

# Regulatory and risk oriented approach to the design and development of medical devices in accordance with Ukraine regulations

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## Abstract

Based on the interpretation of regulatory requirements to describe the approach to risk-oriented medical devices design and development strategy and approaches to their certification in Ukraine market. The approach to the medical devices design and development strategy is described taking into account the classification by level of risk; a tree of decisions on determining the risk class and certification of medical devices according to the requirements of the Technical Regulation № 753 is presented.

## Keywords

design, development, medical devices, regulatory requirements, CMC (chemistry, manufacturing, control), research, development verification, development validation, development analysis, risk, certification, conformity assessment, safety, efficiency, quality

## Introduction

Every day the global pharmaceutical market is evolving and growing at a tremendous rate. The issue of providing people with quality and safe drugs, medical devices, reagents and in vitro devices is growing at the same rate, which is described in the relevant Guidelines of Ukraine (Resolution of the Cabinet of Ministers of Ukraine 2018).

Considering this, taking as the main goal to achieve a high level of patient health and user safety world regulatory requirements aimed at ensuring the continuous and uninterrupted functioning of the global pharmaceutical market.

Mostly, the quality, safety and efficacy of pharmaceutical products are laid down and achieved at the development stage. For the proper production of pharmaceuticals must be determined the control points of the production

processes and the characteristics of the product, which are subject to the most careful and detailed supervision. That is why it is necessary to have a predetermined approach and strategy of product development before any research and approval of the concept of new pharmaceutical elements. Especially for medical devices, since this is a relatively new element of the pharmaceutical market compared to drugs.

## The main part

Chemistry, manufacturing, control (CMC) of a medicinal product is a key stage in the pharmaceutical development process. CMC control starts with the identification of a new chemical compound or substance during drug development and run on during all stages of the product life

cycle. Conduct and control rules of each CMC stage are described in the international regulatory requirements for drugs, compliance with which is a guarantee of compliance with quality standards. Thus, for the Ukrainian market, this is described in the Guidelines “Drugs. Pharmaceutical development (ICH Q8). ST-N MOZU 42-3.0: 2011” (Ministry of Health of Ukraine 2011).

CMC main purpose is to guarantee product quality at all stages of development and manufacture, ensuring the stability and efficiency of each unit of the finished product. CMC Regulatory compliance ensures that, if the manufacturer has made all CMC-specific commitment to regulatory agencies, such CMC practices are carried out.

Each development stage must be controlled, properly analyzed, and documented by CMC. In the developing stage of a new medicinal product, the manufacturer have to form Module 3 of the Common Technical Document (CTD), in which must be described each stage of development according to a clearly defined structure. Thus, the basics CMC rules, set out in the guidelines for manufacturers of medicines, are designed to ensure the production of safe and high quality product from development to commercialization and throughout the drug life cycle.

The situation for medical devices is somewhat different. This difference has also been described by Marshall et al. (2021). Unlike medicines, today medical devices (MDs) are a young concept in the pharmaceutical industry and do not have an exhaustive list of types, forms of release, applications, etc., which greatly complicates the ability to establish clear and universal regulatory requirements for development, safety, and efficacy for all types of medical devices. There are no international classifications of product criteria for medical devices, which are clearly defined and approved for medicines. For example, dosage form, primary packaging, list of active pharmaceutical ingredients and excipients, etc.

In addition, the development of medical devices requires consideration and combination of international regulation requirements, the diverse profile of users and the large volume of scientific base that must be considered in the design process. For example, Maak et al. (2016) described the intersection of the regulatory requirements of the United States of America and Europe, and Martelli et al. (2019) described the changes that have been implemented in the regulatory requirements of Europe in recent years. In addition, according to Thomas et al. (2015) and Privitera et al. (2017), an additional complication is that the development team consists mostly of technological engineers, who are usually not experts in the medical field and often do not have in-depth knowledge of potential users or the intended environment and risks associated with them. Failure to fully comply with all the described requirements may adversely affect to the design of the final concept of the medical device. Such observations are also indicated by Christopher et al. (2014).

Therefore, there is no CMC for medical devices in its common sense, considering the huge variety of products that fall under the concept of MD.

Chemistry, manufacturing, and control. Again, if the last two concepts are easy to understand for medical de-

vices, then the “chemistry” in this case is more difficult. Conventionally, the majority of MD can be divided into drug-like (eye drops, inhalation solutions, injectable implants, etc.), polymer products (syringes, infusion systems, cannulas, etc.) and active (MD works with electricity: tomographs, nebulizers, breathing simulators, software, etc.). In addition, there are a number of other examples of medical devices, such as medical textiles - plasters, gauze, bandages, bandages, etc.; devices made of various metals - titanium adapter, platinum stent, various prostheses and many other additional groups of medical devices.

For medicinal devices similar in form to medicinal products, the concept of “chemistry” is obviously easy to interpret and, referring to the requirements for the development and control of medicinal products, it is not difficult to identify critical points in the life cycle of such products to ensure safety for patient and/or users. And such similarity to medicinal products allows the application of similar concepts and principles to medical devices design and development.

