Clinical strategy as part of pre-submission dialogue between manufacturer and Notified Body

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Introduction

MedTech Europe, AESGP, MedTech &Pharma Platform and COCIR would like **to express their concern that the recently updated *MDCG 2019-6: Requirements relating to notified bodies* revision 5**, while providing further framework for structured dialogue, **has not addressed the ongoing absence of clinical strategy discussion in the pre-submission space. As a result, unfortunately, the gap in clinical evidence expectations will persist – with serious consequences for our industry and for devices continuity**[1].

This situation needs to be addressed by the European Commission and the EU Member States as a matter of priority to enable legacy medical devices and IVDs to transition on time and support the introduction of innovative technologies:

- Clinical strategy is developed by the manufacturer far in advance (months or even years) before the application for MDR/IVDR conformity assessment; hence the need to discuss it before submission of the application for conformity assessment.
- Early alignment on expectations in this area between the manufacturer and the Notifies Body leads to dossiers of better quality and, in turn, reduction of conformity assessment timelines.
- The lack of possibility to discuss clinical strategy pre-submission is expected to have a particularly negative effect on small & medium sized enterprises. Due to their limited resources (financial and personnel) and the already high regulatory burden it will be extremely difficult for SMEs to perform re-working of applications and it might be impossible to re-invest in new data gathering projects.

The MDCG 2019-6 revision 5 outlines types of topics that can be discussed between manufacturer and Notified Body before and after submission of application for conformity assessment. 'Sufficiency of clinical data' is mentioned as an example for post application discussion between manufacturer and a Notified Body. In addition, the updated Team NB Code of Conduct mentions that: ''*Notified Bodies cannot review clinical development strategy as part of structured dialogue*''.

The co-signing industry associations call on the European Commission and the EU Member States to clarify via the foreseen implementing act for application of uniform rules for Notified Body requirements **that pre-submission dialogue between Notified Bodies and manufacturers can include a high level discussion of manufacturer's proposed clinical strategy**. Discussion on a proposed clinical strategy should represent a key aspect of a pre-submission[2] dialogue between the manufacturer and the Notified Body[3].

We suggest in this paper under 'Proposals' concrete principles for how the discussion on clinical strategy could work in practice, which includes possible contractual and transparency measures, should these be needed as additional safeguards.

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[1] 50% of MD and 30% of IVD respondents in the MedTech Europe survey (2024) indicated that at least one application failed or was threatened to fail due to their clinical or performance evaluation.

[2] Note: *pre-submission* - meaning before the submission of application to the Notified Body for conformity assessment

[3] MDCG 2022-14 encourages ''*structured dialogues before and during the conformity assessment process*'' with the intent "*to enhance the efficiency and predictability of the conformity assessment process*."

We would also like to highlight that many major geographies worldwide allow pre-submission meetings to discuss clinical strategy (see Annex I), and we encourage the EU regulators to take inspiration from these best practices. It is also worth noting that in case of medicinal products in the EU such dialogues/meetings are considered standard practice and include advice of the national authority.

What is clinical strategy and why timing matters

1. Clinical strategy

A clinical strategy for medical devices involves creating a detailed clinical evaluation plan/performance evaluation plan (CEP/PEP) and post market clinical follow up/post market performance follow up (PMCF/PMPF) Plan to ensure the device meets regulatory requirements and demonstrates safety and performance outcomes in alignment with the stated clinical benefit(s). The key aspects to be addressed may include:

- What clinical evaluation/performance evaluation pathway is foreseen for the device in question
- What clinical and other pertinent evidence level in relation to the risk class, intended purpose/population[4] and novelty of the device would be considered sufficient to obtain initial CE certification and maintain CE certification for changes to existing devices.
- What options might be considered for generating such clinical evidence pre and post market

Given the diversity of the MedTech industry, there is no one-size-fits-all solution to these questions. For this reason, it is crucial to discuss clinical strategy with the Notified Body on a case-by-case basis upon request by the manufacturer.

2. Predictability

In order to effectively plan clinical activities and resources, the manufacturer needs at minimum a general indication of whether the proposed clinical strategy is deemed acceptable or not. It is clear that Notified Bodies cannot provide consultancy and have to remain impartial as per Annex VII[5]. It is therefore, understood that the clinical strategy discussions as part of pre-submission dialogue are intended to be high level in nature, and Notified Bodies would not be expected to provide any specific advice on how to achieve compliance with regulatory requirements. The co-signing industry associations are of the opinion that this aligns with Annex VII section 1.2.9. which does not preclude *''exchanges of technical information and regulatory guidance between a notified body and a manufacturer applying for conformity assessment''.*

Bringing predictability on clinical strategy early in the pre-submission stage (ideally during the early product development phase) is essential for the predictability of the entire conformity assessment process.

