Holistic Perspective to the Drug-Device Combination Product Development Challenges

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Abstract. The steady growth of life expectancy calls for a new view on the importance of MedTech combination product development. One can envision that to keep a higher quality of life, more people would require some form of therapy depending on their individual state of health. This would require more medical devices of different types and complexity to be designed for specific drugs. However, from a holistic perspective, several challenges emerge in the development of drug-device combination products. An additional layer of complexity appears due to the increasing complexity of the MedTech devices, as they interact with the other systems and products in the design environment. This paper discusses those potential challenges and proposes ways to mitigate them. The primary focus of this work is on the drug delivery systems, such as autoinjectors.

Keywords: Combination Product, MedTech, PLM, Systems Engineering, MBSE, Digital Engineering.

1 Introduction

From 1970 to 2021 life expectancy has been showing a steady growth globally: in the US, life expectancy reached 77,2 years in 2021 compared to 70,7 years in 1970 (9,2% increase). In France, it was 82,5 years in 2021 – 16% growth from 1970 when it was 71,2. Considering the other regions, one can observe a similar trend: in Brazil, the life expectancy has increased from 57,2 years (1970) to 72,8 years (2021) – 27% growth; in Nigeria – from 39,7 years (1970) to 52,7 years (2021) – growth by 33%; in China – from 56,6 years (1970) to 78,2 years (2021) – 38% increase [1]. Although such global crises as pandemics could potentially influence those numbers, nevertheless, if this positive trend continues, one can expect a life expectancy of close to 100 years by 2070 in the most developed countries.

Such improvement in the general population's health is not happening without a significant improvement in the healthcare sector itself. The reason for the metrics improvement is not that people became magically healthier, but because of the ability to receive the treatment earlier and deliver the drug to the patient with a specific disease ensuring he or she can receive it throughout their entire lifetime. Pharmaceutical companies are primarily responsible for drug development, while MedTech device companies – for

the drug delivery systems. In this paper the focus is made on the autoinjectors as one of the types of such systems.

This context is setting an ambitious high-level goal for the Healthcare and MedTech industries, which should act in close cooperation. Reaching such goal requires the integration of the lifecycle processes of how drugs and MedTech devices are developed – both processes meet well established regulatory landscape, managed by the Food and Drug Administration (FDA) in the U.S., the European Medicines Agency (EMA) in Europe, and the other respective regulatory agencies in the other parts of the world.

MedTech product development field deals with uncertainty appearing because of an increasing number of interactions, such as: (1) between components within the system (device) and outside it – with external products and systems; and (2) interactions with external stakeholders, from the MedTech company perspective. For this study, the only second type of interactions is explored with an emphasis on such stakeholders as drug development companies (Pharmaceutical companies), and regulatory bodies (such as FDA or EMA). This paper discusses the challenges associated with the combination product development process considering it from a holistic perspective, combining the systems engineering (SE) and product lifecycle management (PLM) approaches. The Digital Engineering (DE) tool is used to reflect the complexity of the combination product development.

This paper is structured as follows. Section 1 is the Introduction. In Section 2 the literature review is primarily focusing on systems engineering and product lifecycle management as the means for a holistic view of the product (sub-section 2.1), and a combination product through the lenses of such a holistic view (sub-section 2.2). The research method is discussed in Section 3. Section 4 presents the drug-device combination product development challenges – drug-device design processes alignment (sub-section 4.1) and stakeholders capturing (sub-section 4.2). The discussion and conclusion are made in section 5, where the pathway for future research is also outlined.

2 Literature Review

2.1 Holistic View on the Product through the Systems Engineering

A holistic and systemic approach to the product/system and its boundaries is needed to establish a proper view of the system from different stakeholders' perspectives. Systems engineering has grown as the discipline to reduce uncertainty and to manage the complexity in very large acquisition programs, such as in aerospace [2], [3] and defense [4], [5] industries. Over time, systems engineering was applied to other industries, such as automotive [6], [7], oil and gaz [8], and healthcare [9]. Therefore, it is not by coincidence the SE/DE methods and tools are applicable to MedTech and healthcare industries.

