Medical devices, diagnostics & apps

by

Palle Høy Jakobsen
February 2022

ISBN 978-87-94331-11-1

Introduction

Product development in the medical device industry carries less risk, but the rewards are also smaller compared to the pharmaceutical drug industry. A device's success or failure depends very much on how well it can demonstrate safety data and efficacy in the regulatory approval process.
Medical devices (such as injection devices for biopharmaceuticals) are a much more heterogeneous group of products than pharmaceutical drugs, and it is understandable that some variation in clinical evaluations exist.
The estimated time required to develop a medical device varies depending on the source, but typically range from three to seven years from concept to marketing approval or clearance. A major development component within this time is the regulatory process, which varies based on the risk level of the product, and the country selected for regulatory approval.

Many devices never come in direct contact with patients, some do briefly, and others do permanently. There are roughly 1,700 different types of medical devices and 50,000 separate products. There is much more variety in the kinds of companies that invent and develop medical devices than is the case with companies developing pharmaceutical drugs. The device industry is characterised by a large number of small firms; approximately 50% of U.S. medical device manufacturers have fewer than 20 employees. Large companies, however, dominate the industry in terms of sales.
Generally, the sample sizes used in the clinical studies for devices are considerably smaller than is the case with clinical studies for pharmaceutical drugs. Ophthalmic trials, for example, include an average of 280 patients, while all other device trials involve about 150 patients.
Specific cost associated with bringing a device product from concept to market depends on the regulatory path, with low- to moderate-risk devices requiring less capital and time than high-risk devices. A survey of >200 medical device companies outlined an estimated total cost of ~$31 million to bring a low- to

moderate-risk device from concept to market, whereas high-risk products averaged $94 million. These figures are substantially lower than the costs required to develop a novel pharmaceutical drug.
In most industrialized countries, the development of new medical devices is governed by regulatory schemes, either in the form of standards or extended pharmaceutical laws, which focus mainly on safety. In contrast, the U.S. has passed a specific law governing the development of medical devices.

The product profile parameters for medtech products may be different from the product profile of pharmaceutical products. For a diagnostical product, the important parameters relate to the sensitivity and the specificity of the test.
The sensitivity of the test: Did the test correctly identify or detect those that have the disease or condition or have become infected with the disease-causing microorganism.
The specificity of the test: Did the test correctly identify or detect those that do not have the disease or condition or do not have become infected by the disease-causing microorganism.

The diagnostic test may be used for individual patient diagnosis purposes but may also be used for epidemiological studies exploring disease incidence and prevalence. Development of new diagnostic products may be in the direction of better sensitivity and specificity but may also be in the direction of simpler tests or equipment which may be applied more decentralised as seen recently for corona diagnostics.

The cost to launch and commercialise a novel diagnostic test varies a lot from a follow-on diagnostic product where a similar test exists in the market to a new biomarker or a new diagnostic platform in oncology or a chronic disease like rheumatoid arthritis. The total costs of developing a new diagnostic test varies from 20 mio USD to 106 mio USD.

The development structure of a new diagnostic product in comparison with the development structure of pharmaceutical products is outlined in the figure below.

