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Bio- and Medtech Entrepreneurship

2nd Edition

Flaadt Cervini
Dogwiler

Heidrun Flaadt Cervini • Jörg Dogwiler

BIO- AND MEDTECH ENTREPRENEURSHIP

From start-up to exit

Second Edition

Accompanying book to the BioBusiness and MedTech Business advanced programs at Università della Svizzera italiana

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BIO- AND MEDTECH ENTREPRENEURSHIP

From start-up to exit

I was taught that the way of progress is neither swift nor easy
Marie Curie

Accompanying book to the BioBusiness and MedTech Business advanced programs at Università della Svizzera italiana

Contents

The beginning of a journey through life science entrepreneurship

At its very origin, the word "entrepreneur" contains the French verb "entreprendre", which means to undertake something. As early as the sixteenth century, the word had already been used to refer to someone who undertakes a business venture (Sobel, 2007). Today, a more detailed definition has evolved to describe an entrepreneur as a "person who starts, organizes and manages any enterprise, especially a business, usually with considerable initiative and risk" (http://dictionary.reference.com/browse/entrepreneur). The economist Joseph Schumpeter further described the entrepreneur as an innovator implementing changes in the economy by employing new goods or methods of production. Nowadays, many academic scientists not only aim for publication but also for commercial exploitation of their scientific results by creating their own start-up companies. In life science, (start-up) companies are defined as "those companies that apply the possibilities of organisms, cell cultures, parts of cells or parts of organisms, in an innovative way for the purpose of industrial production" where existing technological fields, including biotechnology, pharmacology, biology, chemistry, physics and informatics, are integrated into this definition (Hu and Mosmuller, 2008).

Innovation in bio- and medical technologies is distinct from other types of innovation in general and has been characterized by The World Health Organization (WHO, 2012). They describe certain features as having:

- A regulatory framework to ensure quality, safety and efficacy
- High costs of research and development (R&D) associated with high risks of failure
- Input from the public sector (fundamental research, funding and infrastructure)
- Ethical considerations

Thus, each future and young entrepreneur should be aware that the process of innovation in life science is capital intensive, carries a high risk and is highly regulated. To ensure the best possible outcome in broadening access to an innovation that has substantial value, an educational approach to scientific entrepreneurship is highly recommended. Such an approach enables academic researchers to participate as entrepreneurs in their own research-related start-up company.

The educational gap in life science entrepreneurship at Swiss universities

Top-flight universities in Switzerland attract talented students from all over the world to their scientific study programs and are able to recruit the best scientists. The life science curricula currently offered by Swiss universities, however, are purely scientific and technical in their content. They do not provide detailed insight into the innovation process and thus do not deliver the entrepreneurial knowledge that is needed to turn this knowledge into marketable products and services. This means that students, in most cases, are not familiar with important aspects of the innovation process, such as implementing knowledge in the form of products or services and marketing them successfully. This gap in their education is a major drag on the forces that drive innovation in life science and the commercial development of new treatments or medical devices, and it also slows the creation of new jobs.

Università della Svizzera italiana (USI) in Lugano drew on global market research as a basis for developing new, leading-edge educational programs for bio- and medtech entrepreneurship "BioBusiness" and "MedTech Business". These comprehensive, advanced programs provide young life science companies with the theoretical and project-based practical skills needed to develop, fund and market their innovations and, hence, contribute in a concrete and targeted way to close the gap in the Swiss educational system. Both programs, "BioBusiness" and "MedTech Business", are offered through the Center of Advanced Studies on Entrepreneurship in BioMedicine (CASE BioMed), an autonomous structure within the Faculty of Biomedical Sciences at USI that was established in collaboration with ETH Zurich, University of Basel and University of Zurich.

Our motivation to publish a book on life science entrepreneurship

In 2010, with the introduction of "BioBusiness", USI launched a five-day bioentrepreneurship program for biotech executives. This comprehensive program covers all entrepreneurial aspects, from business opportunity recognition to the exit of a company, crucial to the success of a biotech company. The program was developed from the outcome of a global market research project designed to identify existing offerings in the executive education sector and potential niches for new initiatives. It is based on a new didactic model, developed specifically for this course format, which combines theoretical teaching in

groups with practical project work. The course content is divided into modules grouped into themed blocks that depict the innovation process (starting from the results of scientific research, through to the development of the product derived from this work, to the funding of the company established to market it). In response to the success of "BioBusiness" and to participants' requests, the offering was diversified and supplemented by a new program focusing on medtech entrepreneurship called "MedTech Business". While "BioBusiness" focuses on the development of new therapeutics, "MedTech Business" concentrates on the innovation process for medical technology developments like medical devices or diagnostics.

The purpose of this book is to allow our students better preparation and a retrospective review of the program weeks. In addition, it is to serve as a brief textbook to be used to gain a very first overview of what it takes to set up and finance bio- or medtech companies, and it highlights some crucial aspects on how to create a life science company. As distinct lines between therapeutics, devices and diagnostics are blurring, the book includes chapters, divided into two distinct sections, on bio- and medtech entrepreneurship.

Since it is not possible to provide a general recipe or instructions on how to successfully develop a life science start-up, we have chosen the format of a compendium rather than a classic textbook in order to prepare and deliver the knowledge at hand. The intention is to introduce some of the most essential aspects of bio- and medtech entrepreneurship and to stimulate the self-study process of each future and young life science entrepreneur.

This compilation can either be read as a whole or used as a reference book by selecting individual chapters in the case of specific questions. Nevertheless, it does not substitute or replace the need for additional reading and/or further consulting on the different topics and aspects necessary to launch and set up life science companies. Each chapter is written by a different author, most of them are life science start-up founders, industry experts or venture capitalists. Each author prepared and presented the content from an individual point of view based on own experiences. The resulting heterogeneity in delivering the knowledge is a desired outcome for a multifaceted approach to life science entrepreneurship.

Each chapter begins with a short introduction leading into the specific topic. To familiarize the reader with the topic, in these short introductions particular emphasis was placed on providing some details from existing knowledge and information relevant to each chapter and available from different sources regarding the innovation process to develop new therapeutics or medical technologies in start-up companies. Along with these introductions, to further strengthen the thread that links the different concepts, cartoons illustrate the entrepreneurial challenges and add a touch of humor, lending a lighter perspective to the challenging aspects of life science entrepreneurship.