There were the efforts to use the SE and Model-Based Systems Engineering (MBSE) approaches for MedTech. The attempts to develop good design practices for MedTech development can be traced to two decades ago [10], however digitalization and advanced modeling capabilities could potentially move the design on a new level engaging a more agile [11] and model-based approach. However, systems engineering

methods and tools have been used for the development of combination products in a limited way. For example, in [12] the authors have used SysML as an MBSE tool to represent a high-level system architecture for the drug delivery device, constructing the system model for the system itself and only barely mentioning the issues associated with the combination product consideration. SysML has also been applied to risk and safety management of the medical devices [13]. Simulink model implementation to create software for MedTech is presented in [14]. Requirements capture for the medical device development has been presented as the workbook in [15], focusing on the device only; and in [16] as the Master's Thesis. The model-based representation of the dialysis machine has been presented in [17], and to a wide variety of other applications in the healthcare domain – in [18]. From the value delivery perspective, the MedTech device is only creating a benefit to society when it is combined with the drug, and ultimately, when both entities - device and drug - function as a system to deliver a drug to the patient. Therefore, the combination product should be considered holistically, taking into account the context – packaging, instruction for use, etc.

Systems engineering value increases when its principles and methods are applied across the product lifecycle. The integration of systems engineering and Product Lifecycle Management (PLM) has been studied in the literature and applied to different domains, as both approaches are complementary to each other to facilitate the design process across the product lifecycle [19], [20], [21] establishing a common glossary [22].

2.2 Combination Product through the Lenses of Holistic View

A combination product is "a product comprised of two or more regulated components, i.e., drug/device […] that are physically, chemically, or otherwise combined or mixed and produced as a single entity" [23]. The combination product development involves two or more industries (for example, MedTech company, biotechnology company, and pharmaceutical company) with their own design processes and established procedures, which later should comply with each other and satisfy the regulatory landscape. The opportunity associated with the development of a combination product lies in the ability to combine the best knowledge and practice from all industries involved, revealing a product with greater functionality and, ultimately, becoming a pioneer up the industry standards [24]. Therefore, proper integration of the design processes between all the actors involved in the combination product development is highly needed. Regulatory pathways of combination products development in the USA and in the EU presented in [25] "…could result in a complex scenario for companies marketing the same product in both jurisdictions" [25].

To create new generations of MedTech innovative products, such as drug delivery systems, the product development teams should possess new skills, such as design thinking "to understand user needs" and systems engineering "to manage complexity and ensure interoperability" [26]. Such a setting is calling up for a holistic view of the product under development. The definition of a product and its boundaries vary depending on the perspective: either this is a MedTech device designer, or the Pharma

company designer, or the end user, or even within the MedTech company – e.g. regulatory affairs vs. R&D.

The system view is needed to capture the combination product development complexity from different perspectives and to track stakeholders involved. We hypothesize that when the digital design thread is properly managed in DE environment, the links to all stakeholders can be established and the design knowledge can be managed across the lifecycle.

3 Research Method

The first step of the research method is digging into the state-of-the-art of the MedTech combination product development, holistic view on the product, and stakeholders consideration for such a complex product. This is achieved through the literature review of the related topics described in Section 2.

The second step of the research method (Section 4) is capturing the challenges associated with the device development process and the drug development process, according to the guidance provided by FDA. These challenges are discussed in sub-section 4.1 (misalignment of the drug-device development processes) and in sub-section 4.2 (tracing stakeholders for combination product). To demonstrate these challenges, the MBSE tool is used and applied to the stakeholders consideration.

4 Combination Product Development Challenges

4.1 Drug-device design processes alignment

Figure 1 presents the FDA-regulated processes for drug development (upper part of the Figure) and device development (lower part of the Figure). In the current practice, those processes are conducted in parallel with some level of uncertainty of drug properties for the MedTech company. For the combination product development, the FDA is only describing the general development considerations pointing out that "…because of the breadth, innovation and complexity of combination products, there is no single developmental paradigm appropriate for all combination products" [27]. The combination product development is also regulated by the CFR Combination Product 21 CFR Part 4 [28]. The challenge is related to the misalignment of the processes for the combination product (drug-device) development which would support MedTech with the new products initiation, conceptualization, and realization.

FDA acknowledges that even though the drug constituent of the combination product and the device constituent of the combination product might be approved separately, "new scientific and technical issues may emerge when the drug and device are combined or used together" [27].

