STANDARDISATION AS KEY FOR GLOBAL DIGITAL HEALTH REGULATORY AFFAIRS IMPROVEMENT

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Master Thesis

Master of Drug Regulatory Affairs

Rheinische Friedrich-Wilhelms Universität Bonn

STANDARDISATION AS KEY FOR GLOBAL DIGITAL HEALTH REGULATORY AFFAIRS IMPROVEMENT

Scientific Examination

to obtain the title

"Master of Drug Regulatory Affairs"

of the Faculty of Mathematics and Natural Sciences

of the Rheinische Friedrich-Willhelms-Universität Bonn

submitted by

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from Frankfurt am Main, Germany

Bonn 2019

The studies presented in this thesis were performed in the context of the Master of Drug Regulatory Affairs of the Rheinische Friedrich-Wilhelms Universität Bonn.

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Standardisation as key for global digital health regulatory affairs improvement, Master Thesis, Rheinische Friedrich-Wilhelms-Universität Bonn, Master of Drug Regulatory Affairs

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1 GENERAL INTRODUCTION

"The development of digital technology has disrupted other sectors, notably media, retail and manufacturing, and the health sector is unlikely to remain immune". [1]

[1] E. Topol; The Creative Destruction of Medicine - How the Digital Revolution Will Create Better Health Care; 2012.

Our world today is undergoing three main processes. Firstly, science follows the dogma that organisms are algorithms which process data and that the life of organisms mostly consists of data processing. Secondly, intelligence decouples from consciousness. Before the invention of the internet and its data processing algorithms of today, conscious life forms, namely humans, were also the most intelligent life forms on the planet. Today, people would rather tend to trust Google Maps to explain the way to a point of interest in a foreign city because it knows the way more certainly and faster than any stranger walking down the street. Thirdly, algorithms which process data will increasingly reach a point where they will know us better than we will know ourselves.[2]

A study by Cambridge and Stanford University shows that an algorithm needs to access just 10 likes of a person's Facebook feed to beat a work colleague on knowing the person's personality, 70 to beat a roommate, 150 to beat a parent or sibling and 300 to beat a spouse.[3]

And in the healthcare sector?

A study shows that at a medical centre, out of 5296 prescriptions, 132 medication errors were reported during a one month study period.[4] The University of California San Francisco installed a robotic pharmacy at its medical centre, dispatching more than 350,000 doses of oral and injectable medications without any error.[5] Google provides flu and dengue signal data directly to partners to "nowcast" trends in regions.[6] The US based company 23andMe offers gene tests to find out what the DNA says about ones' health, traits and ancestry for USD 199.[7] Digital pharmaceuticals, such as implantable continuous glucose monitoring sensors for real-time continuous glucose monitoring for diabetes management are now entering the market.[8] [9]

[2] Y. N. Harari; Homo deus: a brief history of tomorrow; 2016.
[3] W. Youyou/M. Kosinski/D. Stillwell; Computers judge personalities better than humans; Proceedings of the National Academy of Sciences; 2015.
[4] P. Janmano/U. Chaichanawirote/C. Kongkaew.; Analysis of medication consultation networks and reporting medication errors: a mixed methods study; BMC Health; 2018.
[5] Pharmaceutical Technology; Verdict Media Limited; [Online]; [Cited: 3 April 2019]; https://www.pharmaceutical-technology.com/projects/ucsf-robotic-pharmacy-san-francisco/.
[6] The Flu Trends Team; Google LLC; [Online]; [Cited: 3 April 2019]; https://ai.googleblog.com/2015/08/the-next-chapter-for-flu-trends.html.
[7] Health and ancestry service; 23andMe, Inc.; [Online]; [Cited: 3 April 2019] https://www.23andme.com/dna-health-ancestry/.
[8] K. D. Barnard, et al.; Journal of Diabetes Science and Technology; [Online]; [Cited: 3 April 2019]; https://www.eversensediabetes.com/wp-content/uploads/2018/07/Acceptability-of-Implantable-Continuous-Glucose-Monitoring-Sensor-1.pdf.
[9] Senseonics Announces FDA Approval to Expand Eversense® CGM Certification to Nurse Practitioners and Physician Assistants; Press Release; BusinessWire; [Online]; [Cited: 3 April 2019]; https://www.businesswire.com/news/home/20181106006086/en.

Some scientists are even claiming to create babies whose DNA has been tailored using gene editing technology CRISPR.[10] The U.S. Food and Drug Administration drafts a guidance on interfaces linking computers to brains.[11]

What impact will today's technological development have on digital health regulatory affairs?

A marketing authorisation of medicinal products is granted to improve lives of individuals and communities in need. Health "regulatory affairs is a desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines, and by the companies responsible for the discovery, testing, manufacture and marketing of these products wanting to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare".[12] In 2017, "EMA recommended the authorisation of 92 medicines for human use, including 35 with a new active substance".[13] However, one of the major challenges for marketing authorisation systems worldwide is to keep them efficient in order to ensure a continuous flow of innovative and needed medicines to enter and stay safe in the market for individuals and communities in need, without unnecessary interruption.[14]

This thesis will start by covering the current development status of digital health regulatory affairs. While the section starts with demarking stakeholders in the way the thesis understands them, the primary goal of this part is to outline typical information steps between industry and health agencies during the medicinal product lifecycle and analyse which digital standards are used for each step. Digital standards will be explained in detail in the following section. After having examined the communication points and their formats to transfer information, potential improvement areas will be captured from a regulatory, industry, public, and technical perspective

[10] A. Regalado; Technology Review; [Online]; [Cited: 3 April 2019]; https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/.
[11] U.S. Food and Drug Administration; Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations [Online]; [Cited: 3 April 2019]; https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM631786.pdf
[12] The Organisation for Professionals in Regulatory Affairs (TOPRA); what is regulatory affairs; [Online]; [Cited: 3 April 2019]; https://www.topra.org/TOPRA_Member/Careers/What_is_regulatory_affairs_/TOPRA/TOPRA_Member/What_is_regulatory_affairs.aspx?hkey=83f01672-bc7f-41ed-b6fe-672acf7791cd.
[13] European Medicines Agency; Annual Report 2017; [Online]; [Cited: 3 April 2019]. https://www.ema.europa.eu/en/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf.
[14] M. Putzeist; Marketing authorization of new medicines in the EU: towards evidence-based improvement, Thesis Utrecht University; 2013.

in order to fuel the general discussion of why it is important to globally harmonise and standardize communication steps and standards used in the lifecycle, cross-disciplinary and - regionally.

The discussion and thesis concludes with a high-level recommendation of actions to further improve standardisation efforts for global digital health regulatory affairs.

It is important to mention, that this thesis focuses on European processes, while using differences to other regions such as the United States (US) for exemplification and argumentation purposes. This was intentionally chosen to keep the complexity of the evaluated steps within the requested scope of this thesis.

2

CURRENT STATE OF DIGITAL HEALTH REGULATORY AFFAIRS

The following sections will define the stakeholders as this thesis understands them and how the thesis will incorporate the stakeholders' perspectives into the analysis of digital standards. Furthermore, the following sections will provide an overview of communication steps between industry and health agencies throughout the lifecycle of a medicinal product. Also, the next sections will detail which digital standards are typically used to transfer the information at the given communication points between industry and health agency during the lifecycle.

2.1 HEALTH REGULATORY AFFAIRS: PRINCIPLE STAKEHOLDERS AND LEGAL FRAMEWORK BASIS

PRINCIPLE STAKEHOLDERS

This thesis focuses on the pharmaceutical disciplines of health regulatory affairs, looking at it from a public, regulatory, industry, and payers' perspective.

PUBLIC

The public is mainly composed of patients receiving medication and healthcare professionals diagnosing and treating patient health issues.

Patients

Medicinal products are developed, distributed, and regulated to improve the lives of humans with poorer mental and or physical conditions. While animals may also be considered patients, this thesis focuses solely on humans. Although the human life expectancy is higher than it was ever before, 95% of humans had at least 1 health related issue in 2013.[15] In 2016, 55 million people died. The diseases proportionally causing the most death to the world's population in 2016 were cardiovascular diseases (32.26%), followed by cancers (16.32%), respiratory diseases (6.48%), and diabetes (5.83%). In general, health is influenced by a human's biology and genetics, lifestyle (e.g. drug abuse, diet), social and environmental factors (e.g. exposure to crime, pollution), the political system and the regulatory environment a human lives in (e.g. vaccination support), as well as the access to healthcare (e.g. correct diagnosis and timely treatment of diseases).[16] This thesis will describe an indirect impact standardised regulatory information transitions may have on patients.

Health Care Professionals

In this thesis, a health care professional may work inside all outlets of the health care sector, including medicine, surgery, dentistry, midwifery, pharmacy, psychology, nursing or other related health professions. A health care professional may also be a public and community health expert operating for the common good of the society. This thesis will describe an indirect impact standardised regulatory information transitions may have on HCPs.

[15] The Lancet. Elsevier Inc. [Online] [Cited: 3 April 2019] https://www.sciencedaily.com/releases/2015/06/150608081753.htm.
[16] M. Roser/H. Ritchie; Our World in Data. [Online] [Cited: 3 April 2019] https://ourworldindata.org/burden-of-disease.

Non-patients

Non-patients, in this thesis, are defined as part of the public as indirectly interested parties of global health, such as family members of patients – without health issues and not being treated with medicines. However, as described above, only 5% of humans tend to have no health issues yearly. This makes almost every human on earth a potential patient.

Public Associations

Organizations such as the Patients Association in the UK help patients with issues regarding medicines and represent interests of patients in front of industry and regulators (associations) to promote the best possible treatments for individuals and communities in need. HCP associations, such as the European Association of Hospital Pharmacists (EAHP) represent HCPs in front of regulators and industry associations. This thesis will rely on information and data from the initiatives of public patient and HCP associations.

REGULATORY

The regulatory system is composed of health agencies and bodies controlling the safe access to medicines. Prior to the regulation of pharmaceuticals, many researching pharmaceutical companies file patents.

Patent Offices

Patents for pharmaceutical products grant the "owner […] the right to exclude others from making, using, offering for sale, or selling his or her invention for a period of 20 years from the filing of the patent application onwards. An invention is any new or useful process, machine, article of manufacture, or composition of matter".[17] In the EU, the communication processes between pharmaceutical company and patent office are usually disconnected from marketing authorisation communication. The time lost during administrative marketing authorisation processes can have an effect on the prolongation of market exclusivity rights, via Supplementary Protection Certificates, SPC.[18] This thesis will only indirectly include the information process between patent offices and health agencies.

[17] B. Lehman; The Pharmaceutical Industry and the Patent System. International Intellectual Property Institute [Online] [Cited: 3 April 2019] https://users.wfu.edu/mcfallta/DIR0/pharma_patents.pdf.
[18] Document 31992R1768; EUR-Lex; [Online]; [Cited: 3 April 2019]; https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX:31992R1768.

Health Agencies

Health agencies are independent governmental third party organizations, such as the European Medicines Agency (EMA) or the United States Food and Drug Administration (U.S. FDA), approving marketing authorisations of medicinal products.

On the one hand, the goal of the European regulation of marketing authorisations of medicinal products is to safeguard the public from low-quality, unsafe, and inefficient treatments, while on the other hand the support of public health, by enabling patients to gain access to medicines without unnecessary delays or shortages of medicines.[19] Subsequently, regulators have to find an appropriate balance between ensuring that decision making for marketing authorisation is based on a positive benefit-risk-profile substantiated with scientifically valid data and the need for access to new medicines. They have to weigh efficacy and safety evidence with inherent uncertainties, while taking into consideration the public need for better medicines to treat existing and new diseases. [20]

However, there are regional differences in the advancement of regulatory systems worldwide. Institutions, such as the coordinating authority of the United Nations, World Health Organisation (WHO), are leading initiatives to advance drug regulatory processes for controlling the access to medicines in adapting regions with the help of tools such as the WHO Global Benchmarking Tool (GBT) for the evaluation of national regulatory systems.[21] Only 20% of regulatory bodies in WHO regions are maturely competent authorities, meaning 80% do not have processes in place to appropriately approve and control drugs.[22] As an example, in South Africa the scientific knowledge tends to be high, while the structure and organization is lacking in comparison to other regions – tending to let years pass until a new drug application can even be reviewed.[23] This thesis will mainly look at communication points between health agencies and industry.