Starting a company and becoming an entrepreneur can be compared to the beginning of a long journey rich in experiences and even in adventures. It is as if one is embarking on a journey with an intended, yet unknown, destination because paths may change along the way, leading to a final journey's end that far exceeds original expectations. Taking inspiration from Steve Jobs who said, "We started out to get a computer in the hands of everyday people, and we succeeded beyond our wildest dreams", we invite you, now, to start such a journey together by exploring the relevant steps necessary to the creation of a life science start-up enterprise.

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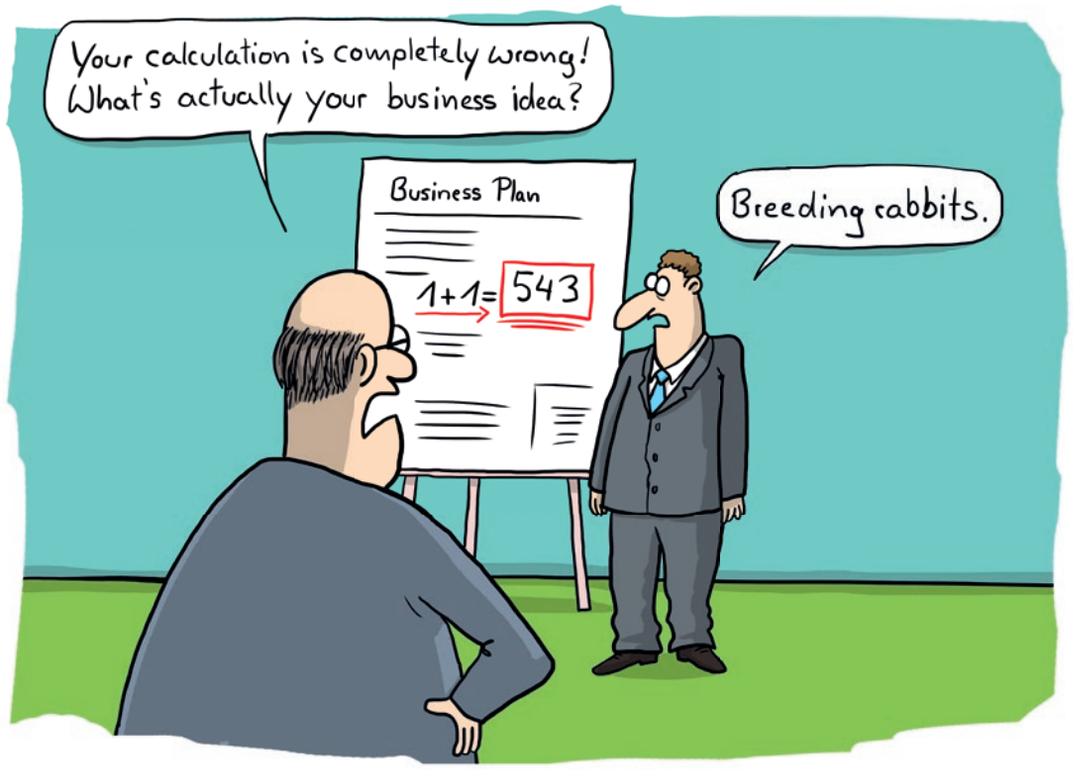
Emerging biotech companies, especially at the beginning, are usually not well equipped with financial and human resources. For this reason, and to avoid unnecessary business risks, each biotech entrepreneur needs to carefully plan the sustainable build-up of the company. The success of each enterprise largely depends, therefore, on a solid business plan.

The business plan represents an individual roadmap guiding one through the whole life cycle of the company, helps decision-making on how to spend time or money and is necessary to attract capital. It contains descriptions of the products/services, the customers or competitors and information on how to generate revenues. The business plan also defines the roles of the employees and the common business strategy (Wells Fargo, 2015).



The specific elements of a modern and effective business plan for hi-tech start-ups are described in the next chapter.

3 Business planning for hi-tech start-ups

Introduction

Rationale for a business plan

Hi-tech start-up companies are often based on unique technology or product opportunities combined with the specialized technology expertise of the founders or founding managers. However, founding managers sometimes tend to overestimate the "intrinsic" value of their project/company, and may underestimate the importance of sound business planning for commercial success to be captured in a business plan. Absence of proper business planning, even at the earliest stages of company development, can delay or even jeopardize the realization of a project and may prevent future commercial success.

Without a diligently drawn-up business plan, a promising project may remain an idea, a dream, or a theoretical concept and its concrete implementation will probably never occur. This is simply because the other stakeholders required for the execution of the project (investors, partners, employees) cannot be convinced that the implementation of the project is feasible. Starting a business without sound business planning can be compared to driving at 100 miles an hour without headlights on a narrow, winding road in the Swiss mountains during a pitch-black night. The risk is simply too high and major disaster is imminent.

While some founding managers may believe that a business plan is a "necessary evil" needed for investors, it should, first and foremost, serve as a useful planning document for the entrepreneurs themselves. Often, details of the project, alternative business opportunities and models, unanticipated challenges and competitors' threats only become apparent once the ideas, concepts and implementation plans are being formulated in writing, and additional research and (re-)thinking is done as part of this creative planning and writing process. Especially for early technology start-ups, business planning largely depends on assumptions rather than on factual or historic information. However, once a set of assumptions has been considered, different scenarios based on other assumptions can be modeled, which might lead to entirely different commercial forecasts that may require the development of different business models and strategies adapted to the different forecasts.

It is almost obvious that without several iterative rounds of (a) planning based on assumptions, (b) challenges to such planning and the underlying assumptions and (c) further refining of the planning and the assumptions, it is impossible to be prepared for success and to prevent disaster.

At the end of such a process, that requires a lot of energy, discipline and tenacity from all parties involved, a business plan should have been created that supports the founders' and the entrepreneurs' vision for the concrete realization of their innovative concepts and ideas. A well-defined and thought-through business plan will also generate confidence and credibility for the founders because it is able to withstand "pressure testing" and challenges by skeptical stakeholders (e.g. investors, team members, partners).

Therefore, while a business plan is most importantly a planning instrument for the entrepreneurs, one that will raise their confidence, it intrinsically serves the purpose of increasing their credibility for potential new stakeholders (incl. investors) to embark on and support the project.