Figure 1 demonstrates that the drug development company might need the device prototype from the device development company after Phase I of the clinical research. It implies that the device company has been working on such prototypes (most likely, a series of Minimum Viable Products MVPs) before this (see device discovery and

concept; and preclinical research – prototype phases at the bottom of Figure 1), which imposes uncertainty for MedTech company on early stages of its device design. Such a work is based on the internal assumptions of drug properties (volume, viscosity, etc.) under development. Figure 1 also captures the iterative nature of the communication between the drug developers and the MedTech device company.

To mitigate the risk of misalignment in the combination product development process, the MedTech design team should have an established communication with the device team at the Pharmaceutical company, shifting and facilitating the discussion on drug properties to the early stages of the product development and advocating that DE/MBSE tools would support this process allowing to traces the design knowledge to a later stages in a systemic way.

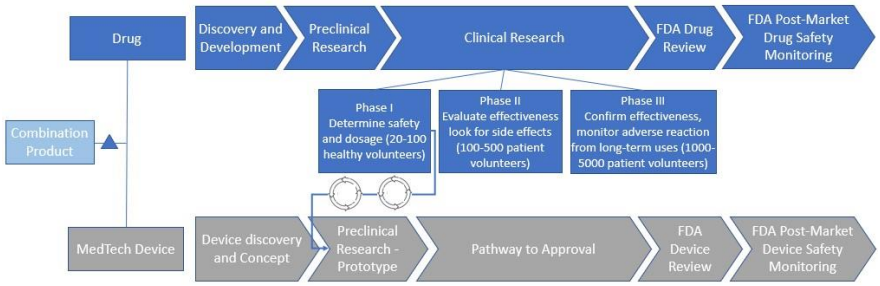

Fig. 1. Combination Product and FDA's drug/device development processes.

4.2 Tracing stakeholders of the Combination Product

Another core challenge is reasoning about the stakeholders of the combination product. As discussed earlier, the combination product is comprised of the device developed by the MedTech company, and the drug, for which the Pharmaceutical company is responsible. Therefore, from the MedTech device company perspective, the Pharma partner is one of the stakeholders, alongside the patients, healthcare practitioners, and regulatory bodies. However, the primary customer for MedTech device company is Pharma. Healthcare practitioner and patients (final users of both – drug and device) are operating the Combination Product. This makes it difficult for the MedTech device company to directly negotiate with the final user. Rather, from the business-to-business perspective, in practice it is working directly with the Pharma partners trying to investigate their requirements, such as drug viscosity, to be able to reduce uncertainty and predict the design space for the prototypes to be developed.

This complexity is reflected in Figure 2, which uses the DE/MBSE tool to capture stakeholders of the combination product development. The Object-Process Diagram (OPD) for the Combination Product is built in the OPCloud environment [29], following the Object-Process Methodology (OPM) [30]. This Figure reflects the complexity for the MedTech company: although it can negotiate with final users, its primary customers are the Pharma partners.

Figure 3 is the Object-Process Language for the combination product in the OPCloud environment, which is automatically generated from OPD and supports the

stakeholders-processes allocation in a natural language, clearly describing who is responsible for what, and which processes are undertaken.

To mitigate the risk of losing an especially important link to specific stakeholder, the DE tools should be used, such as the one presented in Figure 2.