Ethic Committees

Ethic committees in principle ensure that medical experimentation and human research are carried out in an ethical manner, in accordance with national and international law. This thesis will

[19] M. Putzeist; Marketing authorization of new medicines in the EU: towards evidence-based improvement, Thesis Utrecht University; 2013.
[20] Regulation (EC) No 726/2004. European Parliament and of the Council; [Online]; [Cited: 3 April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf.
[21] World Health Organisation; Global Benchmarking Tool; [Online]; [Cited: 3 April 2019]; https://www.who.int/medicines/regulation/benchmarking_tool/en/.
[22] J.L. Valverde/E. Pisani; The Globalisation of the Pharmaceutical Industry, 2016; [Online]; [Cited: 3 April 2019] https://www.ifpma.org/wp-content/uploads/2016/11/The-Globalisation-of-the-Pharmaceutical-Industry-Monograph.pdf.
[23] T. Salmonson; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

incorporate information exchange between industry and health agencies and ethic committees within clinical trial settings.

Notified Bodies

Notified bodies assist and control the conformity assessment of manufacturers of industrial products of various kinds. This also includes the assessment of manufactures for medical devices. This thesis will however focus on pharmaceutical products for humans, and will only indirectly impact specifics for medical devices.

Health Technology Assessment (HTA)

Health Technology Assessment (HTA) examines criteria such as effectiveness, security and costs, taking into account social, legal and ethical aspects of a health treatment – such as a pharmaceutical product. The result of an HTA study is usually published as an HTA report. This should primarily serve as a decision-making aid for health policy issues. Among other things, this includes the incorporation of innovations in the catalogue of benefits provided by (statutory) health insurance companies.

In Europe alone, there are 96 regulatory bodies, either ministries of health or other institutions, such as the Committee for Evaluation and Dissemination of Innovative Technologies (CEDIT) in France, involved in the drug benefit assessment process for reimbursement decisions.[24]

In the United States, on the other hand, there is no national basic or explicit minimum health care benefit package and thus no need for one national HTA body. The FDA review is one form of partial, national HTA, but health care plans need not cover FDA-approved products and plans can cover some products “off-label”.[25] This thesis will only indirectly incorporate the information process between HTA bodies and health agencies.

Regulatory Associations

Communities such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Health Level 7 (HL7), International Organisation for Standardization (ISO), or Organisation for Economic Co-operation and Development (OECD) are

[24] R. Schwarzer; HTA in German-speaking countries. Switzerland + Austria; [Oral Presentation]; 12th Annual Meeting of DNEbM; EbM & Individualized Medicine; Berlin, Germany; 2011.
[25] L. Garrison, Ph.D; An Introduction to Health Technology Assessment in the U.S. and Canada; [Online]; [Cited: 4. April 2019]; http://globalmedicines.org/wordpress/wp-content/uploads/2014/01/Garrison-HTA-US-CAN-July-5-2011-FINAL-7-5.pdf?1478792404

initiatives by regulators and research-based pharmaceutical industry organisations to standardise and streamline scientific and technical aspects of the drug regulatory information exchange process. Most of the information this thesis is working with has directly been affected and or was created by regulatory associations.

INDUSTRY

The pharmaceutical industry researches, develops, manufactures, markets, and distributes pharmaceutical products. Pharmaceutical companies may research and develop new products or produce generic products as medicines to be administered to humans.

The revenue of the worldwide pharmaceutical market in 2017 was USD 1,143.3 billion. That is an increase of 193% from 390.2bn USD in 2001.[26] Healthcare as a percentage of GDP is increasing globally. Approximately USD 7.2 trillion or about 10% of global GDP was spent on healthcare in 2015 across the world.[27] The top 10 countries with the biggest global pharmaceutical markets in the world as of 2017 are the USA ($339.7 million), Japan ($94.3 million), China ($86.8 million), Germany ($45.8 million), France ($37.2 million), Brazil ($30.7 million), Italy ($27.9 million), UK ($24.5 million), Canada ($21.4 million), and Spain ($20.7 million).[28]

The pharmaceutical industry also nourishes service providers, such as consultancies, clinical research organisations, distributors, pharmacies, or information technology solutions providers.

Universities and other academic institutions also provide research benefiting the industry. On the other hand, universities and academic institutions tend to derive benefit from pharmaceutical industry funding.[29] This thesis will mainly look at communication points between health agencies and industry.

Industry Associations

Communities, such as the European Federation of Pharmaceutical Industries and Associations (EFPIA) or German Medicines Manufacture's Association (BAH), create collaborative environments representing the interests of the pharmaceutical industry together with regulators

[26] Statista; Revenue of the worldwide pharmaceutical market from 2001 to 2017 (in billion U.S. dollars); [Online]; [Cited: 4. April 2019]; https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/.
[27] World Health Organisation; Current health expenditure as a percentage of gross domestic product (GDP); [Online]; [Cited: 4. April 2019]; https://www.who.int/gho/health_financing/health_expenditure/en/.
[28] R. Y. Wee; Biggest Pharmaceutical Markets In The World By Country; [Online]; [Cited: 4. April 2019]; https://www.worldatlas.com/articles/countries-with-the-biggest-global-pharmaceutical-markets-in-the-world.html.
[29] A. Singh/S. Singh; The Connection Between Academia and Industry; [Online]; [Cited: 4. April 2019]; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3369181/.

and patient associations. This thesis will rely on information and data from initiatives of industry associations.

PAYER ORGANISATIONS

Payer organisations financially bridge the access to medicines for individuals and communities in need. This mainly includes (statutory) health insurance companies or hospitals. This thesis will only indirectly look at the information process between payer organisations and health agencies.

GENERAL LEGAL FRAMEWORK

Substances that turn into pharmaceutical products are initially prohibited to be researched and developed, tested, and marketed, unless the pharmaceutical company receives a marketing authorisation granted by a health agency.

The European Union's (EU) legislation knows three levels: primary law, secondary law, and accompanying law. The drug development's relevant legal basis is mainly in the secondary and accompanying law, composed of: regulations, directives, decisions, and guidelines. Regulations are immediate legally effective laws across the EU, Directives define common goals to be converted to nationally binding laws. Decisions are binding for the addressee, such as the decision of granting a marketing authorisation in the European centralised procedure.[30] Guidelines implement specifications on the basis of the current state of scientific knowledge in a field for the treatment of explicit issues. Digital standards usually are implemented via guidelines.[31]

[30] N. Eckstein; Arzneimittel - Entwicklung und Zulassung: Für Studium und Praxis; 2018
[31] European Commission; Volume 2B Notice to Applicants Medicinal products for human use; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf.

2.2 DIGITAL INFROMATION TRANSFER IN THE PHARMACEUTICAL PRODUCT LIFECYCLE – INDUSTRY AND HEALTH AGENCIES

The medicinal product lifecycle is composed of research and development, marketing authorisation and post-marketing authorisation processes. The information below does not claim exhaustive completeness, but shall instead succinctly outline the consecutive communication points of contact which a pharmaceutical company has with regulatory bodies during the product lifecycle. It is possible that the information transfer mechanisms during research and development may be reused during the post-marketing authorisation phase – e.g. Adverse Event (AE) reporting might happen before and after a marketing authorisation. These steps will not be described again in the respective other sections, in order to avoid duplication.

RESEARCH AND DEVELOPMENT INFORMATION

The research and development process of a pharmaceutical product on average takes 10-15 years and costs 100 of millions of US dollars.[32] Typically, it comprises the drug discovery phase, non-clinical studies and clinical studies. After the clinical studies have concluded, the marketing application process starts.

DRUG DISCOVERY

Pharmaceutical companies discover drugs through research and development activities in their own or contracted research laboratories. Researching pharmaceutical companies may identify candidates by screening 10 thousands of molecules.[33] Hits from screenings are then tested in cells and in animals. Usually, at this stage, there is little exchange of information between companies and health agencies.

NON-CLINICAL STUDIES

Non-clinical studies, also referred to as pre-clinical studies, are performed on animals in order to test substances and help identify the optimal formulation of a medicinal product. Non-clinical studies typically cover Pharmacodynamics, Pharmacokinetics and Toxicology. Pre-clinical

[32] J.A. Di Masi/H.G. Grabowski, R.W. Hansen; Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs, Journal of Health Economics; [Online]; [Cited: 4 April 2019]; https://www.ncbi.nlm.nih.gov/pubmed/26928437.
[33] J. Heun; [Own Transcript]; Master of Drug Regulatory Affairs, Bonn, Germany; 2018.

studies are also the bridge from animal to clinical studies, such as the first-in-human Phase-I-studies.

Good Laboratory Practice (GLP)

During non-clinical studies, especially, GLP builds the framework of which kind of information to transfer between industry and agencies to ensure quality regarding organizational processes and conditions under which non-clinical studies are planned, conducted, and monitored. In addition, GLP also deals with the recording, archiving, and reporting of these studies. Also, other authorisation regulation fields follow best-practices guidelines, the so called GxP.

GLP compliance may be onsite-audited by health agency inspectors. GLP inspection reports may help structure these audits.[34] Agencies usually schedule these inspections together with the pharmaceutical company – however, inspections may also be spontaneous. A process based Quality Management System (QMS) on quality policies, quality risk management and quality goals, showing e.g. Standard Operating Procedures (SOPs) and change management controls, will be used as information source to prove GLP compliance. Often, the QMS is supported through software and digital data.

DRUG MANUFACTURING

The production processes of the pharmaceutical technology are very different depending on the dosage form. As an example, in the most common form, the tablet, the starting materials are weighed and mixed, usually granulated for better process-ability and then pressed dry to form tablets.[35] These are then often provided with a coating that gives them special properties such as lubricity, acid resistance, shape and colour.

The production must be carried out under controlled, low-germ conditions. Medicines for injection must be prepared sterile. Particularly elaborate, is the production of biological drugs in which small deviations in the process can lead to large differences in potency. The entire production is monitored by an ongoing quality assurance. The nature of the medicinal product, in particular

[34] OCDE/GD(95)114; [Online]; [Cited: 4. April 2019]; https://mobil.bfr.bund.de/cm/349/oecd_principles_glp_09.pdf
[35] R. Becker; Dem Arzneistoff eine Chance – die Arzneiform; In: D. Fischer, J, Breitenbach (Hrsg.); Die Pharmaindustrie; 2010.

identity, content and purity, must be monitored. All manufacturing steps must be documented in detail.[36]

Good Manufacturing Practice (GMP)

The most important guideline for manufacturing, production, quality control and documentation, is the GMP guideline. GMP includes but is not limited to document management for default documents (e.g. SOPs and forms) and records, deviation - and change management of processes, procedures, and methods; qualification of equipment, validation of processes and methods, training of employees, risk management, and internal audits – all involved in the manufacturing processes.

GMP data submitted for marketing authorisation applications for medicinal products will usually be verified by an on-site inspection. A process based QMS, showing e.g. SOPs on validation procedures and change management controls, will be used as an information source to prove GMP compliance. Often, the QMS is supported by software and digital data.

Active Substance Master File (ASMF)

The Active Substance Master File (ASMF), or European Drug Master File (EDMF), or Drug Master File (DMF) is a document that records the pharmaceutical manufacturing and quality assurance of drugs to a drug regulatory agency for the purpose of drug approval.

There is no legal requirement for an ASMF and to submit it to the authorities. ASMFs are often used when the drug manufacturer and the company that wants to market the medicine produced with the drug are different companies. With the help of an ASMF, the manufacturer can in such cases avoid disclosing confidential information to their business partner for the production of the drug.[37]

Therefore, ASMFs usually consist of an open part (also known as applicant's part) and a confidential part (also known as restricted part). The open part, which is also available to the distributor, documents key details of the analysis and quality control which the distributor needs to fulfil in their role as a drug approval holder. The confidential part of the ASMF is only available

[36] T. Jung; Menschen, Prozesse, Material – die Produktion; In: D. Fischer, Jörg Breitenbach (Hrsg.); Die Pharmaindustrie; 2010

[37] EMEA/CVMP/134/02 Rev 1; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/guideline-active-substance-master-file-procedure-revision-1_en.pdf.

to the health authority, which often contains manufacturer secrets – such as the process development for manufacturing.[38]

Both parts of the document are prepared and maintained by the drug manufacturer and reviewed by the health authority. Applicants and distributors only refer to the ASMF in their marketing application after the drug manufacturer has allowed this in an authorisation letter.

"The holder should provide an annual report on the anniversary date of the original submission […] and should provide a statement that the subject matter of the DMF is current".[39]

ASMFs for medicinal products for human use are usually submitted in eCTD format. In Europe, "the use of eCTD is mandatory for all for centralised procedure human ASMF submissions since 1 July 2016".[40]

Plasma Master File (PMF)

The plasma master file (PMF) is a compilation of all the required scientific data on the quality and safety of human plasma relevant to the medicines, medical devices and investigational products that use human plasma in their production.