Lastly, the best planning and definition of the best assumptions at a given point in time do not mean that the business plan is cast in stone. If new insights or unforeseen factors become apparent, the business plan needs to be adapted quickly to these changed parameters, which may need smaller adaptations or even require a complete revision of the strategic positioning and operational planning. This lends weight to the common wisdom that a business plan is a living document that constantly needs to be adapted to changing premises. Especially in a fast moving and dynamic technology field, revisions to business plans may be quite frequent, requiring monthly or quarterly updates in order to stay up to date and to remain a realistic planning instrument for optimal operational execution.

Elements of a business plan

The structure of a business plan follows the simple logic of familiarization to convince an outsider of the business proposition and the commercial attractiveness of the business case – emphasis being on commercial attractiveness. Few stakeholders, and particularly potential investors, will invest in a project if the commercial case is not obvious and if a high likelihood of commercial success and a financial return are not properly demonstrated. Especially for hi-tech start-ups, the founding managers often risk focusing too strongly on the

3

The total assets (e.g. the value) of the company then needs to be balanced against the liabilities and shareholder equity of the company, which, if all connections between the tables have been properly captured, by definition, must be equal to the total assets, the reason why a balance sheet is called a balance sheet. On the liabilities and shareholder-equity side, the company's current and non-current liabilities (e.g. short- and long-term loans) are recorded, but also the share capital as well as any shareholder share-premium. Lastly, the balance sheet also states the accumulated earnings or losses. The latter is actually of interest to the company, because accumulated losses can be offset against taxable profit in the P&L statement for a given reporting period.

Tab. 3: Example of a balance sheet

in CHF	Year 0001	Year 0002	Year 0003
ASSETS			
Current Assets			
- Cash and cash equivalents	100 605	260 505	306 505
- Accounts receivable	0	0	0
- Inventories	0	0	0
- Prepaid expenses	0	0	0
Total current assets	**100 605**	**260 505**	**306 505**
Non-current assets			
- Property, plant and equipment	140 000	390 000	640 000
- Real estate & Property	0	0	0
- Intangible Assets	0	24 000	72 000
- Financial Assets	0	0	0
Accumulated depreciation	14 250	75 056	191 861
Total non-current assets	**125 750**	**338 944**	**520 139**
Other Assets	0	0	0
Accruals and Deferrals	0	0	0
TOTAL ASSETS	**226 355**	**599 449**	**826 644**
LIABILITIES & SHAREHOLDER'S EQUITY			
Current liabilities	0	0	0
Non-current liabilities	0	0	0
Total liabilities	0	0	0
Shareholder's equity			
- Paid-in share capital	28 000	200 000	300 000
- Share premium	835 400	2 063 100	3 462 870
- Retained Earnings/Accumulated deficit	-637 045	-1 663 601	-2 936 226
Accruals and Deferrals	0	0	0
Total Shareholder's equity	**226 355**	**599 499**	**826 644**
TOTAL LIABILITIES & SHAREHOLDER EQUITY	**226 355**	**599 499**	**826 644**

Conclusion

The business plan of a company is an important tool for entrepreneurs that allows them to carefully think through and consider all aspects of their business proposal, including an evaluation of the opportunities and the risks. In addition, a critical component is the detailed planning of the operational execution of the project in order to realize the project and to maximize the probability for commercial success. While a diligently drawn up business plan provides confidence for the entrepreneurs showing that every eventuality has been considered, it also showcases the business case to stakeholders and investors who need to be convinced to embark on the project. Therefore, a diligent and carefully drawn up business plan is an important and critical element for the future commercial success of a business opportunity.

About the author

Ulf Grawunder *is an experienced Swiss Life Science entrepreneur with over 15 years' experience in the therapeutic antibody development industry. With NBE-Therapeutics, he recently founded his second Swiss Biotech company and has been leading NBE-Therapeutics as its CEO since June 2012, for which he has raised CHF 27.5 million VC funding to date. Ulf Grawunder has invented three new patent-pending technologies at NBE-Therapeutics that allow the company to develop highly innovative antibody-based drugs, including next-generation antibody drug conjugates (ADCs) to treat cancer. Prior to the founding of NBE-Therapeutics, Ulf had co-founded the Swiss Biotech company 4-Antibody, sold to US-based Agenus (AGEN). At 4-Antibody Ulf served as founding CEO (2004) and after 2006 assumed the role of CSO. During his tenure at 4-Antibody, he raised about CHF 50 million capital for the company, secured two pharma/biotech collaborations with Boehringer Ingelheim, Germany, and Human Genome Sciences, USA and grew the company to 50 employees. Ulf Grawunder serves on various boards of non-profit and for-profit life-science organizations and is vice-president and board member of the Swiss Biotech Association. He holds a PhD in cell biology from the University of Basel for work on early B cell development performed at the Basel Institute for Immunology. In addition, he holds a Diploma in Technology Entrepreneurship from the Entrepreneur and Business School in St. Gallen at the Hochschule St. Gallen (HSG), Switzerland.*

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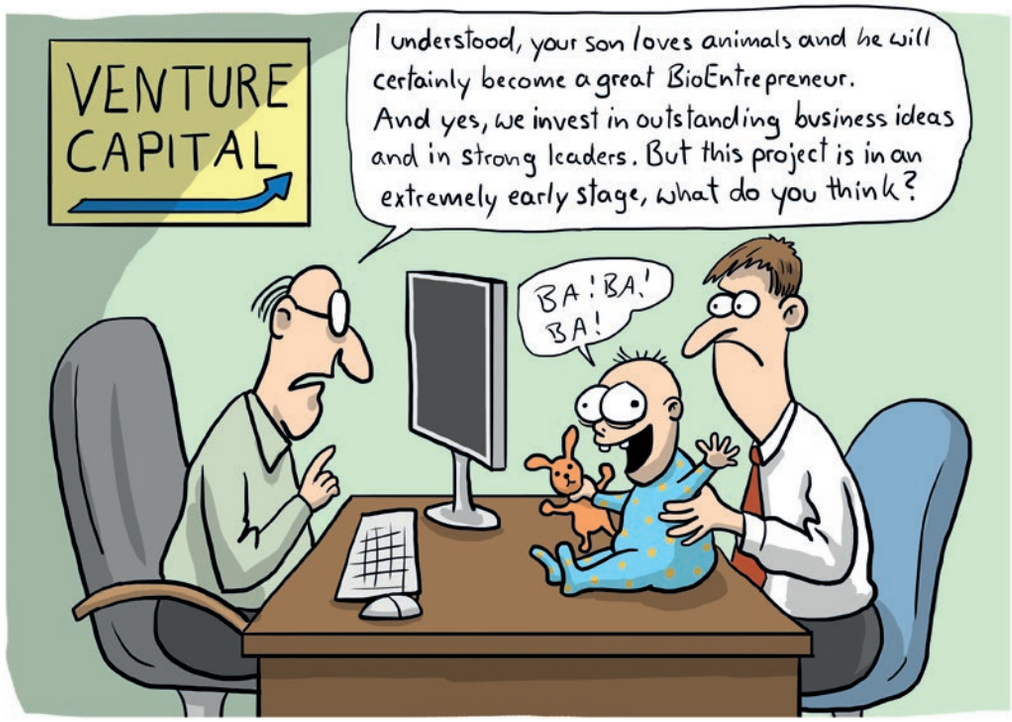
Early-stage start-up companies with a potential to grow need a certain amount of capital. The start-up capital is, for example, needed to cover the cost for research and development (R&D), for the salaries and for additional overheads. Early-stage companies can be financed through grants, private or angel investors, venture capitalists and bank loans.