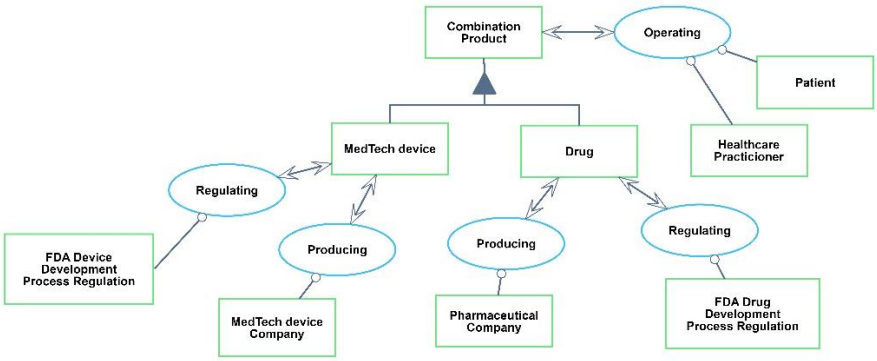

Fig. 2. Object-Process Diagram (OPD) for the Combination Product in OPCloud

MedTech device is an informatical and systemic object.
Drug is an informatical and systemic object.
Combination Product is an informatical and systemic object.
MedTech device Company is an informatical and systemic object.
Pharmaceutical Company is an informatical and systemic object.
Patient is an informatical and systemic object.
Healthcare Practicioner is an informatical and systemic object.
FDA Device Development Process Regulation is an informatical and systemic object.
FDA Drug Development Process Regulation is an informatical and systemic object.
Combination Product consists of **Drug** and **MedTech device**.
Operating is an informatical and systemic process.
Operating requires **Healthcare Practicioner** and **Patient**.
Operating affects **Combination Product**.
Producing is an informatical and systemic process.
Producing requires **Pharmaceutical Company**.
Producing affects **Drug**.
Regulating is an informatical and systemic process.
Regulating requires **FDA Drug Development Process Regulation**.
Regulating affects **Drug**.
Producing is an informatical and systemic process.
Producing requires **MedTech device Company**.
Producing affects **MedTech device**.
Regulating is an informatical and systemic process.
Regulating requires **FDA Device Development Process Regulation**.
Regulating affects **MedTech device**.

Fig. 3. Object-Process Language (OPL) for the Combination Product in OPCloud

5 Discussion and Conclusion

This paper discusses the challenges associated with development of drug-device combination products, focusing on the drug delivery systems as an example. These challenges are identified in two areas. The first is related to the misalignment of the drug-device design processes. A potential mitigation of this risk for MedTech design team is to establish a communication link with the device team in the Pharmaceutical company focusing on the importance of capturing the core design information (such as drug properties) at the early stages of product development, and advocating that MBSE/DE would support this process. For this, a larger study is required. Such a study should involve a large group of design team members to be interviewed on the design process. These design interviews should capture not only the R&D team, responsible for the MVPs development but also broader representatives - marketing, regulatory, and quality, to name a few.

The second challenge is related to the complexity of stakeholders representation. To mitigate the risk of losing a core stakeholder and the data from such stakeholder, the DE tool should be used. For the drug delivery system developer, the primary customer is the Pharma company, while the final user is the patient/healthcare practitioner. To capture this properly, MBSE-based solutions could track that information. This future work would require building the system model within the product boundary (decomposing the drug delivery system on its own subsystems, functions definition and requirements management, and assigning the core team members to those subsystems); and outside the system model – outlining the interfaces with the other stakeholders and systems.

References

1. Our World in Data Homepage, https://ourworldindata.org/life-expectancy, last accessed 2023/01/23.
2. NASA: System Engineering Handbook, SP-2016-61 (2016).
3. Fortescue, P., Swinerd, G., Stark, J.: Spacecraft systems engineering. In: John Wiley & Sons (2011).
4. Dahmann, J.S., Baldwin, K.J.: Understanding the current state of US defense systems of systems and the implications for systems engineering. In: 2nd Annual IEEE Systems Conference, pp. 1-7 (2008). https://doi.org/10.1109/SYSTEMS.2008.4518994
5. Piaszczyk, C.: Model Based Systems Engineering with Department of Defense Architectural Framework. In: Systems Engineering, 14(3), pp. 305-326 (2011).
6. D'Ambrosio, J., Soremekun, G.: Systems engineering challenges and MBSE opportunities for automotive system design. In: 2017 IEEE International Conference on Systems, Man, and Cybernetics (SMC), pp. 2075-2080 (2017).
7. Loureiro, G., Leaney, P.G., Hodgson, M.: A systems engineering framework for integrated automotive development. In: Systems Engineering, 7(2), pp. 153-166 (2004).
8. Golkar, A.A., Keller, R., Robinson, B., de Weck, O. and Crawley, E.F.: A methodology for system architecting of offshore oil production systems. In: DSM 2009: Proceedings of the 11th International DSM Conference, pp. 343-356 (2009).

