewise, we attached an SOP that was prepared for the project as part of the submission dossier. Although appreciated by the regulator, it included relevant but some irrelevant information. This contributed to gaps in the understanding on what parts of the document

pertains to the product and what concerns the research project outcome. A tailored SOP would have been a better approach.

Context of regulatory submission

Furthermore, it should be clearly stated which aspects of the upcoming device approval are intended to be modified and which remain intact. In other words, it is critical to clarify what aspects would follow the classical approval path. In our Q-Submission it would have been helpful to assure the regulator that a deviation from a previously discussed clinical study plan is not under consideration.

Language of communication

The wording of the questions raised in a Q-submission dossier needs to be carefully formulated. For example, in a specific question we aimed to discuss whether the animal trials need to follow the GLP standard. On the contrary, the regulatory interpreted it as we were intending to omit the animal trials altogether.

Best practices and recommendations

We conclude this document with broad observations that range from nuances of addressing in-silico evidence, as well as general learnings that benefit the regulatory process involving in-silico methods for device approval. We summarise some key aspects that this experience report captures and present them here as observations.

Preparation and process

Of specific note, the experience report deliberates the criticality and unique value addition that in-silico methods bring to regulatory processes. Further, it presents a preliminary approach to unearth a strategy that best articulates the use of in-silico methods within the device approval spectrum, after due considerations of strengths and limitations. This remains non-exhaustive and stems from the limited observations noted within the SIMCor regulatory exercise.

As highlighted in Part C of the previous section, the following practical considerations are relevant for an individual contemplating a similar regulatory submission process, for the first time:
- Adhere to the official guidelines of the regulator;
- Formulate a multi-disciplinary team;
- Foresee communication challenges and prioritisation dilemmas;
- Recognise the need for buy-in from stakeholders and secure the support;
- Start ahead of time and align with the priorities of stakeholders.

Last but not least, weigh upon the cross-dependencies on pre-submission preparation and outcome, both in the upstream and downstream process.

Outcomes and lessons learnt

Takeaways: industry perspective

Regulatory authorities are generally open to the use of CM&S to support device safety and effectiveness but have expressed concerns on certain areas. Currently, the classical approach with laboratory tests and animal experiments is seen as more reliable than the validation of computer models. Nevertheless, a combination of in-silico clinical trials and other data sources including literature data, bench tests and clinical tests are recommended by the regulator, in our case the FDA.

The evidence from in-silico-methods need to address all different aspects of device approval such as safety, efficacy and effectiveness with adequate rationale and supporting evidence. ISCTs require a whole chain of evidence in which every link must be reliable. An example presented in the Q-submission was the attempt to validate blood flow simulations by means of 4D-MRI measurement which, however, do not generate sufficiently comprehensible data on the clinical endpoints, such as thrombosis, but also on engineering surrogate parameters, such as velocities and wall shear stresses. As a result, thrombosis cannot be assessed only by relying on in-silico methods. On a different note, no simulation step may be a black box process which might be the case when third-party services/solutions are used, which by themselves are not always certified or where documentation is missing for a comprehensive understanding.

A major benefit of the Q-Submission process is to obtain early feedback on parts of the evidence chain that seem to be weak. The feedback can be used as gap analysis for the research and development and to build capabilities or resources that are still required. Currently, more work is necessary on the model development, for example to what extent model simplifications are acceptable. Also, more resources need to be allocated to overcome the challenges within the in-silico methods for them to be useful for a device approval process.

Future medical device approval processes will obviously only consist of simulations to a proportion. In preparation for future Q-submissions, it is, therefore, crucial not only to list the topics that may be covered in other supplements, but also to state the relationship between the simulations and the other topics. The context of the current supplement should be explained whether earlier supplements are intended to be extended, replaced, altered or remain valid.

In general, reducing sample size in animal or human trials is a future topic for the medical device industry and academic research to explore. Examples of further aspects to consider are influencing the inclusion rate of real-world clinical trials or providing additional insights regarding patient groups, i.e., paediatric populations that are hard to include in clinical trials.

Takeaways: academic perspective

Need for advanced modelling solutions

This feedback regarding the use of computer models for implant approval are helpful for the early stage of developing corresponding models and therefore also of interest for academic stakeholders. Furthermore, insights are gained on which developments and improvements are still needed for a successful implementation of computer models in implant approval in the future.

Transformation of academic work into industry and regulatory process

The academic researchers of the in-silico medicine community have had a first-hand opportunity to see the transformation of our academic work into regulatory evidence. Watching this from the side-lines of the Q-submission process, had offered a glimpse into the hard-reality of challenges and necessary steps to transform a research tool into a medical device approval process.

Need for partnership

With an emerging domain like in-silico trial technologies, the process of regulatory submission has highlighted the clear need for interdisciplinary work. Especially, the role of our academic partners in the consortium to formulate the key themes around in-silico clinical trial design for the industry drive Q-submission, remained a mutually enriching exercise.

Feedback channelizes open challenges

The model-effectiveness related feedback received from the regulators, helps the community to prioritise and channelize on the unmet needs and the critical gaps in the entire ecosystem.

Outlook

This document aims to outline the regulatory process pertaining to the use of in-silico methods for device approval process. The **introduction presented the different engagement strategies and channels** to seek feedback from the regulatory agencies. Subsequently, one-specific example feedback within the project scope was presented in detail in the form of a Pre-Submission within the Q-submission program. To help one get started with adherence to the relevant official guideline, **key highlights from the corresponding FDA guidance document on Pre-submission**[9] were presented in the first part of the procedure section (Part A).

Subsequently, the Part B of the experience report outlines the specific **considerations that are unique and complicated, when dealing with the use of in-silico methods for device approval.** To that end, a high-level non-exhaustive guideline on formulating the scope of approval process are summarised, along with factors that impact the regulatory approval plan. To provide tangible first-hand insights, the example Q-submission process for the PAPS implantable high risk medical device is briefly presented in Part C. Due to confidentiality reasons, we are limited in the details of the entire process. Nevertheless, the report summarises key takeaways for device manufacturers, academic researchers, and possibly also for experts supporting the regulatory process, who are in the forefront of handling in-silico evidence.

Finally, the document concludes with a list **of learnings and best practices** that our team observed or reflected while going through the whole process of regulatory approval for in-silico methods.

To conclude, there are different forums through which we can engage with regulatory authorities, be it in a scientific conference or during an advisory board meeting in a research project or approaching them in a formal approval process. The Q-Submission is not yet an approval but sets the context of the specific market entry of a medical device. As expected, this engagement channel helped us to understand some of the concerns from the authorities with regard to in-silico technologies.

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[9] FDA (U.S. Department of Health and Human Service - Food and Drug Administration): Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, 2023

Appendix

The Pre-Submission of BIO has the FDA reference number Q212597 S004 and remains a confidential dossier. The exemplary Figures below show the cover page of the submission and the associated table of contents.

Figure 3: FDA form for premarket submissions.

Table of Contents

Figure 4: Table of content of the PAPS ISCT Q-Submission.