Wealthy investors prefer to invest their capital in businesses with a long-term growth perspective. This capital is known as venture capital and the investors are called venture capitalists. Such investments are risky as they are not liquid, but are capable of giving impressive returns if invested in the right venture. The returns to the venture capitalists depend upon the growth of the company. Venture capitalists have the power to influence major decisions of the companies they are investing in as it is their money at stake (The Economic Times, (n.d.)).

In 2014, early-stage funding of biotech companies reached a record USD 1.3 billion, an increase of 41% over the USD 956 million invested in 2013 (PricewaterhouseCoopers, 2015). In most cases, a biotech start-up has to complete several subsequent financing rounds (Series A, Series B, etc.) to raise enough capital.



The next chapter describes some key lessons that are essential for start-up companies in the biotech business in order to find and access early-stage venture capital.

9 Venture capital for early-stage opportunities

Introduction

The earliest venture capital-backed enterprise and what we can learn from it

Since the early days of seafaring traders, affluent people have been entrusting their capital to less-affluent, enterprising workers willing to share a portion of the resulting gain with their benefactors. One of the earliest such relationships on record is the one between Christopher Columbus and Castile's King Ferdinand & Queen Isabella, who financed Columbus' voyages across the Atlantic Ocean. Applying modern terminology, Ferdinand and Isabella could be considered as the earliest venture capital investors (Greathouse, 2012).

Columbus' vision was easy to understand, sail west to reach the Far East more quickly, with huge pay-offs on the way. He spent seven years unsuccessfully pitching his business plan to Genoese bankers (fundraising takes time!) before convincing Ferdinand and Isabella to fund his clearly outlandish scheme. In discussions with Isabella and Ferdinand, Columbus didn't have to convince them that locating a shortcut to the spice routes of India was likely a very profitable idea. Rather, he had to address their primary concerns: was he honest, tenacious and competent enough to execute the journey? Interestingly, the traits these royal investors sought in Columbus are surprisingly similar to the characteristics today's investors look for when evaluating start-up teams. Some lessons we can learn from this remain universally true.

Lesson #1: Self-confidence attracts money
Columbus displayed an enormous amount of self-confidence when he eventually convinced Ferdinand and Isabella that a new route to Asia would give Spain new sources of commerce. This kind of self-confidence helps entrepreneurs to raise money and maybe even drive higher valuations for their start-ups.

Lesson #2: "Unreasonable" risks achieve the impossible
Like all entrepreneurs, Columbus miscalculated the risks of his westward voyage, assuming the earth's circumference to be only about 18,000 miles, therefore, stocking only 60 days' worth of food and water. Good entrepreneurs notoriously underestimate the risks involved, if they can be assessed to begin with – an optimism that often pushes people to achieve the impossible.

Lesson #3: Your belief in yourself is contagious
Absolute faith in our vision defines us as leaders. With it, Columbus fended off a near-mutiny by convincing his crew that newly sighted birds and floating vegetation meant Asia was over the horizon. Maybe the first case in history of an entrepreneur being able to pivot a venture to capitalize on changing conditions.

Lesson #4: Initial plan failed but project was nevertheless a financial success
Despite Columbus not reaching India, the project's pay-off to the Spanish Crown as well as to himself was tremendous. Successful founders understand that they will, at some point, need to adapt/evolve their business model. These decisions are often tough but mark pivotal moments in a company's history.

What venture capitalists can bring to the table and how to pick the "right" one

Drug discovery and development are very capital-intensive; companies need to invest hundreds of millions of dollars before they start generating profits. Apart from the scientific uncertainties, financing is probably the greatest risk companies face in their early stages. A common feature of successful biotech companies has been a skillful financing strategy and investments by venture capitalists (VCs). As a general rule, the earlier you can get VC backing, the greater your chances of success.

VCs have, from an early stage, backed about 60% of current public European biotech companies at some point. Late-stage investors, private equity funds, bankers and institutional investors often use the presence of blue chip VC as a first-selection criterion to identify potential start-ups in which to invest. Venture capital can be seen as the very first bit of leverage that an entrepreneur may possess, essentially a key strategic tool. Serial entrepreneurs who have previously accessed venture capital recognize this and are more likely to look for venture capital earlier than first-time entrepreneurs.

Successfully raising venture capital not only gives the entrepreneur access to cash but also to advice, market knowledge, networks and potential future management hires. VCs can help build/grow the start-up company, make it more financially attractive to other potential investors and increase the chances of a company going public. Essentially, the VC acts as a founding partner and provides a solid financial platform from which to build a company.

9 Conclusion

Finding and accessing early-stage venture capital can be a very difficult and confusing process, especially for first-time entrepreneurs. And it certainly doesn't help that the number of VC firms that do take on early-stage projects has dwindled as a result of the financial crisis. Nevertheless, there is still enough capital around to fund most of the exciting projects that can deliver therapies that make a difference at the bedside. Self-confidence, tenacity and boldness are the name of the game just like Christopher Columbus already taught us a long time ago.