9. Griffin, P.M., Nembhard, H.B., DeFlitch, C.J., Bastian, N.D., Kang, H. and Muñoz, D.A.: Healthcare systems engineering. In: John Wiley & Sons (2016).
10. Alexander, K., Clarkson, P.J., Bishop, D. and Fox, S.: Good Design Practice for Medical Devices and Equipment: A Framework. University of Cambridge, Institute for Manufacturing (2001).
11. Glazkova, N., Menshenin, Y., Vasilev, D. and Fortin, C.: MedTech Product Development Framework for Post-Pandemic Era. *In: Proceedings of the Design Society, 2*, pp.1273-1282 (2022).
12. Corns, S., Gibson, C.: A Model-Based Reference Architecture for Medical Device Development. In: INCOSE International Symposium, 22(1), pp. 2066-2075 (2012).
13. Malins, R.J., Stein, J., Thukral, A. and Waterplas, C.: SysML activity models for applying ISO 14971 medical device risk and safety management across the system lifecycle. *In: INCOSE International Symposium*, 25(1), pp.489-507 (2015).
14. Hoadley, D.: Using Model-Based Design in an IEC 62304-Compliant Software Development Process. In MBEES, pp. 129-131 (2010).
15. Ward, J., Shefelbine, S., Clarkson, P.J.: Requirements Capture for Medical Device Design. In: Proceedings of ICED 03, the 14th International Conference on Engineering Design, pp. 65-66 (2003).
16. Wang, H.: Multi-level requirement model and its implementation for medical device. Master's Thesis. Purdue University (2018).
17. INCOSE, The Medical Device Digital Engineering Thread. [online] Available at: https://www.incose.org/docs/default-source/working-groups/healthcare/public-library/2018-se-in-healthcare-conference/the-medical-device-digital-engineering-thread.pdf?sfvrsn=e90897c6_2 (accessed 13.02.2023).
18. Zwemer, D. and Intercax, L.L.C.: Technote: Applications of MBE for healthcare. Intercax LLC, pp.1-15 (2016).
19. Messaadia, M., Farouk, B., Eynard, B.: Systems Engineering and PLM as an integrated approach for industry collaboration management. In: IFAC Proceedings Volumes, 45(6), pp. 1135-1140 (2012).
20. Sharon, A., de Weck, O.L., Dori, D.: Improving project-product lifecycle management with model-based design structure matrix: a joint project management and systems engineering approach. In: Systems Engineering, 16(4), pp. 413-426 (2013).
21. Gerhard, D., Cordero, S.S., Vingerhoeds, R., Sullivan, B.P., Rossi, M., Brovar, Y., Menshenin, Y., Fortin, C., Eynard, B.: MBSE-PLM Integration: Initiatives and Future Outlook. In: International Product Lifecycle Management Enabling Smart X, pp. 1-7 (2022).
22. Pinquié, R., Rivest, L., Segonds, F., Véron, P.: An illustrated glossary of ambiguous PLM terms used in discrete manufacturing. In: International Journal of Product Lifecycle Management, 8(2), pp. 142-171 (2015).
23. FDA Homepage, Combination Product Definition Combination Product Types, https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types, last accessed 2023/01/09 (2018).
24. Couto, D.S., Perez-Breva, L., Saraiva, P., Cooney, C.L..: Lessons from innovation in drug-device combination products. In: Advanced drug delivery reviews, 64(1), pp. 69–77 (2012). https://doi.org/10.1016/j.addr.2011.10.008
25. Rocco, P., Musazzi, U.M., Minghetti, P.: Medicinal products meet medical devices: classification and nomenclature issues arising from their combined use. In: Drug Discovery Today (2022). https://doi.org/10.1016/j.drudis.2022.07.009
26. Kühler, T.C., Schoenmakers, M., Shergold, O., Affolter, S., Bolislis, W.R., Foster, R., Gardner, P., Hruschka, S., Jomini, T., Kaveripakam, S. and Mayerhofer, K.: Development and

regulation of connected combined products: reflections from the Medtech & Pharma Platform Association. In: Clinical Therapeutics, pp. 768-782 (2022). https://doi.org/10.1016/j.clinthera.2022.03.009
27. US Food and Drug Administration, Guidance for industry and FDA staff: early development considerations for innovative combination products, https://www.fda.gov/media/75273/download, last accessed 2023/02/01 (2006).
28. Code of Federal Regulations Title 21 Chapter 1 Part 4, Regulation of Combination Products, https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-4?toc=1, last accessed 2023/02/08 (2023).
29. Dori, D., Kohen, H., Jbara, A., Wengrowicz, N., Lavi, R., Soskin, N.L., Bernstein, K. and Shani, U.: OPCloud: an OPM integrated conceptual-executable modeling environment for industry 4.0. Systems Engineering in the Fourth Industrial Revolution, pp.243-271 (2019).
30. Dori, D.: Object-Process Methodology: A Holistic System Paradigm. Springer (2002).