But for polymer and active MDs, the concept of “chemistry” is not the main focus of development. For products of these two categories, we can define another key concept - “technology”. The technology becomes decisive in the process of manufacturing polymer and active products: casting of components, finished goods assembly, soldering of electrical boards, etc. Approach to technology for medical devices described by Priftis et al. (2017). That is, CMC for medical devices is becoming a broader concept, becoming CTMC - chemistry, technology, manufacturing, and control.

To determine the main scopes and objectives of CTMC, it is necessary to refer to the global regulatory: Design control Guidance for medical device manufacturers (Guidance relates to FDA 21 CFR 820.30 and Sub-clause 4.4 of ISO 9001) (FDA Guidance Documents 1997), Medical Device Regulation (EU) 2017/745, Medical Device Single Audit Program (MDSAP) (MDSAP 2022) and ISO 13485 Medical device quality management system (ISO 2020). These regulatory requirements establish high quality standards for MD to achieve the safety and efficacy of such pharmaceutical products.

Considering the complexity of using a similar approach to drugs for MD’s classification (by form of release, API, indications, etc.), medical devices are classified according to the risk level which determines the degree of their safety for the user and consumer.

- class I - low-risk medical devices (additionally there are I and Is, where Is is a sterile product);
- class IIa - medium risk medical devices;
- class IIb - high risk medical devices;
- class III - highest risk medical devices.

The classification was described in detail by Aronson et.al. (2020) as well.

Such classification is applied in Ukraine market in accordance with the requirements of the Technical Regulation on Medical Devices, approved by the Cabinet of Ministers of October 2, 2013 № 753 (Ministry of Health of Ukraine 2020; Resolution of the Cabinet of Ministers

of Ukraine 2022). In the European Union same classification applied according to the requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical device. This regulatory requirement applies to the territories of all member countries of the European Union such as Bulgaria, Poland, Lithuania, Germany, etc.

The classification rules in the Technical Regulation № 753 (Resolution of the Cabinet of Ministers of Ukraine 2022) are presented in Annex 2 Criteria for the classification of medical devices. The classification rules are based on the intended use, considering the benefit-risk balance of the MD use for its intended purpose under the conditions specified by the manufacturer.

Based on the described in Technical Regulation № 753 (Resolution of the Cabinet of Ministers of Ukraine 2022) classification criteria, a decision tree for determination the risk class of the medical device was developed.

Classification criteria are formed considering the maximum possible variations of medical devices. The decision tree was divided into four blocks based on Annex 2 of the

Technical Regulation № 753 (Resolution of the Cabinet of Ministers of Ukraine 2022):

1. Special rules (Fig. 1);
2. Criteria used for active medical devices classification (Fig. 2);
3. Criteria for non-invasive medical devices (Fig. 3);
4. Criteria for invasive medical devices (Fig. 4).

The requirements of CTMC should be applicable to a wide range of product types, so they do not establish clear methods of control over the design and development process compared to CMC. Instead, they establish the structure and risk-oriented principles that should be used by manufacturers in the MD development and manufacturing process.

This structure and principles are quite flexible, which allows them to be interpreted and applied to any type of medical device. The main goal is to build a process of quality management in the design and development of medical devices, which is traced from the product idea