About the author

Roman Fleck *is currently serving as the CEO of Janpix, Ltd., an oncology-focused start-up company, as well as a Venture Advisor to Medicxi Ventures (formerly Index Ventures Life Sciences). Prior to his current role, he was a Principal at Index Ventures where, among others, he invested in and represented Index on the boards of GlycoVaxyn (sold to GSK), Versartis (NASDQ: VSAS), and Novocure (NASDQ: NVCR). Earlier, he was also involved in Funxional Therapeutics (sold to Boehringer Ingelheim) and Micromet (sold to Amgen). Leading up to his venture career, he worked at Boehringer Ingelheim Pharmaceuticals in Connecticut where he led drug development projects in oncology, inflammation and cardiovascular disease, advancing several compounds from pre-clinical to clinical stage. Roman received a PhD from MIT as well as an MBA from NYU's Stern School of Business. He has authored or co-authored numerous publications in prestigious journals as well as many issued patents.*

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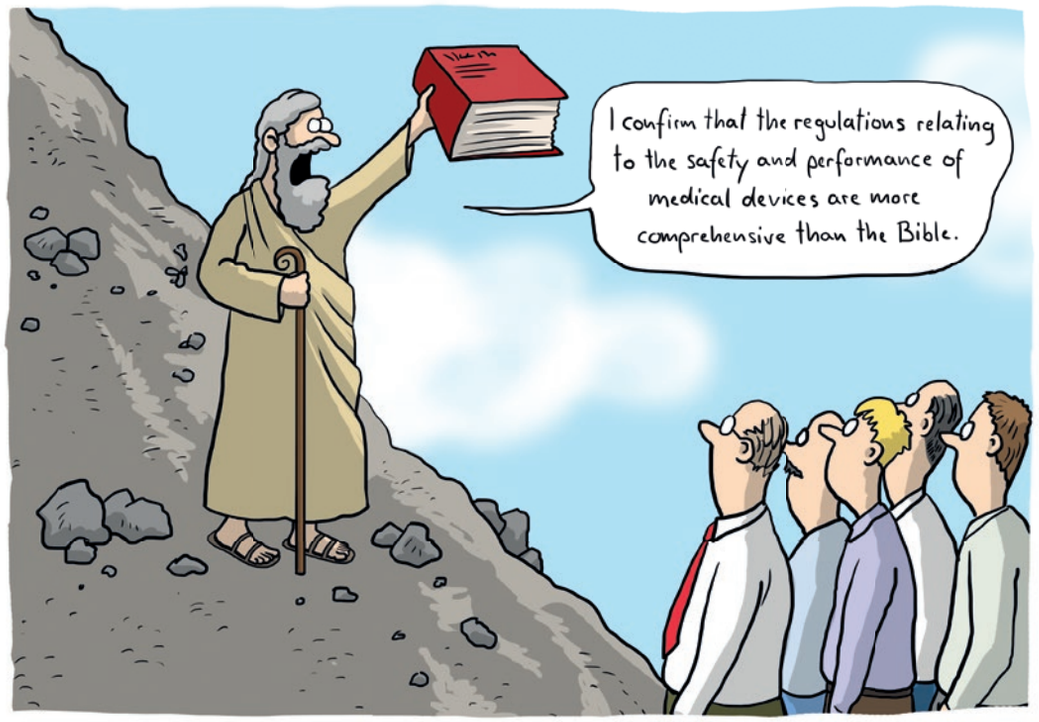
In 1976, the USA established the Medical Device Amendments (MDA), a new regulatory framework for medical devices. Prior to 1976, if a medical device developer wanted to get a product to market, it could be done without any government oversight (Hills, 2014).
In Europe, the first regulatory framework for medical devices was established in 1993. Previously, the legislation and registration process for medical devices varied from country to country. Today, on a pan-European level, medical devices are currently regulated by three directives, the Medical Device Directive (MDD) 93/42/EEC amended by 2007/47/EC, the Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC, and the In Vitro Diagnostic Medical Device Directive (IVDD) 98/79/EC. The new European Medical Device Regulation (MDR EU 2017/745) and In Vitro Diagnostic Medical Device Regulation (IVDR EU 2017/746) are paving the way for full implementation of these regulations on 26th of May 2021, replacing the existing MDD, AIMDD and IVDD directives.

The MDR entered into force on 26 May 2017 and the transitional period ends on 26th of May 2021, the date of application of the regulation. Details depend on the type of device and its classification under the MDD and the MDR. For more information regarding transitional provisions, entry into force and date of application, see Article 120 and Article 123 of the MDR. In contrast to directives, regulations do not need to be transposed into national law. Other aspects remain comparable, e.g. the system with notified bodies.

To be able to bring their products to market on time and for them to be legally compliant, medical device manufacturers must consider the regulatory requirements during the product's life cycle. Through tight cooperation between regulatory affairs and all other involved departments of an organization, medical device manufacturers aim to comply with regulations early in the development phase. In this way, they are able to put their devices legally and successfully on the market, ensuring that safety and performance are in accordance with the intended use.



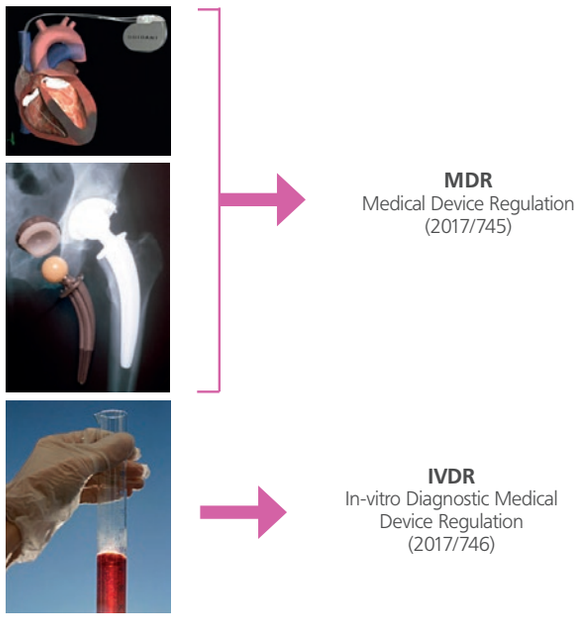
The regulatory framework for medical devices in the European Union is outlined in the next chapter.