The PMF is a separate set of documentation from the dossier for a medicine's marketing authorisation.[41] However, "the file/directory structure used to submit the PMF data should be in accordance with the eCTD specification".[42]

CLINICAL STUDIES

Clinical studies, also referred to as Phase I – III studies, shall test and guarantee the efficacy and safety of substances in humans. Experimenters and patients join Phase I-III clinical studies to gain proof of concept in regards to efficacy and through pivotal trials with large collectives. The

[38] CHMP/QWP/227/02 Rev 3/Corr; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-active-substance-master-file-procedure-revision-3_en.pdf
[39] U.S. Food and Drug Administration; Drug Master Files: Guidelines; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm
[40] European Medicines Agency; Electronic Active Substance Master Files (eASMF) [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eASMF/index.htm.
[41] CPMP/BWP/4663/03; [Online]; [Cited 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/guideline-requirements-plasma-master-file-pmf-certification_en.pdf.
[42] EMEA/512725/2009 V1.0; [Online]; [Cited 4. April 2019]; http://esubmission.ema.europa.eu/doc/eCTD%20Plasma%20Master%20File%20Guidance%20-%20FINAL.pdf.

following lists the communication points between industry and agency during clinical studies consecutively.

Good Clinical Practice (GCP)

GCP refers to internationally recognized ethical and scientific rules for conducting clinical trials. GCP focuses on the protection of study participants and their informed consent as well as the quality of the study results. GCP defines what roles various clinical trial stakeholders play: sponsor (usually a pharmaceutical company), examiner (often a clinic), contract research organization, and ethics committee.

GCP is a QMS which permanently enables the performance of quality controls by monitoring an ongoing study on behalf of the sponsor. For example, this ensures that the data entered in the Case Report Form (CRF) matches the source documents in the clinic.

In addition, the sponsor is required to carry out audits on quality assurance, which will examine the quality of the study's implementation and the study data on sites. Finally, investigators, trial centres and sponsors are monitored through inspections by health agencies. In particular, during the review of marketing authorisation applications, the data submitted there will be verified by on-site inspections. Often, the QMS is supported by software and digital data.

Clinical Trial Application Dossier (CTAD)

The CTAD is a collection of the clinical trial application form, Investigational Medicinal Product Dossier (IMPD), Study Protocol, Investigator's Brochure (IB) – or Summary of Product Characteristics (SmPC), if already marketed – and further clinical documentation.

The clinical trial application form transfers administrative information to the health agency and provides data to base the opinion of the ethics committees in the community to get approval for the start of planned clinical trials.[43] A clinical trial application and clinical data may be submitted electronically via Clinical Trials Information System.[44] The CTAD may follow eCTA format.

[43] 08/ENTR/CT/09 Revision 4; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/application-form2009_en.pdf
[44] EudraCT; Clinical trial application menu; [Online]; [Cited: 4. April 2019]; https://eudract.ema.europa.eu/help/Default.htm#eudract/cta_menu_ov.htm

Investigational Medicinal Product Dossier (IMPD)

The definition of an Investigational Medicinal Product (IMP) is “a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form”.[45]

The IMPD is one of several pieces of IMP related data required whenever the performance of a clinical trial is intended to be proven. The IMPD includes summaries of information related to the quality, and manufacture and control of any IMP, including reference product and placebo, and data from non-clinical and clinical studies.[46]

Guidance on the section headings to be used in a full IMPD exists, although the format is not obligatory. The IMPD can also follow the structure of an eCTD (Module 3).

Investigators Brochure (IB)

The IB is documentation, capturing significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.[47] In case the Investigational Medicinal Product (IMP) already has a marketing authorisation, the summary of product characteristics (SmPC) may be used instead of the IB.[48]

As per ICH E6 (R2) good clinical practice there is a predefined table of contents for an investigator's brochure to follow.

Trial Master File (TMF)

The Trial Master File (TMF) is a collection of documents that individually and collectively allow the evaluation of the general conduct of a clinical trial. This includes the integrity of the trial data and

[45] DIRECTIVE 2001/20/EC; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
[46] INFORMATION 2010/C 82/01; [Online]; [Cited: 4. April 2019]; https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF.
[47] Good Clinical Practice Network; [Online]; [Cited: 4. April 2019]; https://dev.ichgcp.net/75-appendix-2/.
[48] Health Products Regulatory Authority; [Online]; [Cited: 4. April 2019]; https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0001-guide-to-clinical-trial-applications-v12.pdf?sfvrsn=50.

the compliance of the trial with GCP. Both the sponsor of a clinical trial and the investigator create a trial master file.

The content of the TMF is regulated by Directive 2005/28/EC.[49] The TMF contains, e.g., the Investigators Brochure (IB) - or the Summary of Product Characteristics (SmPC) if the investigational medicinal product has a marketing authorisation. The TMF also encloses Case Report Forms (CRFs), and IMP information.[50] In addition to the paper-based Trial Master Files, electronic Trial Master Files (eTMFs) are also being used due to the increasingly complex clinical studies.

Clinical Study Report (CSR)

A Clinical Study Report (CSR) is a content structure to transfer information of e.g. ethics, study objectives, investigational plan, efficacy, and safety evaluation of clinical studies. “In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilised by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form”.[51]

In more detail the report shall incorporate “tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output etc.”.[52]

[49] DIRECTIVE 2005/28/EC; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf.
[50] EMA/CHMP/ICH/135/1995; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/ich-e-6-r1-guideline-good-clinical-practice-step-5_en.pdf.
[51] ICH; Structure And Content Of Clinical Study Reports E3; [Online]; [Cited: 4. April 2019]; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.
[52] ICH; Structure And Content Of Clinical Study Reports E3; [Online]; [Cited: 4. April 2019]; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

As per ICH E3 Clinical Study Reports, the CSR follows a predefined table of content structure. CSRs are part of the eCTD structure in Module 5.[53] Case Report Files (CRFs) are part of the CSR.[54]

Case Report Files (CRFs)

The Case Report Form (CRF) is a questionnaire (paper form or electronic - electronic form eCRF) in which the examination data of a patient (test person), required according to the test plan of a clinical study, is recorded and sent to the sponsor of a clinical study, usually a pharmaceutical company researching a drug. The patient information inside a CRF is usually anonymised.

CRFs typically hold information such as symptoms, medication history, physical examination, haematology, pharmacokinetic profile. CRFs are part of the eCTD structure in Module 5.[55]

Adverse Events (AE) that are recorded in this questionnaire may be listed as a side effect in CRFs when a drug is subsequently approved in the package leaflet. CRFs can also be part of post-marketing communication between agencies and companies.

Adverse Event (AE)

When an adverse event is detected during a clinical trial, its seriousness, causality and expectedness needs to be evaluated.

The seriousness is defined per protocol but usually relates to e.g. death or life-threatening situations. The causality is defined by the event's relation to the IMP. Expectedness is the consistency of the event with available information.

All AE need to be recorded by the sponsor.[56] A Serious and Unexpected Serious Adverse Event (SUSAR) needs to be reported to the sponsor and health agencies in less than 15 days (in case of death less than 7 days). SUSARs are reported through Individual Case Safety Report (ICSR) form data elements arising from clinical trials via Adverse Reaction Databases (ADR Databases),

[53] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf.
[54] ICH; Structure And Content Of Clinical Study Reports E3; [Online]; [Cited: 4. April 2019]; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.
[55] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf.
[56] INFORMATION 2011/C 172/01; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf.

such as EudraVigilance Clinical Trial Module (EVCTM). Additionally, SUSARs must be reported annually in a Development Safety Update Report (DSUR).[57]

Healthcare professionals and patients may use unsolicited communication channels, such as ADR Databases, including U.S. FDA Adverse Event Reporting System (FAERS) or WHO VigiBase.

Development Safety Update Report (DSUR)

The DSUR is the pre-marketing equivalent of the post-marketing Periodic Safety Update Report (PSUR).

The DSUR is intended to be an annual report that should be submitted to regulatory authorities, as appropriate, for as long as the sponsor conducts clinical trials with the investigational drug, or for as long as appropriate to satisfy local requirements. A DSUR should be prepared after the first authorisation of a clinical trial worldwide and the submission should stop when the trial ends. [58]

The main focus of the DSUR is on data from interventional clinical trials of IMPs including biologicals, with or without a marketing approval, whether conducted by commercial or non-commercial sponsors. The DSUR should document all safety information from all ongoing trials that a sponsor is leading, including clinical trials conducted, using an investigational drug whether with or without a marketing approval, i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III); clinical trials conducted using marketed drugs in approved indications, i.e., therapeutic use trials (Phase IV); other therapeutic use of an investigational drug; and comparability trials conducted to support changes in the manufacturing process of medicinal products.[59]

The document is submitted to regulatory agencies and sometimes also to Ethics Committees or Institutional Review Boards (IRBs).[60] When submitting the DSUR to an agency, it can follow two formats. Either a defined DSUR table of content structure or the eCTD format. If eCTD format is

[57] K. Breithaupt-Grögler; Neue Regelung Neue Regelung des SUSAR des SUSAR-Reporting Reporting in der GCP in der GCPVerordnung; [Online]; [Cited: 4. April 2019]; https://www.agah.eu/uploads/tx_news/Breithaupt-Groegler_Kerstin_Neue_Regelung_des_SUSAR-Reporting.pdf.

[58] Heads of Medicines Agencies; Questions and Answers to the Annual Safety Report Frequently asked questions regarding the Development Safety Update Report (DSUR) [Online]; [Cited: 4. April 2019]; http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2011_12_22_Q___A_DSUR.pdf.

[59] EMEA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/ich-e-2-f-development-safety-update-report-step-3_en.pdf

[60] B. Cobert; Drug Safety Update Reports (DSURs) [Online]; [Cited: 4. April 2019]; https://www.c3isolutions.com/blog/drug-safety-update-reports-dsurs/

used, the sponsor needs to consult with the relevant health agency regarding the appropriate placement of content into the eCTD structure.[61]

Scientific Advice

Typically, scientific advice and protocol assistance are given to medicine developers by health agencies. Scientific advice helps to ensure that pharmaceutical companies perform appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing-authorisation.

The health agency gives scientific advice by meeting the pharmaceutical company and answering questions posed by the company. The advice is given in the light of the current scientific knowledge, based on the documentation provided by the medicine developer. There is no predefined structure to these questions. A pharmaceutical company typically can ask for scientific advice at any stage of development of a medicine.[62] Typically, the (last) scientific advice meeting is held 12 to 36 months prior to marketing authorisation application. Questions, answers, and commitments of pharmaceutical company to the agency may be documented and distributed in digital form.

There may be other pre-submission meetings with the health agency prior to the submission of a marketing authorisation. Such as the Regulatory Strategy Meeting, Orphan pre-submission meeting (regarding orphan drug designation), and PIP pre-submission meeting (regarding paediatric requirements).[63] Likewise, questions, answers, and commitments of pharmaceutical company to the agency may be documented and distributed in digital form.

MARKETING AUTHORISATION INFORMATION

A marketing authorisation is an agency-issued approval required to offer, distribute or supply an industrially manufactured, ready-to-use medicinal products. MAs are usually granted for specific indications (i.e. a field of application). The use of an approved drug outside of the approved

[61] EMA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf

[62] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

[63] I. Rager; MAA pre-submission issues and EMA meeting opportunities; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/presentation/presentation-marketing-authorisation-application-pre-submission-issues-european-medicines-agency_en.pdf

indication is referred to as an off-label use. The following describes possible communication elements between industry and agency during marketing authorisation processes.

PRODUCT INFORMATION

The product information is an integral part of the marketing authorisation process. The product information includes the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PL).

Summary of Product Characteristics (SmPC)

The SmPC is a legal document of each approved medicinal product and summarizes its essential characteristics and accompanying information as agreed upon between the marketing authorisation holder (MAH - usually a pharmaceutical company) and the competent health agency. The information in a SmPC is presented in a defined structure.[64]

SmPCs can be requested to be transferred via several standards, such as eCTA, eTMF, eCTD, and xEVPRM.