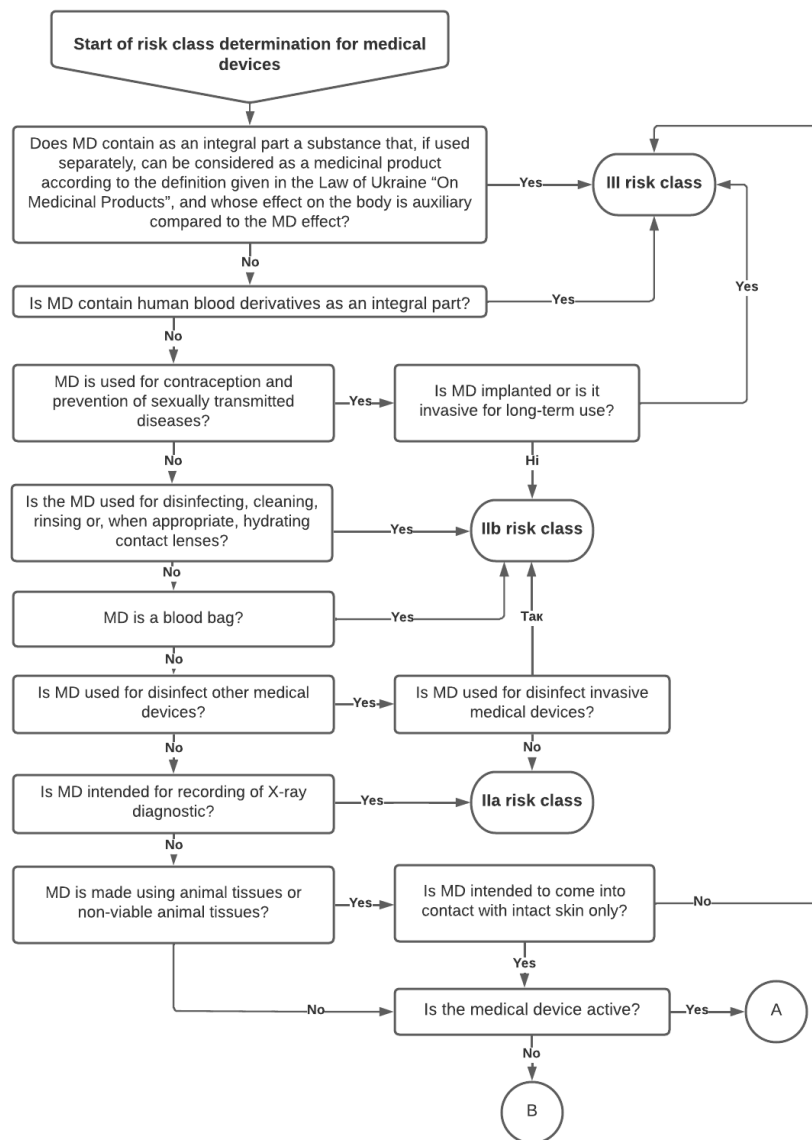
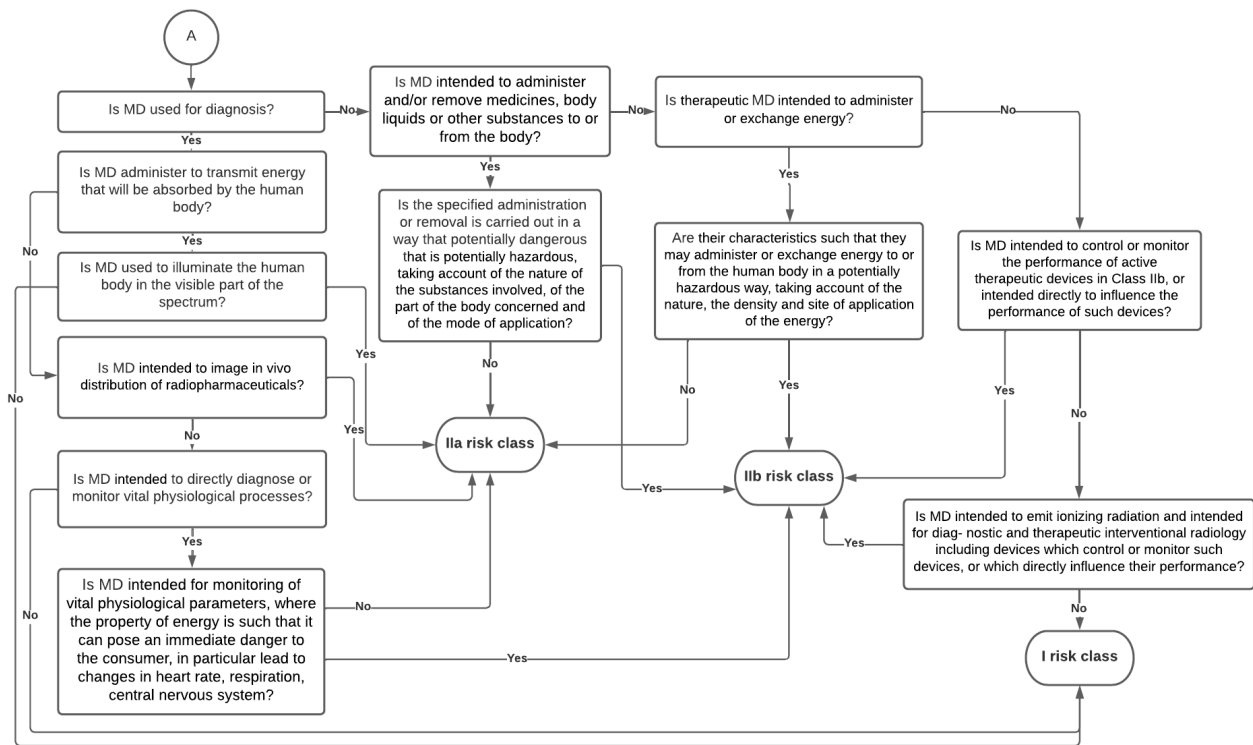


Figure 1. Risk class determination (Special rules).



**Figure 2.** Risk class determination (rules applicable to active devices).

and throughout the MD's life cycle. The described structure consists of the following stages according to the ISO 13485:2016 (ISO 2020):

- Design and development planning;
- Design and development inputs;
- Design and development outputs;
- Design and development review;
- Design and development verification;
- Design and development validation;
- Design and development transfer;
- Design and development changes.