15 The EU regulatory framework in the medical device business

Introduction

This chapter provides an overview of the procedures and requirements for market authorization of medical devices in Europe according to the "New and Global Approach", also called CE (Conformité Européenne) marking. It concentrates on Council Directive 93/42/EEC as amended by Directive 2007/47/EC, also called the "Medical Device Directive" (MDD) and its transition to the new European Medical Device Regulation (MDR EU 2017/745). More information and a guide (blue guide) are outlined at the following website: http://ec.europa.eu/growth/ single-market/goods/. Note that this review is not intended to replace detailed studies of legal texts and the respective guidelines.

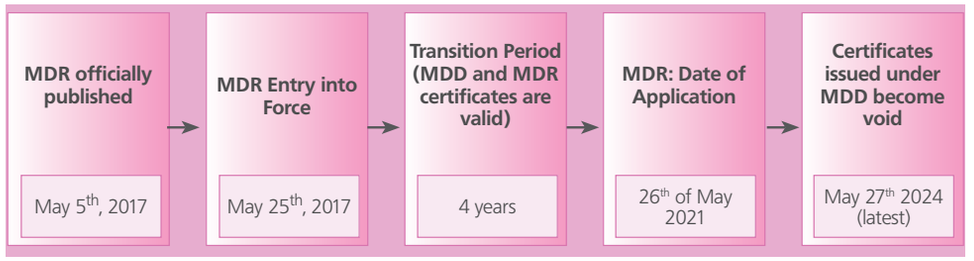
Fig. 1: Transition from European Medical Device Directive to Medical Device Regulation



Source: confinis ag

In order to place medical devices on the market in a legal manner, the requirements set forth by the MDR need to be fulfilled starting from the date of application (26th of May 2021). The transition from MDD to MDR are defined in transitional provisions (articles 120 and 123) as 4 years transition period from the date of the entry into force May 26th 2017 until the date of application (DoA) 26th of May 2021.

Fig. 2: Transition timeline from MDD to MDR



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It is the responsibility of the manufacturer to demonstrate that its product is safe and effective. For this reason, technical documentation needs to be established providing objective evidence that the general safety and performance requirements (GSPR) of Annex I of the Medical Device Regulation (MDR EU 2017/745) have been met. Following that, a conformity assessment needs to be performed, a declaration of conformity (DoC) must be issued and the CE mark needs to be affixed. Depending on the classification of the medical device in question, a notified body needs to be involved in this procedure.

Regarding the 4 years transition period from MDD to MDR: certificates issued by notified bodies in accordance with Directives 90/385/EEC (AIMDD) and 93/42/EEC (MDD) shall remain valid until the end of the period indicated on the certificate, which shall not exceed five years from its issuance. They shall however become void at the latest 3 years after the date of application of the regulation on May 27th 2024.

In the area of medical devices, the applicable legislation in Switzerland and the EU is considered equivalent. The mutual recognition agreement (MRA) with the European Union (EU) makes it possible for a recognized conformity assessment body/notified body in Switzerland to carry out conformity assessments for the EU interior market in accordance with the technical regulations of Switzerland and to place the products on the European market without further controls. This applies to medical devices assessed in Switzerland, since the European Medical Devices Directive has been transposed into Swiss law. Switzerland in turn recognizes conformity assessments carried out by conformity assessment bodies in the EU.

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New requirements of MDR compared to MDD

- In terms of their impacts on manufacturers and products, the Directives and the Medical Device Regulation (MDR) largely share the same basic regulatory requirements. No existing requirements have been removed, but the MDR adds new requirements.
- The MDR places more emphasis on a life-cycle approach to safety, backed up by clinical data. There are more stringent requirements for the designation of notified bodies, with increased control and monitoring by the national competent authorities and the European Commission.
- Certain medical devices are reclassified (up-classification). For instance, the MDR explicitly covers all devices for cleaning, sterilising or disinfecting other medical devices (Article 2.1); reprocessed single-use medical devices (Article 17); and certain devices with no intended medical purpose (Annex XVI).
- The MDR also covers internet sales of medical devices and medical devices used for diagnostic or therapeutic services offered at a distance (Article 6).
- The MDR introduces a clinical evaluation consultation procedure for some class IIb devices and for implantable class III devices by an independent expert panel (Article 54).
- A new Unique Device Identification system (Article 27) will significantly enhance the traceability and the effectiveness of post-market safety-related activities.
- The MDR will also provide increased transparency, with information on devices and studies being made public. The new European Database for Medical Devices (EUDAMED) will play a central role in making data available and increasing both the quantity and quality of data (Article 33).

Further Remarks

Regulations for private label manufacturers

Under the MDD 93/42/EEC retailers, distributors, agents or marketing organizations that do not manufacture products but sell an already CE-marked medical device under their own (brand) name and label it accordingly, are called private label manufacturers (PLM). These companies are not normally involved in the development and/or production of the devices but mainly purchase, store and sell medical devices produced by an original equipment manufacturer (OEM). According to the MDR, PLM and OEM are not defined as economic operators. Nevertheless, these companies are seen as legal manufacturers under the MDR EU 2017/745 and, therefore, must comply with it. The PLM has two options according to Article 16: Either he will act as legal manufacturer or enters into an agreement with a manufacturer whereby the manufacturer is identified as such on the label and is responsible for meeting the requirements placed on manufacturers in this regulation. This means they have to implement a QMS, establish the technical documentation and perform a conformity assessment procedure as decribed above. The consequence is that the full technical documentation needs to be available at the PLM manufacturer.

Market authorization in countries other than the EU

Even though there are several ongoing approaches to harmonize market authorization in other countries (e.g. from the Asian Harmonization Working Party, AHWP), only the EU offers a more-or-less harmonized system. For all other countries in the world, other laws apply that differ from the EU system and may also change quickly. Looking at each country and its regulations separately is inevitable if aiming to sell products in that country.

