The secrets of efficient combination product development

-THE IMPORTANCE OF LABELING AND WHY TALKING TO EACH OTHER MATTERS

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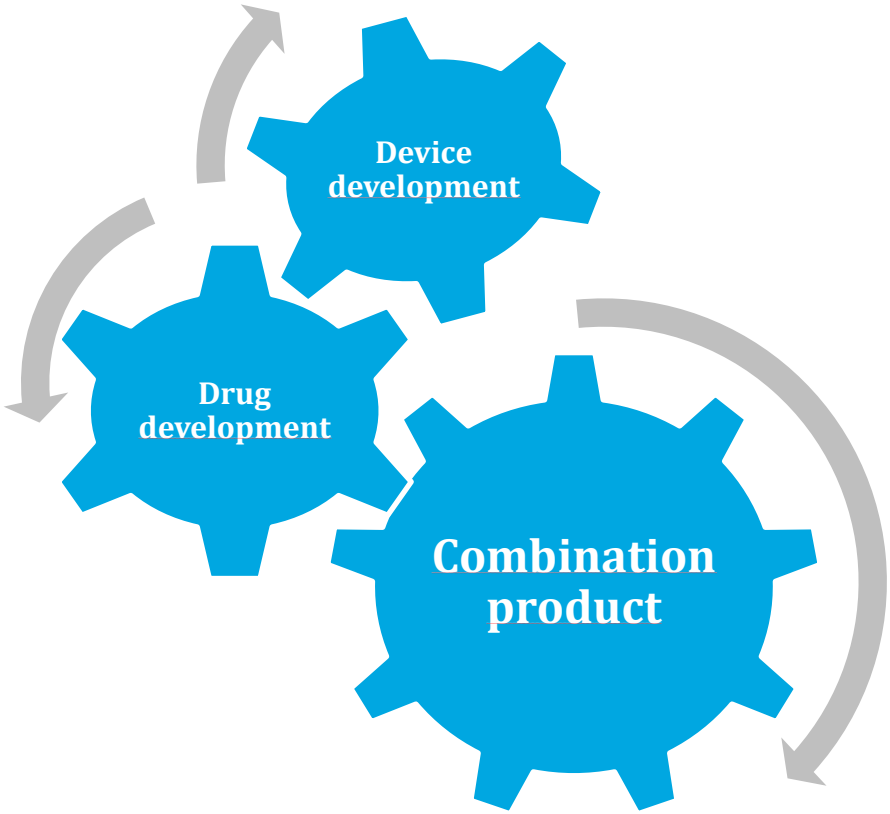
When developing combination products, the local legal requirements are highly variable:

- USA: FDA has laid out requirements for the development and manufacture of combination products in 21 CFR Part 4. In addition to GMP requirements for the medicinal product (12 CFR 210/211), relevant controls (certain sections of 21 CFR 820) for the development of medical devices also need to be fulfilled.

- EU: in case the device is a permanent integral part of the entire product and non-refillable, it will be registered as medicinal product. The applicability of the Medical Device Regulation (MDR) is limited to requirements on safety and performance of the device (Annex I of the MDR).

- CA/AU/ JP: drug-device combination products are mentioned in the local regulations (AUS/JP: no specific definition of a combination product) -depending on the PMOA (primary mode of action) they are regulated as drug or device.

Currently there is no harmonized regulatory approach to combination products destined for a global market, and consequently companies are forced to find their way to manage this challenging situation on their own.



How to start the development of your combination product:

Know your audience:

According to the fundamental principle of the Hippocrates Tradition which forms the basis of medical ethics:

1. primum non nocere (first of all do not harm),
2. secundum cavere (second: be cautious what is wrong with your patient),
3. tertium sanare (third: Cure your patient) (50 BC: Scribonus Largus-Emperor Tiberius Claudius).

What has been described more than 2000 years ago is still valid. It helps to follow a defined protocol right from the start of the development of your combination product.

1. Primum non nocere (first of all do not harm)

In order not to harm the patient ("*primum non nocere*") it is essential to define the needs of your patients and your target group (this includes. everybody that will handle your product: caregivers, HCP etc.). In an ideal setting somebody is involved in the development phase who is familiar with the disease your product is targeting.