Design and development planning is aimed at the first stages of the product idea, which should be based on market analysis, the current state of development of pharmaceutical technologies and the user's needs. By using the risk-oriented approach to the MD development for achieving maximum safety and effectiveness of medical devices for users before making design and development plan it is needed to identify and analyze possible risks. The risk analysis process is based on the idea of developing a new medical device, considering intended use and associated hazards.

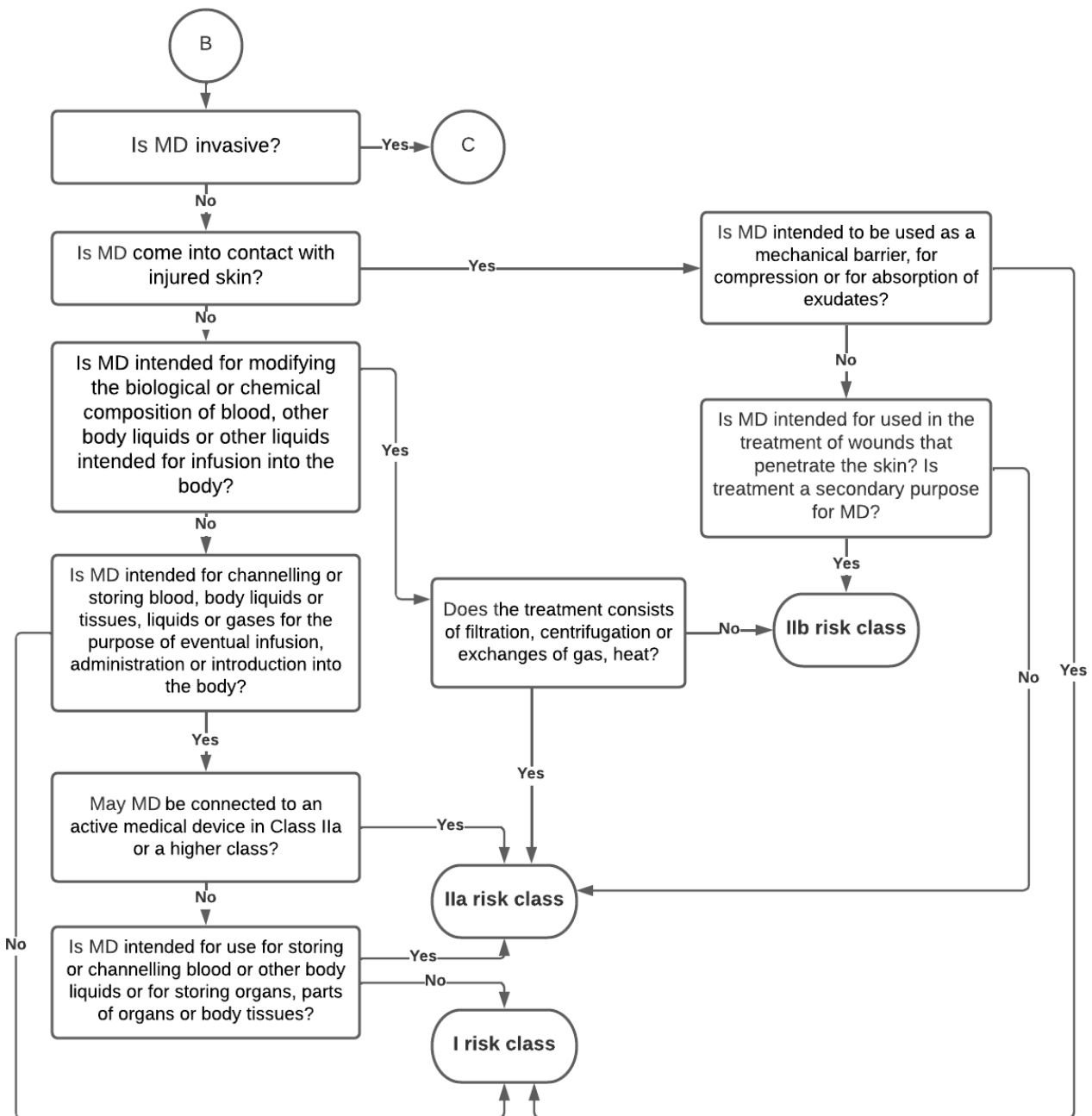
Based on the result of risk assessment, a design and development plan is formed based on the obtained data on the identified control measures the identified risks for reducing the risk level as far as possible.

In addition to describing the main steps of design and development plan, it also includes data analysis, which is necessary to be able to comprehensively consider a new product idea, anticipate the necessary tests and analyze any risks to quality and safety that are important to consider

during design. The main goal of the risk management process is to reduce the level of all anticipated risks as far as possible, as it is impossible to produce a completely safe device with zero risk. The importance of a risk-based approach in development was described by Mounika et al. (2020), and the main principles of the risk management approach for medical devices are presented in ISO 14971:2019 (ISO 2019). This stage focuses on a scientific approach to understanding the concept of the product combined with direct understanding and interpretation of regulatory requirements for successful building of strategy for design and development of new medical device defining all quality attributes, considering product features and type.