Patient Information Leaflet (PL)

The PL is a document that accompanies the package of a pharmaceutical product and contains information about the medicine and its use. For prescription drugs, the deposit is technical and gives doctors information on how to prescribe the pharmaceutical product. This includes which side effects may arise when using the pharmaceutical product. The presentation of side effects in the leaflet is limited to those observed after intended use of the drug.[65] The PL follows its own structure, supported by templates provided by health agencies.[66] PL can be requested by an agency to be submitted via eCTD.

MARKETING AUTHORISATION APPLICATION TYPES

Marketing authorisations may refer to full applications, generic applications, hybrid applications, fixed combination, well-established use, medicines for use outside of the EU; and informed consent. Supplemental information, such as responses to validation issues, questions or letters

[64] O. Fasanya; Draft presentation: Summary of product Characteristics; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/presentation/presentation-summary-product-characteristics_en.pdf
[65] Patient Information Leaflet: Information For the User Sertraline Hydrochloride 50 & 100 Mg Tablets; [Online]; [Cited: 4. April 2019]; https://www.medicines.org.uk/emc/files/pil.8517.pdf.
[66] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-templates

of undertaking, will occur during the application process. Furthermore, marketing applications may include specific obligations, such as Post-Authorisation Safety Study (PASS), and other follow-up measures after potential approval.[67]

Referrals, notifications, transfers of a marketing authorisation, corrections to the published annexes, lifting of suspensions, withdrawals of a marketing authorisation, reformats to a different standard, European public assessment reports (EPAR), and clinical data publications form part of rather more administrative procedures of marketing applications.[68]

Marketing authorisations are submitted following the eCTD structure. Depending on the application type only parts of the eCTD are submitted. As an example, generic applications do not need to provide additional non-clinical tests or clinical trials, but only bioequivalence studies and references to the originator's full application in Module 4 and 5.[69] Marketing applications may have impact on the data to be submitted via xEVPRM.[70]

POST-MARKETING AUTHORISATION INFORMATION

Medicinal treatments' safety will be monitored after a marketing authorisation is granted – sometimes referred to as phase IV studies. Pharmaceutical companies have to maintain communication with agencies to prove that the treatment stays safe during wide-spread market use – a process called pharmacovigilance. The following describes possible communication elements between industry and agency during post-marketing authorisation processes.

Good Pharmacovigilance Practices (GVP)

Further internationally acknowledged GxP practices are GVP, building the outline of which kind of information to transfer to ensure quality regarding organizational processes and conditions under which pharmacovigilance is conducted.

This includes "proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance, the Member States in which the qualified person resides and carries out his/her tasks; the contact details of the qualified person; a statement signed by the applicant to

[67] VOLUME 2A Procedures for Marketing Authorization Chapter 1 Marketing Authorisation; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf
[68] Good Clinical Practice Network; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf
[69] VOLUME 2A Procedures for Marketing Authorization Chapter 1 Marketing Authorisation; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf
[70] EMA/159776/2013; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/electronic-submission-article-572-data-questions-answers_en.pdf

the effect that the applicant has the necessary means to fulfil the tasks and responsibilities [...], a reference to the location where the PSMF for the medicinal product is kept".[71]

The Pharmacovigilance System Master File (PSMF) has an individually defined format and layout, and is linked to xEVPRM with a unique number. GVP compliance may be onsite-audited by health agency inspectors.[72]

Variations

Variations are change requests to existing marketing applications. Variations represent approximately 80% of the work that a typical regulatory affairs employee is involved in at pharmaceutical companies.[73] Variations to existing marketing authorisations can be administrative, such as changes of addresses of MAHs; or more substantial such as the change of a manufacturing supplier or chemical active substance in the product itself. Depending on the change, variations are divided into type IA, type IAIN, type IB, type II, or extensions.[74]

Variations are submitted in eCTD structure, condensed to the modules, sections and components the change request addresses. Variations may have impact on the data to be submitted via xEVPRM.[75]

Risk Management Plan (RMP)

All MAs should include a RMP. A RMP update is expected to be submitted at any time when there is a change in the list of the safety concerns or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities. For example, a change in study objectives, population, or due date of final results.

If, for example, RMPs are a follow-up action of a PSUR, then RMPs can be requested from agencies outside any marketing authorisation procedure as a stand-alone variation. Usually, RMPs are part of a marketing application. However, stand-alone RMPs have templates and should be submitted in CTD section 1.8.2. Electronically, RMPs must be submitted in a working

[71] EMA/816573/2011 Rev 2*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf
[72] EMA/119871/2012 Rev 1*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-iii-pharmacovigilance-inspections_en.pdf
[73] J. Heun; [Own Transcript]; Master of Drug Regulatory Affairs, Bonn, Germany; 2018.
[74] (EC) No 1234/2008; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf
[75] EMA/159776/2013; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/electronic-submission-article-572-data-questions-answers_en.pdf

documents folder together with, but outside of the eCTD. The working document folder is related to the eCTD sequence it was submitted with. This is mainly due to e.g. necessary "tracked changes" versions for SmPCs in Word files for the RMP assessments – as World files technically are not allowed in eCTD.[76]

Periodic Safety Update Reports (PSUR)

The PSUR is the post-marketing equivalent to DSUR. PSUR is a report to be prepared by pharmaceutical companies at fixed intervals to verify a drug's safety and update the risk-benefit ratio evaluation of pharmaceuticals. Pharmaceutical companies are required to evaluate AEs collected around the world and to assess whether this will result in measures for the safe use of a drug, such as whether further application restrictions or additional side effects need to be considered. "PSURs can be submitted in eCTD format […] or NeeS format".[77]

Annual Reassessment

In case a marketing authorisation is granted for a medicinal product under specific obligations or exceptional circumstances (e.g. treatment urgently needed), the safety of the drug will be annually reassessed, irrespective of any spontaneous safety information which is already mandatory to be provided. Annual reassessments are submitted in eCTD format.[78]

Post-Authorisation Safety Study (PASS)

PASS are either mandatory as a part of a marketing authorisation under exceptional circumstances, or voluntary. PASS are additional studies to prove a product's safety, as a commitment by the pharmaceutical company to in return retain the validity of a marketing authorisation. Draft protocols of non-interventional imposed PASS are separate documents and should only be submitted as an annex to the RMP (inside a MA procedure) in module 1.8.2 of an eCTD. Final PASS reports should be submitted in module 5.3.6 of the eCTD.[79]

[76] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plan-rmp-questions-answers
[77] EMA/52449/2015 v9.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/psur/docs/PSUR%20Repository%20user%20guide%20for%20MAH%20submissions.pdf
[78] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/renewal-annual-re-assessment-marketing-authorisation
[79] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0

Post-Authorisation Efficacy Studies (PAES)

PAES are e.g. requested at the time of admitting an initial MA while concerns regarding some characteristics of the efficacy of the treatment are recognized, which, however, can only be resolved after the medicinal product has been marketed.

When the PAES is completed, a final study report must be submitted via a variation procedure. Also, a summary of clinically important efficacy and safety findings obtained from the study are to be submitted in a PSUR. Hence, PAES are to be submitted in eCTD structure.[80]

Urgent Safety Restriction (USR)

An USR is a regulatory activity in reply to a safety indication, implementing a temporary variation to the terms of the marketing authorisation of a medicinal treatment. USR may affect to revise the SmPC and package leaflet. URS follow a standalone submission form.[81]

Post-Authorisation Measure (PAM)

PAMs' goal is to gather data for assessing the safety, quality or efficacy of medicinal products in case additional data is needed post-authorisation to complement the available data from prior marketing authorisation processes. These can e.g. result from specific obligations, PSURs or form part of RMPs. A PAM uses a form to classify a submission. Supporting documentation is submitted via eCTD.[82]

Referral

Referrals are started by the health authority or by the company that has the MA for a pharmaceutical product. Reasons to start a referral are usually safety concerns or disagreements on the benefit-risk ratio on the use of the medicine. There are legislative and historical reasons

[80] EU Module 1 eCTD Specification Version 3.0.2; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eumodule1/docs/EU%20M1%20eCTD%20Spec%20v3.0.2-corr-HHMG-20170502.pdf

[81] CMDh/097/2000/Rev5; [Online]; [Cited: 4. April 2019]; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/USR/CMDh_097_2000_Rev5_2017_02-clean.pdf

[82] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers

for a referral.[83] Referrals' supporting information may be submitted in eCTD format.[84] Following a referral, the MA procedure number needs to be changed via xEVPRM.[85]

Renewals

MAH have to submit a renewal of a marketing authorisation within five years of its approval to retain validity. A renewal application should be submitted to the agency 9 months before the expiry date of a marketing authorisation, the latest. Renewal applications are submitted in eCTD format.[86] Renewals must be notified to EMA no later than 30 days after their submission via xEVPRM.[87]

Transfer of Marketing Authorisation

MAs can be transferred from one MAH to another company, being a different legal entity. A marketing authorisation transfer may be reasonable for several reasons, such as the merger of two or more companies or simply one company may see an investment opportunity where the other firm doesn't see one anymore. Transfers of marketing authorisations are submitted in eCTD format and are to be notified to the health agency via xEVPRM.[88]

Expiry of Marketing Authorisation

MAs need to be renewed to retain their validity. However, it could be that the MAH decides against marketing a medicinal product with a MA for e.g. economic reasons. Here the term "marketing" means placing authorized products into the distribution chain, out of the direct control of the MAH. MAH can only keep authorized products out of the market for 3 years before the sunset clause causes the expiration of the marketing authorisation. To renew the application before its expiration, a renewal procedure, submitted in eCTD and notified via xEVPRM needs to be triggered.[89]

[83] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures
[84] VOLUME 2A Procedures for Marketing Authorization Chapter 1 Marketing Authorisation; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf
[85] EMA/159776/2013; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/electronic-submission-article-572-data-questions-answers_en.pdf
[86] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/renewal-annual-re-assessment-marketing-authorisation
[87] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/data-submission-authorised-medicines-article-57
[88] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-procedural-qa/transfer-marketing-authorisation-questions-answers
[89] EMEA/180079/2005; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-application-so-called-sunset-clause-centrally-authorised-medicinal-products_en.pdf

PRODUCT CLASS DIFFERENCES

Depending on the product characteristics, a marketing authorisation can follow different evaluation processes.

Advanced Therapy Medicinal Products (ATMPs) are products with cutting-edge new ways to treat diseases. ARMPs can profit from priority review mechanisms.[90]

Orphan Drugs are medicines used to treat rare diseases. Orphan drugs may benefit from fee deductions.[91]

Paediatric Investigational Plans (PIPs) are mandatory for any pharmaceutical product applications to increase the number of paediatric medicines. Waivers to not conduct PIPs are granted in exceptions. General Paediatric medicine applications are reviewed by a Paediatric Committee (PDCO).[92]

Conditional approval mechanisms for medicines addressing life-threatening conditions enable MA to be granted, despite open concerns regarding safety, efficacy and/or quality. Annual reassessments monitor these concerns. However, the need for the product to save lives in this case is higher (e.g. during epidemics).[93]

The adaptive pathways approach shall improve timely access for patients to new medicines. This mechanism applies primarily to treatments in areas of high medical need and where patient numbers make the collection of data difficult.[94]

Compassionate use grants the usage of a medicinal product without MA. This shall make potential treatments available to patients that have no treatment alternatives on the market while also not able to enter clinical trials.[95]

[90] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview
[91] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-designation/questions-answers-orphan-designation-application
[92] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation
[93] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
[94] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways
[95] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use

In general, all product classes have to follow the steps described in the previous section and follow the product lifecycle – hence they have to transfer research and development information, marketing authorisation information, and post-marketing authorisation information to the agency. Broadly speaking, the same information steps as described in the sections before are used for this.

SUMMARY

Regulated and streamlined communication between industry and agency is essential to transfer information on the safety, quality and efficacy of investigational and marketed medicinal products effectively. The chapter before lays out a variety of standardized points of information used for each phase. What is already apparent is that sometimes standards are reused for different communication steps within different phases, while isolated standards tend to be installed for other communication steps. E.g. in research and development phase, the DSUR can use eCTD while eCTA follows its own format. In post-marketing authorisation phase PSUR reuses eCTD. Before this thesis evaluates the impact of the differences in communication point formats and standards, digital standards for the information transfer between industry and agency are described in the following chapter.