- An establishment of clinical strategy leads to specific actions for the manufacturer (e.g., development activities, designing and executing pre- and post-market clinical activities, product testing/validation, product launch) and human/capital resource investment over a period of

[4] A pre-submission discussion can also help manufacturers choose the right location for their clinical investigations, e.g. Europe or outside of Europe.
[5] MDR Annex VII section 1.2/ IVDR Annex VII Section 1.2.

several years. It is hence necessary to engage in dialogue as early as possible in the clinical development process.

- If the manufacturer does not receive feedback during the device development phase whether their clinical strategy is acceptable, the clinical data gathered in support of the submission may later be determined insufficient or misaligned with the stated clinical benefit. As an illustration, 50% of MD and 30% of IVD respondents in the MedTech Europe survey (2024) indicated that their clinical or performance evaluation for at least one application, was significantly challenged by their Notified Body. It is therefore critical that the clinical strategy – which is in line with Notified Body expectations – be defined early to avoid unnecessary adjustments later in the process, which will benefit patients, healthcare professionals and manufacturers.

The current situation represents significant costs with a potential impact on EU investment decisions, resources deployment for both manufacturers and Notified Bodies, but most importantly a delay in product availability for the patient e.g. a delay of up to 2-3 years for new products and potential patient ethical considerations. Further, in the case of companion diagnostics, these delays can result in the delayed availability of co-developed testing essential for the selection of medicines for patients. A functional and timely pre-submission discussion on clinical strategy may prevent these challenges.

Proposals:

1) **MDR implementing act to clarify clinical strategy discussion is possible pre-submission**

As mentioned, the recently published MDCG 2019-6 revision 5 includes 'Sufficiency of clinical data' as an example for post application discussion. The discussion on clinical strategy should take place **before submission'**' in order to increase predictability and timely availability of medical devices and IVDs. Therefore, the undersigned industry associations strongly suggests that wording to this effect is included in the foreseen implementing act for application of uniform rules for Notified Body requirements. The content of such early discussions would be similar to those envisaged during the conformity assessment, and hence it would not represent a conflict of interest. Manufacturers develop their Clinical development plans (CDPs) and Clinical/Performance evaluation plans (CEPs/PEPs) months or even years in advance of conformity assessment application submission to allow sufficient time for gathering of all required clinical data from clinical investigations and/or other activities. Being able to discuss clinical strategy only after the application submission has been made is too late and the clinical investigations and/or other activities are in most cases already completed.

2) **How could pre-submission discussion on clinical strategy work?**

The pre-submission discussion on clinical strategy should not be considered as part of the process by default. In order to make efficient use of Notified Body resources, it should only take place if there is a real need identified by the manufacturer.

We include here a proposal of key elements for transparent and efficient pre-submission dialogue on clinical strategy without jeopardising the Notified Body's independence or impartiality:

- A summary document or presentation should be provided to the Notified Body in advance of the scheduled meeting to facilitate appropriate preparation and inclusion of attendees with applicable clinical background.
- During the meeting manufacturer presents their proposal for clinical strategy
- Notified Body provides high level input on the direction of clinical strategy (are you on the right path/not); Notified Body does not provide suggestions on how to fill gaps in clinical data
- Notified Body may provide input on clinical strategies deemed not acceptable
- Meeting minutes are prepared by the manufacturer and sent to the Notified Body for comments/corrections
- Meeting minutes and meeting material may be shared by the Notified Body with a Competent Authority, if desired
- Follow-up meetings may be organized if necessary

It could also be envisaged that manufacturer and Notified Body sign an agreement for conformity assessment already at pre-submission stage ahead of discussion on clinical strategy.

Conclusion:

MedTech Europe, AESGP, MedTech & Pharma Platform and COCIR strongly urge the European Commission and the EU Member States to clarify in the foreseen implementing act for application of uniform rules for Notified Body requirements that **high level discussion of clinical strategy** can take place 'before submission of the application'. This will allow alignment on expectations between manufacturers and Notified Bodies; thereby reducing the likelihood of rejections and improving predictability of the conformity process. Pre-submission discussion on clinical strategy can significantly help in ensuring timely availability of devices for healthcare professionals and patients.