The input data describes the functional and operational requirements for the device identified during planning in the process of its intended use, a list of clear regulatory requirements that are essential in determining, the list of required tests and trials. If the manufacturer has experience in developing of the devices this the same design, this section also indicates and analyzes information about similar products, their comparisons and conclusions that may affect the development of a new MD.

The outputs data demonstrate the actual course of design and development, including any changes in strategy, based on the results of laboratory tests if available and the results of all practical tests, ensure the availability and traceability of control over the supplier chain of raw materials, packaging, components, production or services. At this stage, all the key characteristics of the product are determined to achieve its functional goals, determining the final profile of the medical device.



**Figure 3.** Risk class determination (Non-invasive devices).

In the end of each design and development plan stage the systematic analysis of the design and development is carry out of the relevant stage - design and development review. The review is conducted to confirmation of compliance planned and implemented actions and activities, as well as to assess the results of each stage, which allows to move forward on the path of development. The review is conducted in accordance with the planned and documented dates specified in the medical device design and development plan for:

- assessment of compliance of results at each stage with the established requirements and criteria;
- identification and implementation of necessary corrective actions in case of discrepancies.

Verification is carried out to demonstrate the compliance of the planned concept (input data) with the final one (output data). For this manufacturer have to document and reflect the critical points of verification and methods of its implementation.

Validation is one of the most important stages of design and development and is carried out to demonstrate that the medical device meets the requirements of users and fulfills its intended purpose and is safe and effective when used as intended under the manufacturer’s conditions.

An additional unit of validation is the usability of the medical device, ie taking into account the human factor when using the device, the ease and accessibility of understanding the principle of operation and interpretation of the data. Russell (2018) proposes to determine five dimensions of Usability:

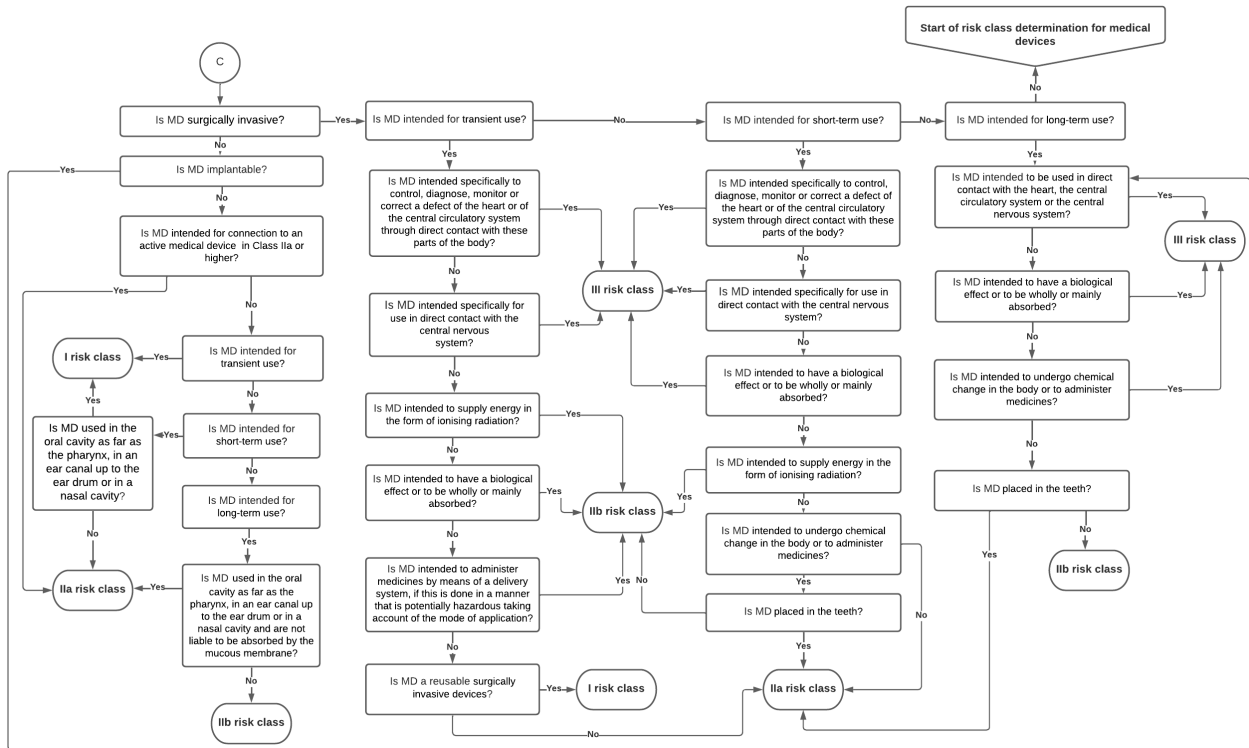


Figure 4. Risk class determination (Invasive devices).