2.3 DIGITAL STANDARDS FOR INFORMATION TRANSFER

Digital standards define how information is transmitted between industry and health agencies in electronic form during certain steps of the medicinal product lifecycle. In the following please see a description of digital standards used during the lifecycle of a medicinal product. Please be informed that the list does not claim exhaustiveness. The main reason for that is that the dynamics of the standard development might not allow capturing all initiatives at a certain point in time. Also, the technical depth of standards should for this thesis not surpass a certain level to keep macro-perspective improvement potentials inferable. As an example – although Stability Data Standards could be eCTD and eSafety data within eCTDs, the detailed level of eSafety will not be described.[96] Also data exchange standards, such as CDISC's Dataset-XML v1.0 will not be described in detail.[97]

RESEARCH AND DEVELOPMENT DIGITAL STANDARDS

The following describes the digital standards, through the help of which manufacturing, non-clinical – and clinical trials information will be delivered to health agencies during research and development phase of a medicinal product.

CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM (CDISC)

CDISC is an accepted standard for the organisation and submission of data for the evaluation of drug study results – such as the Standard for the Exchange of Non-Clinical Data (SEND) and Study Data Tabulation Model (SDTM). Extensible Markup Language (XML) and Document Type Definitions (DTD) criteria are used to define the standards.

SEND is used to submit non-clinical data in tabulated standards to agencies. SDTM describes the content structure of tables in which the case reports from clinical trials documented in individual case report forms can be summarized and submitted to an agency.

Furthermore, CDICS defines standards for planning and analysis of study data as well as study data exchange.[98]

[96] U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/forindustry/datastandards/stabilitydatastandard/default.htm
[97] Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards/data-exchange/dataset-xml
[98] Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards

ELECTRONIC CLINICAL TRIAL APPLICATION (E)CTA

Applications for the authorisation of a clinical trial must be submitted in a paper version and the application form as well as the documents to be attached must in addition, also be submitted to the federal competent authority on an electronic data carrier. Often, this is referred to as the clinical trial application form and supporting dossier.[99] As an example, the German Federal Institute for Drugs and Medical Devices (BfArM) and Paul-Ehrlich-Institute (PEI) push for a uniform European submission format to follow a specific structure.[100]

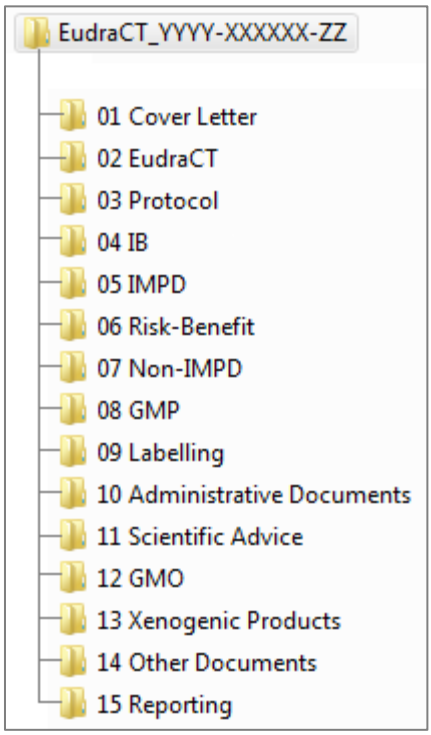

Figure 1 Structure of the CTAD electronic data carrier

As can be seen in figure 1, next to IB and IMPD information on clinical trials, GMP information on how the substance and IMP is manufactured needs to be provided.

CLINICAL DOCUMENT ARCHITECTURE (CDA)

The Clinical Document Architecture (CDA) is an HL7 XML-based standard for the exchange and storage of clinical content.

[99] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

[100] Federal Institute for Drugs and Medical Devices; [Online]; [Cited: 4. April 2019]; https://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/news/ElectronicSubmission.html

Metadata, such as the patient, the involved healthcare professionals, and information about the document itself are given a high-level structure (i.e., machine-readable) in the so-called CDA header. The actual medical documentation can be stored structured in the so-called CDA body.[101]

The CDA body entails the actual clinical contents such as questions, observations, diagnoses, medication, therapies, information on resubmissions, appointment suggestions, etc. The documentation can be subdivided into sections. Text formatting functions such as lists and tables are available.[102] The CDA specification differentiates between 3 levels.[103]

CDA Level 1: Representation of existing clinical documents in XML, focusing on layout and basic formatting of free text (sections, highlights, tables).

In addition to Level 1, CDA Level 2 emphasizes on interoperability while preserving Level 1 free text content. Level 2 adds a consistent structured description and structure of the content (type of document, sections, and subsections). The individual components are classified by standardized codes and code systems.

CDA Level 3 adds machine-readable details, so that e.g. transmitted laboratory values can be automatically entered in the laboratory table of the recipient.

For all three levels, however, the primacy of the information contained in the free text (narrative block), the machine-readable data and structures are always complementary and can facilitate the processing of information and support.[104]

CLINICAL TRIALS INFORMATION SYSTEM

The clinical trials information system (formerly the EU clinical trial portal and database) will be a single entry point for submitting clinical trial information in the EU, which will be stored in the system.[105] The system will be a central management platform/dashboard for the users.[106] EMA will make information stored in the system publicly available, subject to access rules. The sponsor,

[101] Health Level 7; [Online]; [Cited: 4. April 2019]; http://hl7.de/themen/hl7-cda-clinical-document-architecture/
[102] R. H. Dolin,et. al.; The HL7 Clinical Document Architecture; 2001.
[103] K. U. Heitmann; The Clinical Document Architecture (CDA); 2003.
[104] K. U. Heitmann; Standard für elektronische Dokumente im Gesundheitswesen – die Clinical Document Architecture Release 2.; 2005
[105] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation
[106] EMA/42176/2014 Rev. 1, Corr.*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/functional-specifications-european-union-eu-portal-eu-database-be-audited_en.pdf

authority and public will have respective workspaces. The clinical trial application form and supporting dossier will cover all regulatory and ethics assessments from the concerned member states. It will also include the public registration of the clinical trial and any subsequent updates.

ELECTRONIC TRIAL MASTER FILE (ETMF)

In an effort to improve interoperability of eTMF data among clinical trial stakeholders, an eTMF standards initiative under the OASIS open standards development organization was initiated for the development of a global eTMF standard.[107] "The TMF is used by auditors and inspectors to assess the compliance of the trial with legalisation and guidance and by sponsors, monitors and investigators for the management of the trial […]".[108]

There are a minimum of 53 documents that are considered essential (where appropriate to the trial such as IB, CRF, CSR, defining the content of an (e)TMF.[109] The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.[110]

ADVERSE REACTION DATABASES (ADR DATABASES)

The EudraVigilance Clinical Trial Module (EVCTM) is "a centralised European database of adverse events (AE) to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA)".[111]

The system is composed of a gateway, web reporting application, database management system, data warehouse and analysis, and adverse drug reaction reporting portal. Information on AEs are reported and made available to the public. Data submission must thereby be in accordance with MedDRA & Standard Terminology and medicinal products (Article 57 / Extended EudraVigilance

[107] OASIS; [Online]; [Cited: 4. April 2019]; https://www.oasis-open.org/news/announcements/electronic-trial-master-file-etmf-specification-v1-0-published-by-the-etmf-tc
[108] EMA/INS/GCP/636736/2012; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-good-clinical-practice-compliance-relation-trial-master-files-paper/electronic-management-audit-inspection-clinical-trials_en.pdf
[109] Section 8 of ICH GCP and Section 3 of the Volume 10 TMF Guidance; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf
[110] Good Clinical Practice; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf.
[111] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/glossary/eudravigilance

medicinal product dictionary (XEVMPD)). Agencies, marketing authorisation holders, and (non-)commercial sponsors of clinical trials work with the data.[112]

Correspondingly, U.S. FDA employs the FDA Adverse Event Reporting System (FAERS). The WHO services VigiBase, "the largest database of its kind in the world, with over 19 million reports of suspected adverse effects of medicines, submitted, since 1968 […]."[113] "By the end of 2017, EVCTM held a total of 12,451,826 ICSRs, referring to 7,948,873 individual cases (one case can relate to more than one ICSR owing to follow-up information supplementing and updating initial reports). In total, 402,690 cases were submitted from interventional clinical trials and 7,546,183 from the post-authorisation setting of the medicinal products".[114]

INDIVIDUAL CASE SAFETY REPORT (ICSR)

The ICSR form is populated using the electronic ICH-E2B(R3) data elements and is submitted to ADR Databases.

Structured data are strongly recommended in electronic transmission, and provisions have been made for including information in this way. However, structuring the data also implies the use of controlled vocabularies, which are not yet available for some data elements. Electronic transmission of individual case safety reports should be implemented with the "Medical Dictionary for Regulatory Activities (MedDRA), where applicable."[115]

However, ICSR identifiers "allow mapping of international terminologies for routes of administration, dosage forms and units of measurement, as well as controlled identifiers to enable cross-border identification of pharmaceutical products and mapping to their core components, e.g. substances" [116] – in collaboration with the ICH M5 EWG, ISO developed a set of standards to enhance exchange of information for medicinal products – namely, ISO standard Identification of Medicinal Products (IDMP).

[112] EudraVigilance Components & Functionality Introduction; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/presentation/presentation-eudravigilance-components-functionality-introduction-training-module-phv-m2_en.pdf
[113] World Health Organisation; VigiBase; [Online]; [Cited: 4. April 2019]; https://www.who-umc.org/vigibase/vigibase/
[114] R. Postigo, et. al.; EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection; [Online]; [Cited: 4. April 2019]; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5990579/
[115] E2BM Data Elements for Transmission Of Individual Case Safety Reports; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073092.pdf
[116] E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide – Data Elements and Message Specification; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm275638.pdf

MARKETING AUTHORISATION DIGITAL STANDARDS

ELECTRONIC APPLICATION FORM (EAF)

The eAF is a form that administratively classifies the type of application. It e.g. defines the procedure type such as centralised, mutual recognition, decentralized or national; and lays fundamental information to an understanding of the kind of application. There are currently plans to replace replace the PDF eAFs with the CESP Application Dataset Management Module (CESP Dataset Module).[117]

ELECTRONICAL COMMON TECHNICAL DOCUMENT (ECTD) (V3.2.2)

The eCTD "covers the submission of electronic regulatory information for all human medicinal products […]. This includes prescription, over the counter medicines, innovative and generic product submissions. The product types include small molecules, biotech products, herbals, vaccines, homeopathics and blood products".[118]

The eCTD "does not apply to the electronic submission of pre-marketing authorisation (MA) information such as scientific advice, clinical trial applications, Orphan drug designations, [Paediatric Investigational Plan] PIP submissions and related submission correspondence as well as dossier content explicitly excluded from the commonly maintained electronic dossier." [119]

The structure of an eCTD is based on the non-electronic version CTD, which is divided into five Modules:[120]

1. A regionally dependent, administrative part (Module 1) for organizational information for the relevant health agency receiving the submission of electronic regulatory information,
2. A summary and general overviews part (Module 2), making Module 3, 4, and 5 more accessible.
3. A quality part (Module 3), documenting chemistry, manufacturing and controls data (CMC data),

[117] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html
[118] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf
[119] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf
[120] ICH; M4 : The Common Technical Document; [Online]; [Cited: 4. April 2019]; https://www.ich.org/products/ctd.html

4. A safety part (Module 4), documenting all non-clinical study information, and
5. An efficacy part (Module 5), detailing all clinical study data.

Parts of the eCTD are used for the submission of an electronic version of specific regulatory information such as PMF or ASMF. Please refer to PMF or ASMF for more detail.

In relation to the paper based CTD, the eCTD especially made transparency over the lifecycle of submitted regulatory information from agency and industry perspective possible.

In eCTDs, Extensible Markup Language (XML) is used to represent hierarchically structured data in the format of a text file that is readable by both humans and machines. The index.xml and xx-regional.xml for the backbone of Modules 2 to 5 and Module 1 for the relevant region, and the util folder (with e.g. stylesheets for visual presentation of certain content) in particular, make this possible.

The Portable Document Format (PDF) is used in electronic documents so that they can be faithfully reproduced, independently of the original application program, the operating system or the hardware platform. The goal has been achieved and is reflected in ISO standard series 32000 (ISO 15930 for PDF / X).[121] PDFs in eCTD have Optical Character Recognition (OCR) enabled to enable searches for specific words.

The eCTD is currently either planned, adopted and/or implemented as mandatory submission format in more than 40 regions in the world.[122]

NON-ECTD ELECTRONIC SUBMISSION (NEES)

The non-eCTD format for electronic submissions is often used in case eCTD cannot be supported. This may have technical reasons.