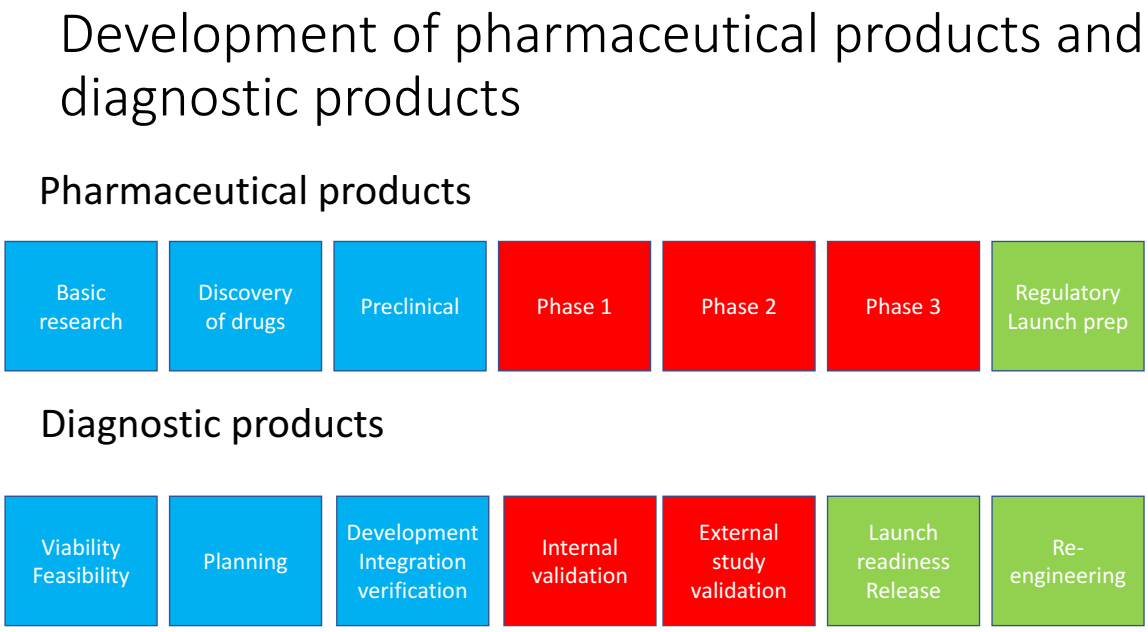

Figure. R&D activities for pharmaceutical drug products and diagnostic products.

A companion diagnostic is a diagnostic test used as a companion to a therapeutic drug to determine its applicability to a specific person. Companion diagnostics are co-developed with drugs to aid in selecting or excluding patient groups for treatment with that particular drug on the basis of their biological characteristics that determine responders and non-responders to the therapy, see figure below.

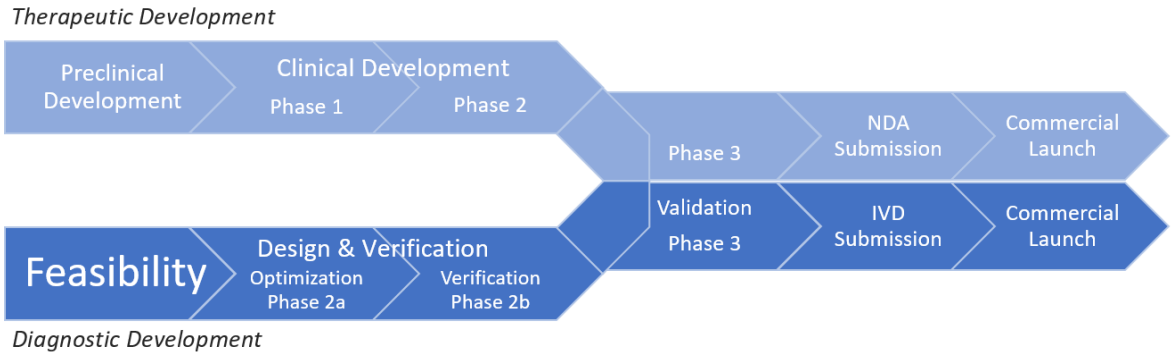

Figure. Integration of companion diagnostic and pharmaceutical drug development activities.

Medical device approval process.

The regulatory processes for devices including diagnostics are as follows.

<u>In the US.</u>
FDA approves the marketing and sales of a device for certain specific clinical indications, indication for use (IFU). Cost-effectiveness has no part in the FDA´s assessment of new technologies.

Devices have different pathways to approval based on their classification:

Class I devices are the simplest devices, posing the smallest risk and require only general controls. This class includes crutches and band aids.

Class II devices are of moderate risk. They require a 510(k) Pre-Market notification prior to marketing. This class includes wheelchairs and tampons.

Class III devices are of high risk, they usually require a Premarket Approval Application (PMA) prior to marketing. Around 40 to 50 PMAs are approved each year in the US. If the FDA defines a device as class III device, similar devices will always be a class III device, except if the FDA approves a reclassification petition and down-classifies the device. All competitors that develop similar

products have to pursue the PMA process in order to market their device in the US. This class includes heart valves.

Roughly half of all medical devices fall within Class I, 40-45% in Class II, and 5-10% in Class III categories. Roughly three-quarters of Class I devices are exempt, meaning that they do not require FDA clearance to be marketed (Yock P.G. et.al. 2015).

The 510(k) premarket notification.
A 510(k) application demonstrates, that a new device is substantially equivalent to another device that is already on the market without a PMA. In order for a new device to be found substantially equivalent to a predicate device, it must have the same indication for use, have technological characteristics that are similar to the existing device and not raise any new questions of safety and effectiveness in those areas where there are differences with the predicate device. If FDA agrees that the new device is substantially equivalent, it can be marketed. Clinical data are not required in most 510(k) applications; however, if clinical data are necessary to demonstrate substantial equivalence, the clinical studies need to be conducted in compliance with the requirements of the Investigational Device Exemption (IDE) regulations, Institutional Review Board review and informed consent (Yock P.G. et.al. 2015).