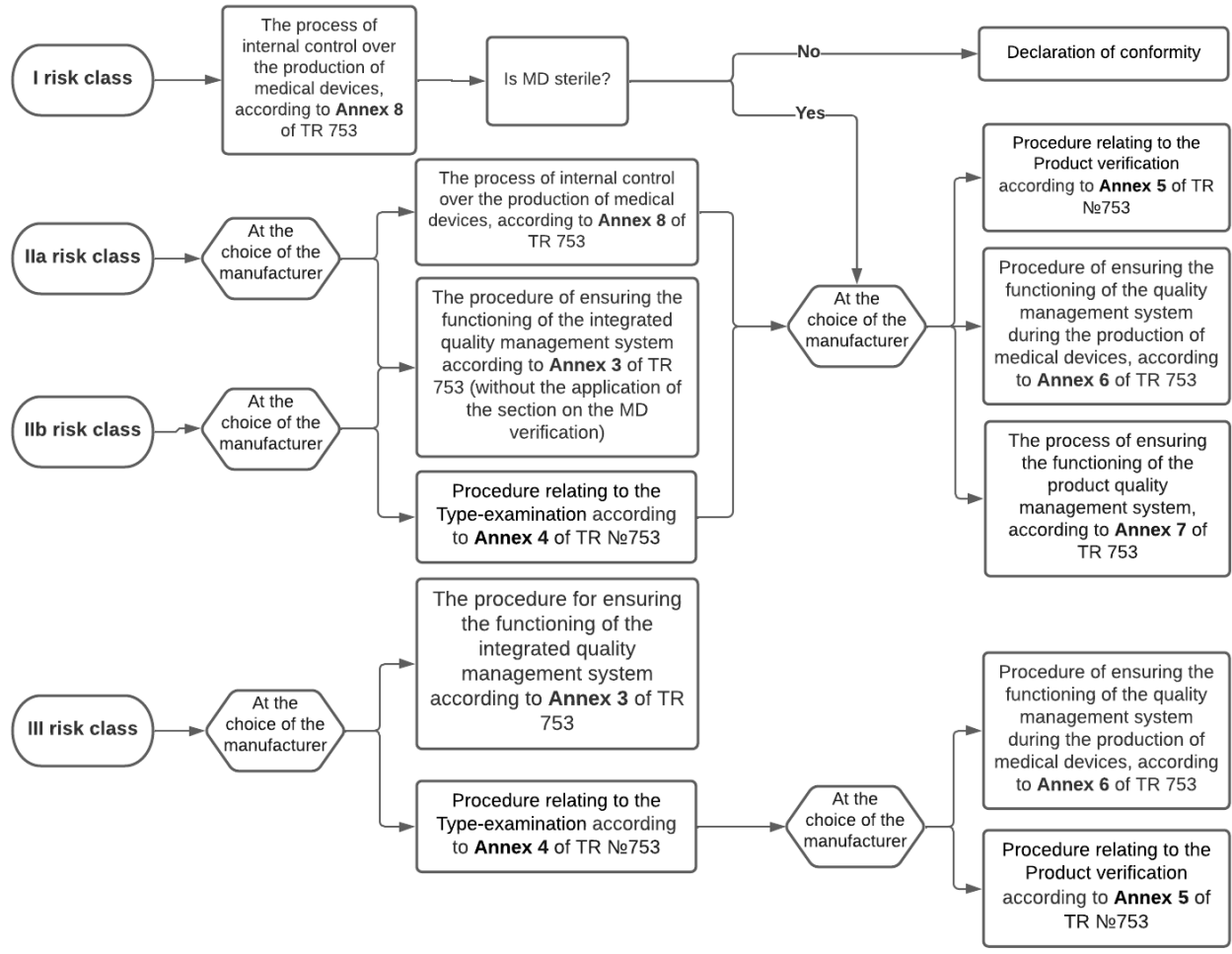


Figure 5. The way of conformity assessment according to the Technical Regulation № 753.

- Learnability refers to the ability of users to quickly and correctly start using new medical device, as well as to develop skills in a reasonable time.
- Efficiency is whether the MD allows users to perform tasks easier than working without the device.
- Memorability refers to how easily users can return to the system after a period of inactivity and remember important functions, and interactions.
- Error resistance and remediation refers to how well the system prevents errors or handles errors when they occur.
- Satisfaction refers how pleasant it is to use the system.

Validation documentation is presented in the form of retrospective development data based with all laboratory and research studies, and perspective data filled with data on production batches and control of critical production points throughout the life cycle of the MD.

The design and development transfer is the final stage of development. The transfer must ensure that the initial design and development data have been verified for compliance with the production requirements.

The transfer to production realized after analysis and approval of all product specifications and quality management system documents or quality control procedures and methods.

In other words, the design and development transfer demonstrate the process of scaling up production by transferring technology from laboratory to industrial conditions.