“Similar to eCTD NeeS will support that users have a compiled view of the information submitted in the appropriate place in the dossier over time […]. The difference from an eCTD is that the two relevant XML files, the index.xml and eu-regional.xml for the backbone of Modules 2 to 5 and Module 1 for the EU, respectively and the util folder are not present, so navigation through a NeeS

[121] PDF 32000-1:2008; [Online]; [Cited: 4. April 2019]; https://www.adobe.com/content/dam/acom/en/devnet/pdf/pdfs/PDF32000_2008.pdf
[122] J. Archer; A. Nixon; U. Vollmer; Practical Experience & Proposal for eCTD Implementation Regulatory Information and & Technology Expert Group; [Oral Presentation]; EFPIA; 2017.

is based on electronic Tables of Content, bookmarks and hypertext links".[123] Apart from that, NeeS follows the same file folder structure as eCTD.

An advantage of NeeS is that no technical requirements other than e.g. naming convention of PDF files and the structure of the documents to be submitted are needed. However, there are certain drawbacks in comparison to eCTD, e.g. the lifecycle operations (what changed over time in the submitted regulatory information) is harder to understand. Hence, data in NeeS format tend to be less electronically reusable.

GATEWAY / WEB CLIENT

While the submission of information (such as eCTDs) via CDs/DVDs is technically possible, more and more applicants now trust gateways to transmit information to relevant health agencies. The eSubmission Gateway and the eSubmission Gateway Web Client are electronic submission channels that allow the applicants to submit documents supporting all types of applications for human and veterinary medicines to the Agency securely over the internet, in structured and non-structured formats.[124]

The use of the eSubmission Gateway and the Web Client is mandatory for all human and veterinary submissions. The Gateway and the Web Client users will benefit from an automated confirmation of the technical validation feedback and an automated upload to the agency's eCTD review system. It is mandatory to use XML delivery files for submissions via the eSubmission Gateway and the Web Client.[125]

In addition, the Common European Submission Portal (CESP) provides a secure mechanism for the exchange of information between applicants and regulatory agencies, making submission of an application once to reach all required agencies.[126] Agencies encourage the use of only one

[123] European Medicines Agency; Harmonised Technical Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU V.4.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/NeeS%20eGuidance%20Document%20v4%200_final%20for%20publication%20Nov%202013.pdf
[124] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/esubmission.html
[125] European Medicines Agency; PSUR Repository; [Online]; [Cited: 4. April 2019]; https://psur-repo.ema.europa.eu/psur-ui/prepare/submission.html
[126] Heads of Medicines Agencies; Common European Submission Portal; [Online]; [Cited: 4. April 2019]; https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f

channel and to let them then search, browse and download eCTD submissions as well as distribute it to other (national) health authorities via the so called Common Repository.[127]

POST-MARKETING AUTHORISATION DIGITAL STANDARDS

Standards from the research and development and marketing authorisation phase may be reused in the post-marketing authorisation phase. E.g. AEs must be reported after the products market introduction in following PASS. ICSR is a possible medium to transfer the information. The AE could also be transmitted via eCTD in a DSUR or PSUR. To avoid duplication, only non-mentioned standards so far in the thesis will be described in the following sections. In return, some of the standards listed in the following section may already be used for information transfer in earlier lifecycle steps – e.g. the IDMP standard will be used to transfer information on authorised or investigational medicinal products.

IDENTIFICATION OF MEDICINAL PRODUCTS (IDMP)

The ISO IDMP standard will be implemented more and more on a global basis on four domains of master data in the pharmaceutical regulatory processes: substance, product, organisation and referential (SPOR). “The ISO IDMP standards specify the use of standardised definitions for the identification and description of medicinal products for human use. Their purpose is to facilitate the reliable exchange of medicinal product information in a robust and consistent manner. They help to ensure wide interoperability across global regulatory and healthcare communities, which is critical in ensuring accurate analysis and unambiguous communication across jurisdictions”.[128]

The main application areas of IDMP in the regulatory context will be pharmacovigilance, regulatory submissions, clinical trials and GMP inspections, covering the entire medicinal product lifecycle, including products in development, investigational products, products under evaluation and authorised products. The “ISO IDMP format is an extension of the current information available in the xEVMPD. In addition, some conceptual differences are introduced which will need to be taken into account whilst performing the data migration.”[129] IDMP includes extensive changes compared to xEVMPD, as it covers way more data in a much more granular manner.

[127] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/central_repository.HTML
[128] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview
[129] EMA/732656/2015; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/introduction-iso-identification-medicinal-products-spor-programme_en.pdf

IDMP SPOR is currently being implemented in an phased approach. Organisations - and referential data can already be accessed, while substances - and products data will follow soon.[130]

EXTENDED EUDRAVIGILANCE PRODUCT REPORT MESSAGE (XEVPRM)

The xEVPRM populates the Extended EudraVigilance medicinal product dictionary (xEVMPD), also referred to as the Article 57 database. XEVPRM is a tool to submit and retrieve medicinal electronic pharmacovigilance data to health agencies on authorised or investigational medicinal products. xEVPRM will be replaced by the ISO IDMP format once the phased implementation of SPOR master data is completed.[131] Please refer to Identification of Medicinal Products (IDMP) for further details.

MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES (MEDDRA)

The ICH developed MedDRA to be used in the registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale. MedDRA is a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for human medical products. Regulatory authorities, pharmaceutical companies, clinical research organisations and health care professionals use MedDRA assisting with e.g. safety signal detection. One common tool is standardized MedDRA Queries (SMQs). [132]

STRUCTURED PRODUCT LABELLING (SPL)

The Structured Product Labelling (SPL) is a document mark-up standard approved by Health Level Seven (HL7) and adopted by U.S. FDA as a mechanism for exchanging product and administrative data regarding topics such as drug route of administration, package type terminology, unit of presentation, and more. SPL is the US equivalent of IDMP. “It is most likely that U.S. FDA will take-over these standards [IDMP] in near future”. [133]

[130] European Medicines Agency; SPOR data management services; [Online]; [Cited: 4. April 2019]; https://spor.ema.europa.eu/sporwi/
[131] EMA/732656/2015; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/introduction-iso-identification-medicinal-products-spor-programme_en.pdf
[132] Medical Dictionary for Regulatory Activities; [Online]; [Cited: 4. April 2019]; https://www.meddra.org/how-to-use/support-documentation/english
[133] IDMP1; [Online]; [Cited: 4. April 2019]; https://www.idmp1.com/wiki/spl/

FAST HEALTHCARE INTEROPERABILITY RESOURCES (FHIR)

FHIR is a standard developed by HL7. It supports the exchange of data between software systems in the healthcare sector. FHIR describes data formats and elements as so-called “resources” and provides an interface to exchange them.

FHIR aims to accelerate health care data interoperability across a wide range of currently disparate systems. Currently supported data types include allergies, conditions, immunizations, lab results, medications, procedures, and vitals.[134] FHIR focuses inter alia on switching from narrative text to structured data. “With FHIR, narrative only exists for the resources at the root of each section. With CDA, as an example, narrative exists for each section”.[135] FIHR is currently frequently used in patient environments such as electronic health records (EHR).[136]

SUMMARY

Digital standards help to get evidence on a product’s characteristics within its respective lifecycle phase from industry to agencies in a more efficient and effective manner. The chapter before shows that a variety of often distinct digital standards exist for the transmission of arguably the same data on quality, safety, and efficacy between healthcare stakeholders throughout the medicinal product lifecycle. This tends to lead to inefficiencies in data transmission between stakeholders. E.g. must arguably the same data be maintained and sent in several standards to the agency? The following chapter will look into improvement potentials for digital information transfer between agencies and industry in more detail – and open up the viewpoint on digital standards used to include a public and technical perspective next to regulatory and industry views.

[134] Apple Inc.; [Online]; [Cited: 4. April 2019]; https://www.apple.com/healthcare/health-records/
[135] Health Level 7; [Online]; [Cited: 4. April 2019]; https://www.hl7.org/fhir/ehr-fm.html
[136] Health Level 7; [Online]; [Cited: 4. April 2019]; https://www.hl7.org/fhir/ehr-fm.html

3

POTENTIAL IMPROVEMENT AREAS FOR THE DIGITAL INFORMATION TRANSFER IN GLOBAL HEALTH REGULATORY AFFAIRS

Based on the analysis of the previous sections, in the following, improvement areas from regulatory -, industry -, and public perspectives with regards to the usage of digital standards will be described. The standpoints of the improvement areas are global.

3.1 REGULATORY PERSPECTIVE

HETEROGENEOUS DIGITAL STANDARDS

Regulators tend to lack consistency between global digital standards alongside all industry intersecting communication points throughout the lifecycle, which causes inefficiencies. This shall be exemplified through the examples of ASMF, PMF, CTA, IB, IMPD, eAF, and eCTD.

The PMF should be submitted in eCTD format. The PMF may require "Word copies of Annexes A and II – V […] in addition to the PDF for the purposes of review" – although Word files technically speaking are not allowed in eCTD. [137],

In EU, the CTA requires IB, IMPD, study reports, study plans, and study plan amendments. Sometimes, for nonclinical data and clinical use of the IMP, the IMPD cross references to the IB. The submission of study reports is not mandatory when submitting the IMPD. The sponsor, however, should make them accessible on the request of agencies.[138] In the US, the submission of study reports is mandatory at this stage.[139]

In the EU, the German health agencies try to push a standalone (e)CTA format, while the IMPD can follow non obligatory guidance on the section headings or the structure of an eCTD (Module 2 and 3). The CTA and IMPD equivalent in the US is Investigational New Drug application (IND). In comparison to IMPD, the IND tends to require more detailed study information and follows the eCTD structure. Canada on the other hand, is testing the practicability of accepting CTAs in eCTD format as of March 2019.[140]

When submitting a DSUR to an agency, it can follow two formats: Either a defined DSUR table of content structure or the eCTD format. If the eCTD format is used, the sponsor needs to consult with the relevant health agency regarding the appropriate placement of content into the eCTD

[137] EMEA/512725/2009 V1.0; [Online]; [Cited 4. April 2019]; http://esubmission.ema.europa.eu/doc/eCTD%20Plasma%20Master%20File%20Guidance%20-%20FINAL.pdf.
[138] Biopharma Excellence GmbH; [Online]; [Cited 4. April 2019]; http://www.biopharma-excellence.com/news/2018/3/2/from-impd-to-ind-same-but-different
[139] Biopharma Excellence GmbH; [Online]; [Cited 4. April 2019]; http://www.biopharma-excellence.com/news/2018/3/2/from-impd-to-ind-same-but-different
[140] Health Canada; [Online]; [Cited 4. April 2019]; https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-ectd-pilot-clinical-trial-regulatory-activities.html

structure.[141] This may vary depending on the agency, even perhaps the person consulting the sponsor.

Before submitting an eCTD, eAF classifies the type of application and further administrative details. When submitting documentation via eCTD then, the type of application and further administrative details will again be transmitted via metadata in the Module 1 XML.

Also, different interpretation of standards tend to lead to different data submission requirements per region for the industry.

The eCTD, although technically specified as the same from at least Module 2-5, shows regional differences. E.g. in the Canadian Module 2, section 2.3 Overall Summaries is one document.[142] In the EU, this section is separated into different nodes. In Module 5, some regions require additional attributes in Study Tagging Files (STFs) that are not required in other regions (e.g. EU). Therefore, a workaround with so called node extensions, that 'ignore' the additional stored information of STFs allow these to be submitted in EU.

In the EU, on the other hand, RMPs can only be submitted in a 'working documents' section together with, but outside of the eCTD. This is mainly due to that e.g. 'tracked changes' versions for SmPCs in Word files are necessary for the assessment – and Word files are technically not allowed in eCTDs. Other regions tend to not work and accept 'working documents'.

In Asia the ASEAN Common Technical Dossier (ACTD) finds its application. Mainly ASEAN member states support the format – hence, Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Viet Nam. The ACTD is divided into 4 parts instead of the 5 modules in the eCTD. The overviews and summaries section from module 2 in eCTD is placed in overviews sections of each quality (part 2), safety (part 3), and clinical (part 4) documentation part.[143]

[141] EMA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf

[142] Boehringer Ingelheim, Glaxo-Smith Kline, Image Solutions Inc, Lundbeck Inc, Merck, Pfizer, sanofi-aventis, Takeda, and ePharmaCMC; [Online]; [Cited: 4. April 2019]; http://www.triphasepharmasolutions.com/Resources/Industry%20Book%20of%20Knowlege%20Quality%20Overall%20Summary%20(QOS)%20in%20eCTD%20format.pdf.