The premarket approval application (PMA) pathway is required for devices that represent the highest risk to patients and/or significantly different from existing technologies in use within a field. PMA is necessary to market a device that is not substantially equivalent to a device marketed in the US approved under 510(k). The PMA process is more complex than the 510(k) process, and the review time is about one year longer. Unlike most 510(k), a detailed manufacturing section is required. This application often requires clinical data from a pivotal study, typically a large randomized clinical trial. This clinical activity often constitutes the single largest expense and the biggest risk in the entire bio-design innovation process.
The formal FDA review period for PMA submissions is 180 days but the review period can be extended with up to 180 days. Clearance to begin clinical testing must be granted by the FDA via an IDE (Yock P.G. et.al. 2015).

In Europe.

In the European Union notified bodies play a similar role for medical device development as the FDA in the US. The notified bodies are controlled commercial organisations that can review medical devices in development and issue a CE-mark, necessary for certain devices for marketing approval. Once a medical device has obtained the CE-mark, it can be marketed in the entire

European Union. In the US, the manufacturer of a class III device must prove that the device is safe and effective, usually requiring a large randomised prospective clinical trial. In Europe, the manufacturer must show that the device is safe and its used as intended by the manufacturer. This usually can be demonstrated in a small clinical trial involving less than 50 patients. This major difference between the US and Europe makes it much more costly to obtain a marketing approval in the US (Yock P.G. et.al. 2015).

The medical device directive, implantable medical devices and in vitro diagnostic medical devices are transposed into national laws with a more centralised EU regulation planned. Regulatory approval in the EU is signified by a "CE" mark of conformity. Medical devices bearing the CE marking can circulate freely and be sold and marketed according to the approved indications throughout app. 31 European countries (Yock P.G. et.al. 2015).

Wearables.

Wearables may transform information and understanding of people´s health status. Wearables include:

- Hearing devices to boost hearing
- Contact lenses that monitor glucose levels
- Heart rate monitor patch
- Wristbands that monitor heartbeat, blood pressure, calories burnt
- Smart pills that monitor medication
- Insole sensor that measures weight bearing, balance and temperature

Apps.

Medical mobile app development has become important. It may take 1 – 18 months to develop an App depending on the complexity (4-9 months normal). The costs vary according to the features of the app, rate per hour, expertise etc. A small app costs $3.000 – $8.000, A more complex app costs $50.000 - $150.000 and finally a gaming app costs $10.000 - $150.000. Costs cover deployment, testing, app administration, infrastructure, features, design & planning.

In 2013 the FDA issued guidance for the regulation of mobile medical applications (apps) in the US, which developers of these technologies can use to help determine if they will face oversight from the agency.
In general, if a mobile app is intended for use in performing a medical function (i.e., for diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease), it is a medical device, regardless of the platform on which it is run.

If the outgoing data from the mobile app becomes patient specific, and that information can potentially lead to clinical diagnosis, then it is highly likely to be regulated.

Reimbursement of device products.

In the US, reimbursement for medical devices is handled by both public and private insurance programs. Centers for Medicare and Medicaid Services are regulating the largest public healthcare program, Medicare. Medicare processes in one year more than one billion claims from over one million providers.
The US has hundreds of private insurance carriers. US healthcare spending is split roughly equally between Medicare (20%) and private insurers (21%), household spending (28%), state and local government, including Medicaid (18%), other private insurers (7%) and other federal spending (5%).

Each country has a reimbursement system which is characterized by its own unique policies and requirements. Health care financing may be public or private.

Business models for devices and apps.

Business models for mobile health applications and devices, along with their related service offerings, are quickly proliferating in two broad categories: technologies targeted at consumers and those aimed at physicians and institutions.

Thus, in relation to mobile health applications and online health services, many companies are attempting to have patients pay for their technologies directly through an over-the-counter business model rather than applying the usual prescription business model. Companies developing app´s with health applications face a number of choices. They need to consider if they can generate meaningful intellectual property rights (such as copyright, industrial design, trademark or patents) for their product, or if they will compete on the basis of other activities such as marketing and service. They also need to consider who is their customer, the health care payer (like a hospital, city or municipality), the prescriber (such as the medical doctor or the nurse or the municipality worker) or the user (patient or citizen). Different payment structures may be established like a purchase price, pricing a service fee, a fee per use or a license fee such as a monthly subscription fee for a continued use of the app.

References and information sources

Yock P.G., Zenios S., Makower J., Brinton T.J., Kumar U.N., Jay Watkins F.T. & Denend L. BioDesign. The process of innovating medical technologies. Cambridge University Press, ISBN 978-1-107-08735-4,2015.

Web information available includes:
Company databases: Orbis, Compustat
Market research and industry reports produced by many companies including Frost & Sullivan and Evaluate.
Press releases, company websites, annual reports (for public firms)
Conferences and industry events
Industry experts