After successful transfer of the project from laboratory to production, review, verification, and validation of the project in terms of which safety, efficacy of the medical device and compliance with regulatory requirements are proven, the product becomes ready for production in industrial conditions and marketing to its target user.

From July 1, 2015, to obtain a permit for the sale of medical devices on the Ukrainian market, it is mandatory to assess compliance with the requirements of the Technical Regulation № 753 (Aronson et al. 2020). The way of conformity assessment is chosen depending on the classification of the product according to the risk class, which is presented in Fig. 5.

The approach presented in Fig. 5 is not intended for devices which are custom-made or intended for clinical investigations.

Technical Regulation № 753 (Resolution of the Cabinet of Ministers of Ukraine 2022) came into force on 1 July 2015 based on harmonization with European legislation, namely Council Directive 93/42 / EEC of 14 June 1993 on medical devices. However, given that on May 26, 2021 in the European Union, Directive 93/42 / EEC was replaced by the Medical Device Regulation (EU) 2017/745 (Fink and Akra 2020; Tarricone et al. 2020; Antich-Isern et al. 2021), we can expect to change the Ukrainian legislation in the near future.

After placed MD on the market, the manufacturer must provide a change management process that reflects any changes during the life cycle, assessing the significance of these changes and the risks associated with them. This

process is directly related to the risk management process for medical devices, which is controlled by ISO 14971 (ISO 2019): 2019. As part of this process, any records of changes, their analysis and actions caused by these changes must be kept and maintained.

To demonstrate compliance with all regulatory requirements and achieve the safety and efficacy of medical devices, all of these steps must be documented and monitored for each unit of product. The level of detail required to present information and the amount of research required is directly proportional to the level of risk of the medical device. All records are compiled into a documents package, which is updated and supplemented throughout the life cycle of each medical device. In different regulatory requirements, such a package of documents is presented differently:

- Design history file (FDA) (FDA Guidance Documents 1997);
- Design and development file (ISO 13485) (ISO 2020);
- Design Dossier (MDR).

Despite the different name, the goal is the same - to establish and control the target product quality profile, critical production process parameters and critical attributes of safety and efficiency, changes control in product life cycle and vigilance on medical device in all markets, and record development history (Lebanova et al. 2011).

Due to the formation of the average name, there is a concept of the Design and Development Dossier, which reflects and demonstrates compliance with all the requirements of the CTMC for medical devices.

MD design and development dossier contained all documents that consistently reflect the history of design and development of a medical device, including the production of research and batches production, quality control and transfer to production, as well as all other consecutive actions that reflect information on quality, safety and efficacy of medical device or medical device family.

Thus, similar to the structured Module 3 of the Common Technical Document with reflection of all CMC requirements for medicinal products, for medical devices the concept of the Design and Development Dossier is equivalent, which comprehensively and in detail describes and reflects compliance with the requirements, the history of its development and production.

## Conclusion

This integrated approach allows manufacturers to develop and build a strategy for the design of any type of medical device, regardless of its level of complexity, and provides regulators with easily accessible and traceable information for comprehensive control of safety and effectiveness of MD in the process of conformity assessment and ensuring uninterrupted operation of global medical devices market, based on a high level of health protection for patients and users. Due to the specifics of the product, a concept of

CTMC has been identified for medical devices - chemistry, technology, manufacturing, and control, which allows a deeper and comprehensive describe the concept of design and development of medical devices from the idea and through all MD's life cycle.

Based on the analysis of the Technical Regulation №753 requirements, a decision tree was developed to determine the risk class of the medical device at the development stage and approach to the conformity assessment procedure to scale production of new MD and its commissioning.