[143] The ASEAN Secretariat Jakarta; ASEAN COMMON TECHNICAL DOSSIER; [Online]; [Cited 4. April 2019]; https://asean.org/storage/2017/03/68.-December-2016-ACTD.pdf

INCOMPLETE DIGITAL INFORMATION EXCHANGE

Similar data submission requirements for different standards alongside the lifecycle tend to cause duplication of the same data to be provided to the agencies in different stages of the product lifecycle. This shall be exemplified in the following by comparing ASMF, PMF, DSUR, PSUR, Scientific Advice, AR Database, CTA, eTMF, IB, IMP, eCTD, NeeS, and XEVPRM.

ASMFs for medicinal products for human use are usually submitted in eCTD format. Also, the PMF "file/directory structure used to submit the PMF data should be in accordance with the eCTD specification".[144] However, the PMF is a separate set of documentation from the dossier for a medicine's marketing authorisation.[145] This means that the same information tends to be submitted via a different procedure (marketing application instead of PMF), though in the same format (eCTD) again.

The ICH E2F states that "some of the information contained in the DSUR, such as safety findings, inclusion of serious adverse reactions in line listings, and discussion of relevant articles from published literature can also be provided in PSURs for marketed products that are the subject of ongoing clinical trials. Therefore, some overlap is expected between the DSUR and PSUR […]". A PSUR can be grouped for multiple products.[146] However, the PSUR then needs to be a standalone eCTD with individual lifecycle, tending to isolate data from the products, adding a further maintenance layer on it. E.g. if changes are made in one of the products' eCTDs, this needs to be reflected in the PSUR eCTD as well, as the submissions need harmonised lifecycles and the combined PSUR eCTD cannot be used for products that have different eCTD lifecycles.[147] In any case, PSURs can be submitted in eCTD or NeeS. What looks like a simplification for companies without eCTD experience, tends to impact efficiencies on evaluating and processing medicinal product safety data, since NeeS tends to be less digitally process-able than eCTD. PSURs and DSURS also capture ARs. ARs are additionally stored in ADR Databases.

Scientific advice and protocol assistance gives critical guidance on e.g. how study designs can lead to successful evaluation and hence efficiently support the drug evaluation process. Today,

[144] EMEA/512725/2009 V1.0; [Online]; [Cited 4. April 2019]; http://esubmission.ema.europa.eu/doc/eCTD%20Plasma%20Master%20File%20Guidance%20-%20FINAL.pdf.
[145] CPMP/BWP/4663/03; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/guideline-requirements-plasma-master-file-pmf-certification_en.pdf
[146] EMA/52449/2015 v9.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/psur/docs/PSUR%20Repository%20user%20guide%20for%20MAH%20submissions.pdf
[147] EMEA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/ich-e-2-f-development-safety-update-report-step-3_en.pdf

discussions, outcomes, decisions and actions tend to not follow a predefined structure that could be reused for other standards. E.g. does eCTD "not apply to the electronic submission of pre-marketing authorisation (MA) information such as scientific advice", although outcomes of scientific advice will impact the contents of eCTD.[148]

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form in an eTMF.[149] CTA, as stated above, contains the IB, IMP information and CRFs. Also, the eTMF system contains, again, the IB - or SmPC if the investigational medicinal product has a marketing authorisation. The eTMF also encloses CRFs, and IMP information. All named information will also be again part of the marketing authorisation application in the end – thus eCTD, if regionally applicable. xEVPRM data may require a copy of the SmPC as well.

References to information in non-eCTD submissions must be made in eCTD section 1.4.4. A cross reference document indicating where to find information in non-eCTD documents needs to be placed there. This document must state the "(1) the application number, (2) the date of submission (e.g., letter date), (3) the file name (if applicable), (4) the page number (if necessary), and (5) the submission identification (e.g., submission number, volume number if paper, electronic folder if applicable) of the referenced document."; all metadata already provided to the agency via forms and electronic submission.

There may be more examples, however, the exemplification above shows that the same information tends to be required at different stages in the lifecycle in different forms and shapes. This tends to cause inefficiencies for agencies, mainly through maintaining the information in disunited formats and struggling to have one complete connected picture without relying on different data sources and standards.

VARIETY OF PROCESS ALTERNATIVES

Regulators tend to lack common processing understandings of standards. As an example, the Gulf Cooperation Council (GCC) accepts an eCTD dossier for multiple strengths but tends to require different eCTD dossiers for multiple dosage forms.[150] In the EU, typically, an eCTD dossier

[148] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf.
[149] Good Clinical Practice; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf
[150] [Practical Experience of LORENZ Life Sciences Group]

will cover all dosage forms and strengths of a product.[151] Thailand tends to request industry splitting the 3.2.S sections by manufacturer, while this is not necessary in other regions.[152]

Furthermore, regulators tend to lack one global common vocabulary for similar processes. eCTD Module 1 and administrative metadata are different per region. These represent mostly slight differences in understanding (how to name) typically similar procedures (e.g. Variation (EU) vs. Change (US)) and the usage of administrative forms require an implementation of administrative data concepts per region, although these may be harmonized for most regions – since underlying procedures tend to be similar. Another example may be that the same information request for an ASMF can also be called European Drug Master File (EDMF), or Drug Master File (DMF). These marginal (naming) differences may have relevant impact on data processing possibilities across regions.

However, regulators tend to also lack globally harmonized processes. E.g., the U.S. FDA offers a Fast Track Status and Rolling Review to the industry. In the EU, no comparable procedures exist. While the US Accelerated Approval can be compared with the EU Conditional Approval, the EU offers the Exceptional Circumstances process to which no comparable US procedure exists.[153]

In any case, (electronic) application forms tend to be inefficient to be filled out and signed and then attached to an electronic submission that is full of metadata indicating the purpose of the application.[154]

Regulators tend to further fuel an inefficient standards system with further inconsistent guidelines. E.g. EMA policy 0070 for making clinical data more transparently accessible was, from its underlying purpose important and correct, but implemented without assessing technical feasibility and guiding on the impact on 'lifecycling' eCTD submissions.[155] This tends to differentiate the lifecycle of eCTD submissions from other regions.

[151] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf
[152] [Practical Experience of LORENZ Life Sciences Group]
[153] M. Wegner; [Own Transcript]; Master of Drug Regulatory Affairs, Bonn, Germany; 2018.
[154] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eaf/
[155] EMA/90915/2016 Version 1.2; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en.pdf

The EU does not recognize an orphan drug status granted in other regions, since the criteria for orphan designations are not harmonised internationally.[156] While clinical trials are staring to be accepted between regions, the lack of harmonisation of further mutual acceptance processes tends to slow down information transfer between stakeholders.

In some regions, such as the US, patent offices are part of the medicinal products evaluation process. Other regions, such as the EU, tend to split the information transfer. The same tends to apply for Health Technology Assessments (HTA), following the approval of a drug. In Europe alone there are 96 regulatory bodies, either ministries of health or other institutions, such as the Committee for Evaluation and Dissemination of Innovative Technologies (CEDIT) in France, involved in the drug benefit assessment process for reimbursement decisions.[157] In the United States, on the other hand, there is no national basic or explicit minimum health care benefit package and thus no need for one national HTA body. The FDA review is one form of partial, national HTA, but health care plans need not cover FDA-approved products, and plans can cover some products "off-label".[158] Data used, analysed and assessed during regulatory processes, such as the application for marketing authorisation, especially in regards to efficiency, can give evidence to HTA. However, regulatory bodies tend to not share relevant data to support HTA – in 2017, only "5% of scientific advice was given jointly with health technology assessment (HTA) bodies' and EMA".[159]

It may be argued that heterogeneous standards make it harder to share relevant information between all stakeholders. Sharing data with supporting standards across regions and disciplines (such as clinical, MA, post-marketing, but also patent and HTA) – would potentially gain in productivity on the evaluation and safety monitoring of medicinal treatments.

[156] European Medicines Agency; [Online]; [Cited: 4. April 2019];https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-designation/questions-answers-orphan-designation-application
[157] R. Schwarzer; HTA in German-speaking countries. Switzerland + Austria; [Oral Presentation]; 12th Annual Meeting of DNEbM; EbM & Individualized Medicine; Berlin, Germany; 2011.
[158] L. Garrison, Ph.D; An Introduction to Health Technology Assessment in the U.S. and Canada; [Online]; [Cited: 4. April 2019]; http://globalmedicines.org/wordpress/wp-content/uploads/2014/01/Garrison-HTA-US-CAN-July-5-2011-FINAL-7-5.pdf?1478792404
[159] European Medicines Agency; Annual Report 2017; [Online]; [Cited: 3 April 2019]. https://www.ema.europa.eu/en/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf

DISCONNECTED INFORMATION TECHNOLOGY (IT) INFRASTRUCTURES

When processes are more aligned cross regionally, homogeneous IT infrastructures may propel the information transfer between all stakeholders. However, in general, regulators tend to be lacking in global communication and collaboration through heterogeneous IT infrastructures.

There tend to be few (established) global technological communication channels amongst agencies and/or ethic committees. There is e.g. no real-time sharing of information on clinical trials or signal detection, and no inspections between the US and EU (and other regions). ADR Databases, such as EVCTM, VigiBase, and FAERS tend to not be automatically connected. When looking, for example, at EMA's plan up to 2020, no integration to other regions' databases is planned.[160] Also, regionally shared databases are rare - EMA reported silo databases inside disciplines – which tends to hold back collaboration since information is rather stored heterogeneously per discipline instead of shared cross functionally, by e.g. linking and mapping systems.[161]

There is also a prevalence of multiple repositories with similar purposes (sending, receiving, distributing and evaluating information on the safety, quality and efficacy of a medicinal product), such as eSubmission Gateway, CESP, PSUR Repository, Common Repository, Clinical Trials Information System. This tends to increase the ways in which potentially similar information is stored, hence a duplication of data is unavoidable. E.g. information in the Clinical Trials Information System will end-up in an eCTD submission that goes through a gateway.

Smoother infrastructure (connections) may have a positive effect on how data on matters with mutually accepted review standards (e.g. clinical trials, inspections, signals) could cross regionally be assessed more efficiently.

SHORTAGE OF RESOURCES

Regulators need to adhere to timelines for reviewing submissions.[162] This tends to put reviewers under pressure. In some regions, such as Africa, reviewers are dependent on joint reviews, since there tends to be less know-how in certain scientific areas. But also from a process perspective,

[160] EMA/100194/2018; [Online]; [Cited: 4. April 2019];
https://www.ema.europa.eu/en/documents/other/eudravigilance-operational-plan-milestones-2018-2020_en.pdf
[161] G. Neuwirther; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.
[162] European Medicines Agency; [Online]; [Cited: 4. April 2019];
https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/submission-dates/procedural-timetables

due to prioritized resource usage, it can take up to 6 years until a new medicine marketing application is on the desk of a reviewer.[163]

Also at EMA, multinational teams can be necessary for assessments, e.g. with work-sharing for more efficient reviews.[164] The EMA and U.S. FDA have started accepting respective inspection reviews on manufacturing sites to also save resources.[165] In the EU, political changes tend to effect the upkeep and know-how build-up of EMA.[166] In China, reviewers and clinical experts tend to also simultaneously be site-inspectors at the manufacturing and pharmaceutical companies.[167] Completely new pharmaceutical treatments, such as digital therapeutics, are increasingly entering the market. Agencies need to find know-how for reviewing parts of new treatments. Topics such as understanding algorithms and the way algorithms are built will become a prominent topic at agencies.[168]

Streamlining digital information exchange needs to be prioritized against other resource shortages. However, especially improving the way information can be transferred between regulators and made transparent for many stakeholders in the regulatory field faster may positively impact resource shortages by e.g. by sharing reviews and assessments in real time with agencies around the world – further strengthening joint reviews or work-sharing.

[163] [Practical Experience at LORENZ Life Sciences Group]
[164] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers
[165] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/news/eu-us-mutual-recognition-inspections-medicines-manufacturers-enters-operational-phase
[166] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit.
[167] X. Qin; [Own Transcript]; DIA Europe Conference, Basel, Switzerland; 2018.
[168] T. Senderovitz; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

3.2 INDUSTRY PERSPECTIVE

INEFFICIENCIES THROUGH HETEROGENEOUS DIGITAL STANDARDS

On a global scale, industry tends to suffer under inefficiencies to comply with heterogeneous digital standards. As an example, preparing an US IND on the basis of an EU IMPD – and vice versa – is not a copy and paste exercise.[169] One has to understand the detailed differences of standards used (CTA and eCTD) and which data submission depth is required (e.g. less study details in the EU as in the US). Another example: The SmPC is inter alia part of eCTA, eTMF, marketing application (hence eCTD and RMP), and xEVPRM data submissions. One variation (e.g. additional indication) will trigger changes that need to maintain the same information in different places. Please see HETEROGENEOUS DIGITAL STANDARDS for more examples.