About the authors

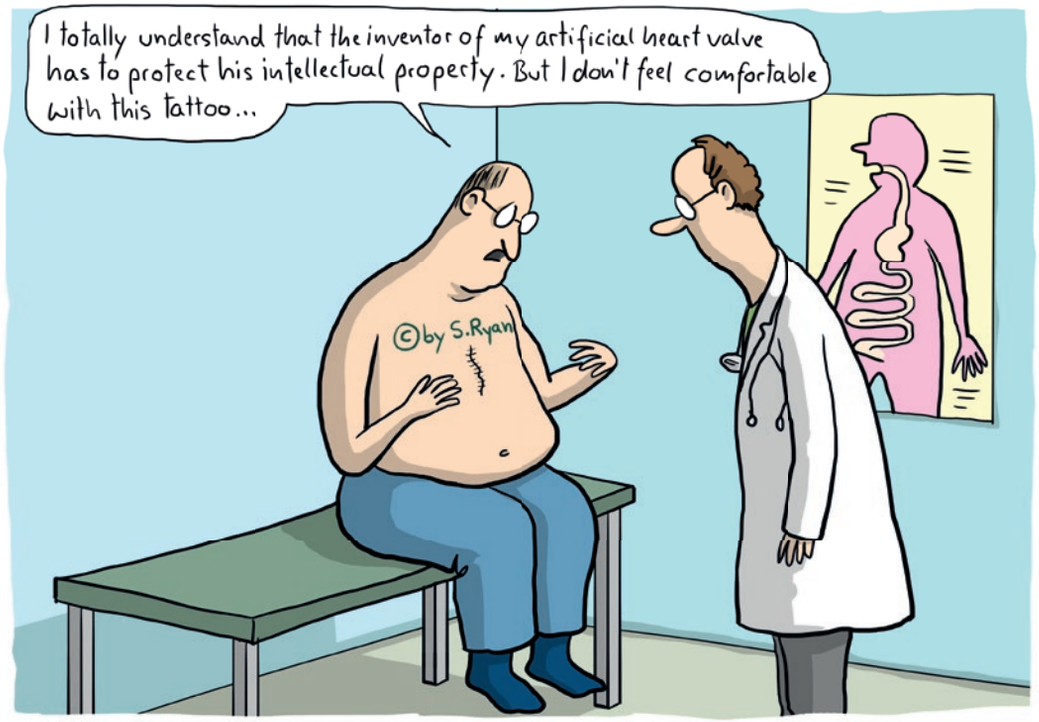
Beat U. Steffen *Founder, Chairman & CEO of confinis ag, (Switzerland and USA) holds an MSc in electrical engineering, an executive MBA and has 20+ years of experience in medical device and combination product development/manufacturing/quality management/regulatory affairs. He worked for Disetronic and Ypsomed and was responsible for a number of development projects from the first idea to successful registration and commercialization as well as infrastructure projects.*
He founded confinis ag in 2005. Besides providing professional services and advice to clients in the medical device, pharmaceutical and biotech field (with particular expertise and experience in combination products), he works as a freelance auditor with a focus on EN ISO 13485 and Council Directive 93/42/EEC, MDSAP (Medical Device Single Audit Program) and MDR EU 2017/745 (designation pending) for SQS and DQS. He is also a lecturer in design control at Berne University of Applied Sciences and for MDR and combination products at sitem insel (MAS in Medical Device Regulatory Affairs and Quality Assurance).
In addition to confinis, he co-founded Medical Human Factors AG in 2016, a company specialized in evaluating the use-related safety, effectiveness and usability of medical products and confinis CPM in 2018, a virtual workplace that provides senior-level clinical project staff and functional service professionals to gather clinical data.

Adrian Gammeter, *Senior Consultant confinis ag, BSc in microtechnology and diploma as quality manager NDS HF. 10+ years of experience in medical device development, manufacturing, quality management and regulatory affairs at Ypsomed and Integrated Scientific Services. Expert for test and measuring methods at Berne university of applied science (Medical Technology Center). Experience in automotive & industry development and quality management. 3 years quality and regulatory affairs manager at COMET AG Industrial X-Ray Technologies. Since 2018 Senior Consultant at confinis with a focus on quality management, regulatory affairs and technical documentation of medical devices and combination products.*

17.1

Medtech inventors inevitably deal concurrently with high investments and high risks. In addition, medical technologies are sometimes difficult to develop but can be easily reproduced. To maximize commercial exploitation and to limit market access for competitors, protecting intellectual property (IP) is usually an important step for the commercialization of new technologies.

As an indication of the industry's commitment to innovation, in 2013 more than 10,000 patent applications in medical technology were filed with the European Patent Office (EPO) – equivalent to 7% of the total number of applications and more than in any other technical field (Eucomed, 2013).



The following two chapters describe some aspects regarding the enforcement of IP rights and the need of a medical device start-up company to ensure that it has freedom to operate (FTO) regarding IP rights for its commercial activities. For a general introduction to IP rights and more information on the patenting procedure, the reader should refer to the chapter on IP rights in the first section of the book.

17.2 Avoiding patents that block medical device innovation by managing freedom-to-operate risks

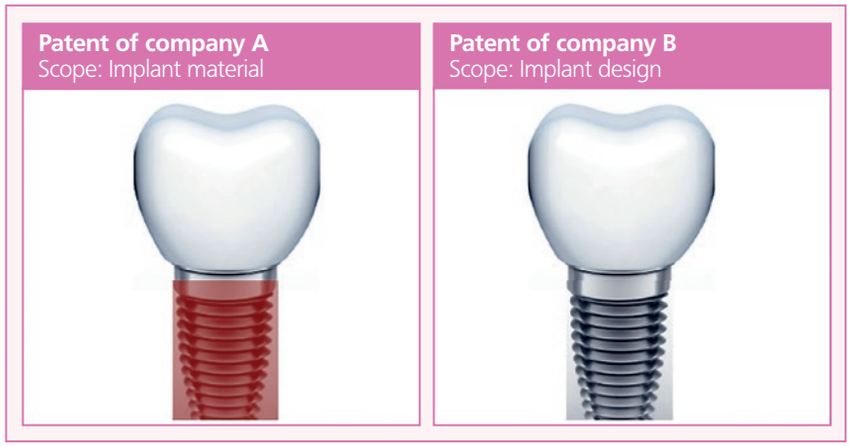
Introduction

Many start-up companies that develop medical devices focus their intellectual property (IP) activities on the protection of their innovations using patents. However, while ownership of a patent gives a company the right to exclude others, it does not necessarily provide a right to commercialize the invention claimed in their patent (for example by making or selling it). The reason for this is that a company can only commercialize an innovation if no relevant prior patent rights owned by others exist (Hoffmann and Wahl, 2014). This means that companies need to have freedom to operate (FTO). The scope of this text is limited to FTO with regard to patents. Other IP rights are outside of the scope of this text.

While the focus of a previous chapter was on the use of patents in excluding others (see chapter on "Enforcing intellectual property" by P. Felder), the focus of this chapter is on the resulting need of a medical device start-up company to ensure that it has FTO for its commercial activities.