## References

- Antich-Isern P, Caro-Barri J, Aparicio-Blanco J (2021) The combination of medical devices and medicinal products revisited from the new European legal framework. *International Journal of Pharmaceutics* 607: 120992. <https://doi.org/10.1016/j.ijpharm.2021.120992>
- Aronson JK, Heneghan C, Ferner RE (2020) Medical Devices: Definition, Classification, and Regulatory Implications. *Drug Safety* 43: 83–93. <https://doi.org/10.1007/s40264-019-00878-3>
- Christopher JV, Yunqiu Li, Ann B (2014) Integration of human factors and ergonomics during medical device design and development. *Applied Ergonomics* 45(3): 413–419. <https://doi.org/10.1016/j.apergo.2013.05.009>
- FDA Guidance Documents (1997) Design Control Guidance For Medical Device Manufacturers. Guidance for Industry. FDA-2020-D-0957. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-control-guidance-medical-device-manufacturers>
- Fink M, Akra B (2020) Regulatory clearance: How are outcome measurements critical? <https://doi.org/10.1016/j.injury.2019.10.071>
- ISO (2019) Medical devices – Application of risk management to medical devices. ISO 14971:2019.
- ISO (2020) Medical devices – Quality management systems – Requirements for regulatory purposes. ISO 13485:2016.
- Lebanova H, Grigorov E, Getov I (2011) Materiovigilance - Basic Concepts and Legislative Framework. *Pharmacia* 58(1–4): 98–103. <https://doi.org/10.13140/2.1.1846.4329>
- Maak TG, Wylie JD (2016) Medical Device Regulation: A Comparison of the United States and the European Union. *Journal of the American Academy of Orthopaedic Surgeons* 24(8): 537–543. <https://doi.org/10.5435/JAAOS-D-15-00403>
- Marshall J, Morrill K, Gobbe M, Blanchard L (2021) The Difference between Approval Processes for Medicinal Products and Medical Devices in Europe. *Ophthalmologica* 244(5): 368–378. <https://doi.org/10.1159/000517522>
- Martelli N, Eskenazy D, Déan C, Pineau J, Prognon P, Chatellier G, Sapoval M, Pellerin O (2019) New European Regulation for Medical Devices: What Is Changing? *CardioVascular and Interventional Radiology* 42: 1272–1278. <https://doi.org/10.1007/s00270-019-02247-0>
- MDSAP [Medical Device Single Audit Program] (2022) Medical Device Single Audit Program (MDSAP). <https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap>
- Ministry of Health of Ukraine (2011) Настанова «Лікарські засоби. Фармацевтична розробка (ICH Q8). СТ-Н МОЗУ 42–3.0:2011», затверджена Наказом МОЗ України від 03.10.2011 р. № 634 [Guidelines “Medicines. Pharmaceutical development (ICH Q8). ST-N of the Ministry of Health 42–3.0: 2011”, approved by the Order of the Ministry of Health of Ukraine dated 03.10.2011 № 634]. [in Ukrainian] <https://compendium.com.ua/uk/clinical-guidelines-uk/standartizatsiya-farmatsevtichnoyi-produktsiyi-tom-1/st-n-mozu-42-3-0-2011/>
- Ministry of Health of Ukraine (2020) Наказ МОЗ України від 22.01.2020 р. № 142 про затвердження методичних рекомендацій із застосування Технічного регламенту щодо медичних виробів, затвердженого постановою Кабінету Міністрів України від 02 жовтня 2013 року № 753 [Order of the Ministry of Health of Ukraine dated 22.01.2020 № 142 on approval of methodological recommendations for the application of the Technical Regulation on medical devices, approved by the resolution of the Cabinet of Ministers of Ukraine dated October 2, 2013 № 753]. <https://www.apteka.ua/article/531551> [Date of application 19.02.2021]
- Mounika G, Swaroop S, Chella G (2020) Trends in Development of Medical Devices. <https://doi.org/10.1016/B978-0-12-820960-8.00008-3>
- Priftis S, Grigorov E, Georgiev S, Yanakieva A (2017) Health Technology Assessment of Medical Devices. *Zdravna Politika i Menidjement [Health policy and management]* 17(2): 68–73. [In Bulgarian]
- Privitera MB, Evans M, Southee D (2017) Human factors in the design of medical devices - Approaches to meeting international standards in the European Union and USA. *Applied Ergonomics* 59(Part A): 251–263. <https://doi.org/10.1016/j.apergo.2016.08.034>
- Resolution of the Cabinet of Ministers of Ukraine (2018) Постанова Кабінету Міністрів України від 5 грудня (2018)р. № 1022 Державна стратегія реалізації державної політики забезпечення населення лікарськими засобами на період до 2025 року [Resolution of the Cabinet of Ministers of Ukraine of December 5, 2018 № 1022 State strategy for the implementation of state policy on providing the population with medicines for the period up to 2025]. [in Ukrainian] <https://www.kmu.gov.ua/npas/pro-zatverdzhennarski-mi-zasobami-na-period-do-2025-roku>
- Resolution of the Cabinet of Ministers of Ukraine (2022) Постанова Кабінету Міністрів України від 2 жовтня 2013 р. № 753 Про затвердження Технічного регламенту щодо медичних виробів [Resolution of the Cabinet of Ministers of Ukraine of October 2, 2013 № 753 On approval of the Technical Regulation on medical devices]. <https://zakon.rada.gov.ua/laws/show/753-2013-%D0%BF#Text> [Date of application 20.01.2022]
- Russell JB (2018) Human Factors in Medical Device Design: Methods, Principles, and Guidelines. *Critical Care Nursing Clinics of North America. Critical Care Nursing Clinics of North America* 30(2): 225–236. <https://doi.org/10.1016/j.cnc.2018.02.005>
- Tarricone R, Ciani O, D'Acunto S, Scalzo S (2020) The rise of rules: Will the new EU regulation of medical devices make us safer? *Injury - International Journal of the Care of the Injured* 51(Supplement 2): S67–S70. <https://doi.org/10.1016/j.ijim.2020.07.012>
- Thomas J, Hagedorn Ian R Grosse, Sundar K (2015) A concept ideation framework for medical device design. *Journal of Biomedical Informatics* 55: 218–230. <https://doi.org/10.1016/j.jbi.2015.04.010>