2. Cavere

This includes considering the indications and limitations for your specific combination product-be cautious what is wrong with your patients ("*Cavere*").
These limitations could be of physical nature as your target patient group might have physical disabilities (like RA patients with reduced dexterity; people with sight problems etc.). This information is essential when starting the development process for a combination product as all these factors play an important rule in the success or failure of the development of any combination product.
Just to give some examples: some characteristics of the drug product (higher viscosity) might affect the functions of the device (gliding force) and this might have severe consequences for the target patient group (patients with impaired dexterity) and it might also affect transport validation (accidental release of a needle-safety device). Biological products usually require refrigeration (2-8°C)-cold storage might have an impact on the device etc.

Any factors that have an impact on the drug part, might also have severe consequences on the device part.
It has been shown to be extremely important to identify the needs of the stakeholders (patients, caregivers and HCP) during the design planning phase and at the beginning of development of the combination product as any failure in this area might lead to an expensive re-design at a later point.

3. Tertium sanare

Your product should help and ideally cure the patient. This can only be achieved if the needs and limitations of the target population have been systematically identified and addressed. Your product (drug and device part) should aim to cure or stop the progress of a disease and make the life of your target group easier.

Why talk to each other?

Firstly: because you are a human being and humans like to connect (some more - others less …).

The development of Combination products is more complex than the development of traditional medical devices or medicinal products. The increased complexity comes from the interrelation between the drug and the device.

Drug and device development both follow a systematic approach: Device development follows design controls and drug development follows the Quality by design principles. Proactive risk management is an essential requirement for both.

The key principle to a successful development of a combination product is good communication between the two groups right from the start.

In case there is just a small breakdown of communication at the beginning of the project this will result in incomplete definition of use cases and user needs which in turn will result in even greater discrepancies during subsequent development phases.

In case not all needs of the target group have been covered from the start of the project and this is discovered at a later project stage it will affect the progress of the development and the commercialization of the combination product. This might cause significant delays in the launch activities. All these factors are costly results of not talking to each other.

During the approval process of any combination product even small changes in one part might have severe consequences on the other constituent part. Talking to each other is the single most important success factor in the development of combination products.

In case you are outsourcing parts or most of your development, it is highly recommended to also involve your third party in the various steps of your development project. Any feedback (internally or externally from Health Authorities or other third parties) might have a profound impact on further development and even during the maintenance phase. Sharing the feedback with your external service provider will enable them to have a better understanding of your and the product's needs and these can then likely be addressed in a timely manner.

Start right first:

To streamline all the necessary activities and to make an efficient development process of any combination product it is essential to involve a cross-functional team right from the start.

This team should consist of members from the drug and the device development as well as from Regulatory Affairs (RA), labeling, supply chain, Quality Assurance (QA), Manufacturing, Marketing and Commercial Operations (and IT: in case of software solutions).

It is essential to bring all the functions together around one table as starting right will save a lot of time, energy and money.

Why care about labeling?

Because this function connects the dots.

The label of your product includes all essential information for a safe use of the combination product and it gives the first impression of the product. The patient information is an easy-to-read summary based on the core document of your product including the essential product characteristics and device information.

To bring your drug together with the device to the patients in a safe way it needs to be

- labeled
- packed
- and it needs to be accompanied with a patient information leaflet (PIL) as well as the Instructions for Use. This information needs to be easy to read and at least in Europe, the PIL needs to be user-tested with your target patient group. In some instances, also risk minimization materials such as patient alert cards etc. might be needed.
- finally, successful transport validation needs to be demonstrated.

The device will most likely need to undergo human factor testing, which will reveal any problems that an actual user may have with the device function and the description in the IFU. All this information is put together in the labeling documentation.

One key factor for the successful start of a combination product is one core document (Target Product Profile (TPP) / Company Core data sheet (CCDS) including the Master label for the device) that forms the source for all local labeling documents.

The current environment of increasingly complex labeling regulations and guidance's is especially challenging for combination products marketed in several regions, which demand worldwide consistency of prescribing and patient information.

Labeling is a critical tool for the safe and effective use of prescription drugs, biologics, and medical devices. Its purpose is to deliver the essential information needed by patients, and stakeholders to make informed decisions on the product and its use.

Conclusions:

Patients and stakeholders need a safe and easy-to-use combination product that meets their expectations worldwide. The pharmaceutical industry is forced by the market to act in a very flexible and cost-efficient way to develop their combination products globally as legal requirements vary from region to region.

To meet the expectations of all stakeholders, it is essential to define the users and their needs at the very beginning of any combination product development project and to involve a cross-functional team from the start as the costs of early communication failures will increase significantly in the later stages and might ultimately lead to a costly delay in the launch of your combination product.

One crucial function that connects the dots is Labeling, which ideally is involved in the development process of innovative, generic and biosimilar combination products right from the start.