Annex I: International practice:

Country	*# 1 Possibility to request consultation and on proposed technical & clinical evidence before submission: Yes/ No*	*If # 1 yes How early prior a submission is this possible?*	*If # 1 yes How many meeting could be allowed?*	*If # 1 yes Are those consultations free, if not what is the cost?*	*If # 1 yes Are there official minutes?*	*Is there a path in place facilitating review and registration of innovative device & link to regulations*
US	**Yes**	Any time – This is done through a formal request for FDA feedback through the Q-Submission Program.	Feedback may be written and/or through a formal meeting (face to face or teleconference). There is typically one meeting per pre-submission	Yes	Yes – minutes are to be taken by the applicant and sent to US FDA as part of the pre-submission process.	Yes: Breakthrough Devices Program | FDA **TAP:** https://www.fda.gov/medical-devices/total-product-life-cycle-advisory-program-tap/tap-overview **Safer Technologies Program (STePa**) https://www.fda.gov/medical-devices/how-study-and-market-your-device/safer-technologies-program-step-medical-devices
China	**Yes,** but usually the feedback could be very generic from the authority (unless innovative device or other clinical urgency device).	Any time – but the more specific the question is, the better the answer	Emails – can be sent anytime. The authority will usually respond in 1-2 weeks. On site consultation – once a month with limited slots open to applicants. Each applicant may be given 10-15 minutes to talk with reviewers f2f.	Yes, it is free.	Yes. There is email feedback.	Yes. Innovative product could enter green channel. 国家药监局关于发布创新医疗器械特别审查程序的公告（2018年第83号）
Japan	**Yes**	Depends on the consultation category (clinical, bench testings, literature review) There are also consultation categories that can be applied before development begins or in the early stages of development.	For each consultation, there will be one final face-to-face meeting. There will be multiple rounds of inquiries before the face to face meeting. Follow-up meetings are also possible.	Not Free. Costs vary depending on consultation category. 2,000 USD to 16,000 USD.	Yes.	Sakigake designation system: Strategy of SAKIGAKE by MHLW | Pharmaceuticals and Medical Devices Agency Medical equipment with high medical needs: 医療ニーズの高い医療機器等の早期導入に関する要望対象の拡大と要望の募集について｜厚生労働省 In any case, designation is required, which is complex.

Australia	**Yes**	Any time – this is done via a pre-submission meeting request Pre-submission meetings with TGA | Therapeutic Goods Administration (TGA)	Typically one pre-submission meeting but follow-up meetings can be requested.	Free	Applicant can create a meeting record with actions and share with meeting participants (TGA will acknowledge within 2 weeks)	There is also the option to seek priority review for which certain criteria must be met. The criteria for priority applications includes breakthrough technology offering a major clinical advantage of existing technology: Understanding priority applicant determination rules for medical devices including in-vitro diagnostics (IVDs) | Therapeutic Goods Administration (TGA) The priority application submission fees are much higher, approx. $11k AUD
Korea	**Yes**	1.Pre-review (Limited to rare/innovative/ newly developed device) 2.Pre-review (Limited to rare/innovative/ newly developed device) No limitation	One time No limitation	Yes free Not free	No but official result letter including QnA and feedback for submission documents	Notification of Application for Integrated Review of Innovative Medical Device Designation in 2024(No. 2023-619)
Canada	**Yes** – 3 types: 1)Presubmission 2)Pre-clinical 3)Novel technology	No set limit	1 meeting per request. 20-minute presentation only; does not allow for written summary like US does.	Free	Company responsible for taking minutes and submitting to HC for comment.	ATP pathway: Regulating advanced therapeutic products - Canada.ca Draft guidance on advanced therapeutic products framework: Overview - Canada.ca
Brazil	**Yes**	Any time.	There is no limit. However, it depends on the agency's judgment whether additional meetings are necessary.	Yes, free.	Yes. ANVISA is responsible for taking of minutes and the company can suggest corrections	Can request a meeting through the electronic system of ANVISA and the agency will evaluate if it is applicable.

About us

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions. www.MedTecheurope.org

The Association of the European Self-Care Industry (AESGP) is a non-profit organisation which represents the manufacturers of non-prescription medicines, food supplements and self-care medical devices* in Europe, an area also referred to as consumer healthcare products. https://aesgp.eu/
**Self-care medical devices are generally available without medical prescription and are self-administered*.

The Medtech & Pharma Platform (MPP) Association focuses on the combined use of health technologies, including: Medicinal products, Medical devices and Digital technologies. www.medtech-pharma.com

COCIR is the European Trade Association representing the medical imaging, radiotherapy, health ICT and electromedical industries. Founded in 1959, COCIR is a non-profit association headquartered in Brussels (Belgium) with a China Desk based in Beijing since 2007. We provide a wide range of services on regulatory, technical, market intelligence, sustainability, standardisation, international and legal affairs. COCIR is also a founding member of DITTA, the Global Diagnostic Imaging, Healthcare IT and Radiation Therapy Trade Association. https://www.cocir.org/

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