For example, dental implant company A owns a patent for an innovative material for dental implants. Company A wants to sell an implant that contains this material (Fig. 1). Unfortunately, competitor company B owns a patent for the overall design of company A's implant. Therefore, B's patent prevents A from selling its implant.

Fig. 1: Company A owns a patent for an implant material and company B owns a patent for a dental implant design (hypothetical example)



FTO means that for a given product, no patent from any third party is infringed. However, FTO is always analyzed with regard to a specified time frame because patents are in force for a limited duration. Furthermore, FTO is analyzed relating to a particular country because patents are territorial rights (Krattiger et al. 2007). It has to be kept in mind, that there is never absolute certainty that all relevant third-party patents have been identified in an FTO analysis (for example, because of the limitations of every patent search). Therefore, while a company will aim to minimize FTO risks, a residual FTO risk will always remain.

Managing FTO risks is essential for start-up companies developing medical devices. For example, these companies may need to demonstrate to potential investors that they understand the FTO risks related to their planned products and that these risks are sufficiently low. Alternatively, a start-up company may want to analyze the FTO before spending money on the next phase of one of their product development projects. After all, no company wants to invest in products that cannot be sold.

17.2

These problem patents tend to have a broad scope, are often owned by leading competitors, and have sometimes already been enforced in legal proceedings. For example, for many years, medical device companies developing new stent implants were well advised to consider the so-called "Palmaz patents", the fundamental patents for stents that have been enforced in high-profile litigations for patent infringement.

Later during product development, the FTO analysis is updated independently of whether it started early during the innovation process or not. This update will result in a more detailed analysis of the planned product (late-stage FTO analysis). It is usually a good idea to update the FTO analysis before important business decisions have to be made. For a medical device start-up company this could be before contacting venture capital investors in order to obtain funding. Another particularly important time point to update the FTO analysis and risk mitigation measures will be after the design specifications have been finalized (around the development milestone of the design freeze) and before commercial activities start. The availability of the final design specifications of course benefits this update of the FTO analysis. There is usually a need for a more complete assessment of FTO risks and for appropriate mitigation measures at this stage because commercial activities are about to start. Therefore, this later FTO analysis aims to provide an exhaustive understanding of all problem patents that are in force in a specific set of countries or markets where commercial activities are to take place. The final assessment of the FTO risks by a patent attorney is often called an FTO opinion.

Conclusion

A medical device start-up benefits from close integration of the FTO process into the innovation/product development process. This allows the product development team to consider FTO risks throughout product development and to avoid or reduce at least some of these risks. This means that an FTO analysis is done at an early-stage of the innovation process and then updated while product development progresses. The early-stage FTO analysis focuses on the most important problem patents and is very different from the detailed FTO analysis done later during the innovation process. This limits the costs of FTO-related activities and also reflects the challenges of doing a detailed FTO analysis early during product development when features are not well defined.

This structured approach to FTO reduces the risk of the commercialization of a medical device innovation being blocked by a problem patent and of the device not achieving its ultimate purpose of improving patient care.

About the author

Franz Wittwer *is a biomedical scientist and innovation manager who has worked in the healthcare industry for more than 10 years. He is currently a senior innovation manager at Biotronik, a global medical device company. He is responsible for managing Biotronik's intellectual property and innovation pipeline and for ensuring the alignment of IP and innovation management. In the past, Franz Wittwer has held different positions in innovation management, intellectual property management, and biomedical research at companies in the United Kingdom and Switzerland. Franz has a PhD in molecular biology (University of Zurich), an MSc in IP management (Queen Mary University of London), and an MBA (University of Warwick). He is a member of the International Institute for IP management (I3PM), and of the Licensing Executives Society (LES).*

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Glossary of abbreviations and acronyms

AD	Alzheimer's disease
ADC	Anti-body drug conjugate
ADME	Absorption, distribution, metabolism and excretion
AHWP	Asian Harmonization Working Party
AIMD	Active implantable medical device
AIMDD	Active Implantable Medical Devices Directive
API	Active pharmaceutical ingredient
ATMP	Advanced therapy medicinal product
B2B	Business-to-business
B2C	Business-to-consumer
BLA	Biologics license application
BoD	Board of Directors
BTT	Breakthrough therapy
CA	Critical activities
CAPM	Capital asset pricing model
CASE BioMed	Center of Advanced Studies on Entrepreneurship in BioMedicine
CAT	Committee for Advanced Therapies
CDA	Confidential disclosure agreement
CE	Conformité Européenne
CEO	Chief Executive Officer
CEP	Clinical evaluation plan
CER	Clinical evaluation report
CF	Cash flow
CFO	Chief Financial Officer
CHMP	Committee for Medicinal Products for Human Use
CI	Cochlear implantation
CIP	Clinical investigation plan
CMC	Chemistry, manufacturing and control
CMDh	Committee for the Mutual Recognition and Decentralized Procedures, human
CMDv	Committee for the Mutual Recognition and Decentralized Procedures, veterinary
CMF	Cranio-maxillo-facial surgery
CML	Chronic myeloid leukemia
COGS	Cost of goods sold
COMP	Committee for Orphan Medicinal Products
CP	Centralized procedure
CRI	Colorectal interventions
CRO	Clinical research organization or Contract research organization
CS	Cardiac surgery
CSF	Critical success factors
CSO	Chief Scientific Officer
CT	Computed tomography
CTI	Commission for Technology and Innovation
CVMP	Committee for Veterinary Medicinal Products
DCF	Discounted cash flow
DM	Disease modifying
DMF	Drug master file
DoC	Declaration of conformity
DRG	Diagnosis-related group
DS	Dental surgery
EA	Exclusivity agreement
EC REP	EC representative
EBITDA	Earnings before interest, taxes, depreciation and amortization
EEA	European Economic Area
EEC	European Economic Community
EFTA	European Free Trade Association
EMA	European Medicines Agency
EN	European standard
ENT	Ear, nose and throat
EPC	European Patent Convention
EPO	European Patent Office
ERi	Expected return for a security
ERm	Expected market return
ES	Endoscopic surgery
EU	European Union
EUDAMED	European Database on Medical Devices
EUDRALEX	European Union legislation in the pharmaceutical sector
EY	Ernst & Young
FDA	Food & Drug Administration
FFAH	Fatty acid amide hydrolase
FMEA	Failure-mode and effect-analysis

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