Different legislations and regulations require companies to employ (costly) experts within the existing diverse regulatory affairs system. IT solution landscapes need to technically output data in compliance with, arguably unnecessarily different 'variants' of standards (e.g. eCTA in own format or as an eCTD). If a company is in parallel registering products in a non-electronic, paper-based region, such as larger parts of South America, this adds to the complexity. Nevertheless, also "in part-electronic areas some NCAs may still require paper copies of some documents in addition to e.g. NeeS".[170]

The industry must keep internal product characteristic information up to date and – even as important – link dependencies of changes to a product characteristic to regionally different digital standard variants to transfer the information correctly. This proves especially complicated if industry employs external companies, such as service providers for clinical studies and internal information maintenance has external – thus less controllable aspects to it.

Adhering to digital standard variants tends to cause inefficiencies, hence leading to costs for pharmaceutical companies that can negatively affect time-to-market of treatments for individuals and communities in need.

[169] Biopharma Excellence GmbH; [Online]; [Cited: 4. April 2019]; http://www.biopharma-excellence.com/news/2018/3/2/from-impd-to-ind-same-but-different

[170] European Medicines Agency; Harmonised Technical Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU V.4.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/NeeS%20eGuidance%20Document%20v4%200_final%20for%20publication%20Nov%202013.pdf

LACK OF ACCESS TO RELEVANT DATA TO ACCELERATE RESEARCH

As digital standards tend to be isolated by product lifecycle process steps – research and development, (non-) clinical studies, marketing authorisation, and post-authorisation; (the most current state of) data from all disciplines tends to be more difficult to be shared. As an example, PSURs can be submitted in eCTD format or NeeS format – eCTD being better electronically process-able than NeeS. However, also eCTD may be non-supportive for data sharing systems in regards to research data.[171] Content in eCTDs is in narrative and unstructured text. Parts of eCTD submissions can sometimes not be processed further electronically because of missing DTD and XMLs.[172]
Could current research findings of the industry be compared against existing data from another industry stakeholder? Data that could correlate and stay in cause and effect relation to other submitted safety information tends to not be cross examined. This makes it harder to motivate that pharmaceutical companies cooperate to compete better for the good of global society.[173]

Imagine pharmaceutical company A is researching a topic in which pharmaceutical company B has a breakthrough finding. However, pharmaceutical company B is not pursuing the finding further since the economics of a potential product (e.g. the worked out study design with agency) would not pay out to the organisation. There could be no fit to the existing product portfolio, letting marketing and distribution costs operate on a too low scale and producing too high costs. For pharmaceutical company A, however, this could be a major step forward. Economics could be sorted out between both companies in any way. Today, such cooperative exchanges tend to be difficult. Acquisitions in a stage of research and development happen.[174] However, it can be assumed that digitally better process able data streams alongside the lifecycle could augment cooperative research.

CHALLENGE TO MONITOR SAFETY

As for post-marketing, monitoring the continuous safety of a pharmaceutical product tends to be difficult since the access to potential data is challenging.[175] AEs are reported from unsolicited sources, such as spontaneous reports, literature, internet; and solicited sources, such as

[171] N. Brun; [Own Transcript]; DIA Europe Conference, Basel, Switzerland; 2018.
[172] [Practical Experience at LORENZ Life Sciences Group]
[173] H.V. Perlmutter; D. Heenan; Cooperate to Compete Globally; [Online]; [Cited: 4. April 2019]; https://hbr.org/1986/03/cooperate-to-compete-globally
[174] D. Roland; Pfizer Adds to Big Pharma's Gene-Therapy Deal Streak; [Online]; [Cited: 4. April 2019]; https://www.wsj.com/articles/pfizer-adds-to-big-pharmas-gene-therapy-deal-streak-11553081391.
[175] T. Senderovitz; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

contractual agreements; and regulatory authority sources.[176] AEs are reported via e.g. DSUR/PSUR, ICRs, or websites to authorities. However, consumers may report AEs differently - e.g. via social media, and "[…] if an MAH becomes aware of an adverse reaction on a website that it does not manage, the MAH should review the case and determine whether it should be reported".[177] Billions of people use social media channels today. The shift of healthcare data into these channels might even accelerate, as companies look into possibilities to integrate 'chatbots' as doctors into communication applications such as WeChat.[178] Accessing safety data through this form is harder than ever before. Though existing data transfer standards may have limited impact on how AEs tend or tend not to be reported to industry and or agencies, safety monitoring could probably benefit from more homogeneous standards and connected IT infrastructures on the regulators' site.

[176] ICH; Post-Approval Safety Data Management: Definitions and Standards For Expedited Reporting E2D; [Online]; [Cited: 4. April 2019]; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf
[177] CPMP/ICH/3945/03; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf
[178] The Medical Futurist; [Online]; [Cited: 4. April 2019]; https://medicalfuturist.com/china-digital-health

3.3 PUBLIC PERSPECTIVE

The public perspective will be described out of patients' and health care professionals' viewpoints.

PATIENTS

INSTANT AND TRANSPARENT ACCESS TO PRODUCT INFORMATION

Patients tend to lack relevant (safety) information to treatments they or their relatives take during the time of a treatment. This may differ with regards to the treatment. A treatment for a very narrow patient size, for example, presumably has health care professionals in more instant exchange with patients, potentially cutting the information gap more. However, measured with today's technological communication possibilities, the information transmission from an AE to a patient taking a treatment is comparatively long.

A SUSAR needs to be reported to the sponsor and health agencies in less than 15 days (in case of death less than 7 days).[179] This means someone could have died from a drug a patient is taking 7 days before the agency actually knows about the incident. All expected AEs, including SARs are reported within the PSUR if marketed, or DSUR if still under development. This means a SAR can have happened months before it will be reported to an agency.[180]

In a DSUR/PSUR new events would be listed as expected. Amendments to marketing applications would need to get approval before new PLs would be implemented in new packages of the pharmaceutical product. Pharmaceutical companies tend to make updated PLs available through online services, by stating that "it is possible that the leaflet in your medicine pack may differ from this version because it may have been updated since your medicine was packaged".[181] However, following the physical package leaflet communication route, only if buying an actually new product, or knowing about an updated PL version, a patient would understand new expected events – up to months after they happened. Although URS may require a "recall and distribution of the new packaging information"; it can be expected that the information on safety issues will take comparatively long to transmit to relevant patients – also duo to the fact that one products

[179] K. Breithaupt-Grögler; Neue Regelung Neue Regelung des SUSAR des SUSAR-Reporting Reporting in der GCP in der GCPVerordnung; [Online]; [Cited: 4. April 2019]; https://www.agah.eu/uploads/tx_news/Breithaupt-Groegler_Kerstin_Neue_Regelung_des_SUSAR-Reporting.pdf.
[180] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs
[181] Datapharm Communications Limited; [Online]; [Cited: 4. April 2019]; https://www.medicines.org.uk/emc/product/1159/pil

are “released into the distribution chain”, they tend to be out of the direct control of the MAH.[182] [183]

Especially when incorporating the technological advancements of today, it can be assumed that a patient could be informed if the medicine they take has an AE somewhere else in the world in the moment she is being treated with the product – in real time. Couldn’t tools such as smartphones, social media and messaging be connected to safety information and assessments of drugs? This may even include information to educate on the prevention of diseases in the first place.

Agencies tend to make information on assessments available online. The EMA uses the European Public Assessment Reports (EPAR) on the EMA webpage for that.[184] The U.S. FDA is trying to implement something called MedWatch E-list, an email subscription service for treatments and medical devices a patient uses – tending to go in a direction of push- instead of pull communication.[185] The challenge however is to provide information in an understandable manner for patients, but on the other hand to provide the information in the right way so that patients do not panic and, for example, not unnecessarily stop taking medicines although they are generally safe, which would cause their health conditions to actually worsen.

FALSIFIED MEDICINES

The WHO estimates that “1 in 10 medical products in low- and middle-income countries is substandard or falsified”, including pills, vaccines and diagnostic kits.[186] “Those products usually contain sub-standard or falsified ingredients, no ingredients or ingredients which include active substances in the wrong dosage, thus posing an important threat to public health”.[187]

In Europe, legally required anti-tampering devices and unique identifiers for packages signify an attempt to make pharmaceutical products more secure. In the pursuit of this goal, there is an

[182] CMDh/097/2000/Rev5; [Online]; [Cited: 4. April 2019]; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/USR/CMDh_097_2000_Rev5_2017_02-clean.pdf
[183] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/notifying-change-marketing-status
[184] European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section
[185] U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/Safety/MedWatch/ucm168422.htm
[186] World Health Organisation; [Online]; [Cited: 4. April 2019]; https://www.who.int/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified
[187] DIRECTIVE 2011/62/EU; [Online]; [Cited: 4. April 2019]; https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF

initiative called securPharm.[188] The initiative proves that more integrated technological communication standards between health agencies and industry – and especially the less controllable supply and distribution chain, could possibly have a higher impact on preventing falsified medicines to be marketed.

HEALTH CARE PROFESSIONALS (HCP)

FALSE DIAGNOSIS

HCPs tend to not receive relevant information to correctly treat patients, individually – at the right time. Information on treatment history, current treatment and effectiveness statistics – incorporating all medicinal products that a patient takes at the time of diagnosis, can be outdated depending on the information channel an HCP chooses.

"Five years after graduation, half of what [a doctor] learns will probably be wrong – but no one knows which half. Regardless of how much medical progress has been made over these past centuries […] there will always be limitations on how much information any doctor can know, let alone master.[…] A recent RAND Corporation report shows that preventable medical errors in hospitals result in tens of thousands of deaths per year; preventable medication errors occur at least 1.5 million times annually; and, on average, adults receive only 55% of recommended care, meaning that 45% of the time, doctors get diagnosis wrong".[189] "Right now, cancer and heart disease get a ton of attention, but since medical errors don't appear on the list, the problem doesn't get the funding and attention it deserves".[190]

Although there may be different, systematic reasons for false diagnosis, standardized technological data transfers could aid doctors to get the right information at the right time for the correct diagnosis and may have an impact on saving lives. Since safety and efficacy information on potential new treatments comes from potential patients (from clinical trials), and doctors treat patients, this may be the place in the lifecycle of medicinal product where all data comes together.

[188] SecurPharm; [Online]; [Cited: 4. April 2019]; https://www.securpharm.de/
[189] P. H. Diamandis, S. Kotler; Abundance: The Future Is Better Than You Think; 2012
[190] Johns Hopkins; Study Suggests Medical Errors Now Third Leading Cause of Death in the U.S.; [Online]; [Cited: 4. April 2019]; https://www.hopkinsmedicine.org/news/media/releases/study_suggests_medical_errors_now_third_leading_cause_of_death_in_the_us

The FHIR HL7 standard is used by mass electronic devices and software developers to access health records through daily accessible devices – such as a smartphone.[191]

Also, smartphones become more relevant in clinical studies.[192] Apple owns a patent to turn a smartphone into a device that captures biomarker data, by detecting blood pressure or the amount of oxygen in the blood, electrocardiogram, or EKG and gauge stress. [193] Apple already provided watches to certain studies including mindfulness and physical activity, virtual therapist for arm recovery in stroke, patients, AI support for adherence in psychiatric care, reducing hyperactivity in ADHD, migraine, and binge eating. [194] Novartis is examining whether its FocalView app is effective and usable in capturing visual function for people with degenerative eye disorders. The app is validated against traditional visual testing that is typically performed in conventional clinical settings. This can potentially open the doors for facilitating clinical trials outside of traditional sites (esp. for digital therapeutics). To get 10,000 people enrolled in a medical study, normally it would take Novartis a year and 50 medical centres. With the help of the app Novartis could enrol 400,000 + participants within a year from different geographies.[195]

Research and development standards, such as CDISC tend to connect and build on FHIR.[196] It could be expected that HCPs might retrieve more relevant information if further digital standards throughout the medicinal product lifecycle integrate to patient driven data standards – potentially helping to prevent errors in the medication process and make diagnosis more accurate.

[191] Apple Inc.; [Online]; [Cited: 4. April 2019]; https://developer.apple.com/documentation/healthkit/samples/accessing_health_records
[192] Apple Inc.; [Online]; [Cited: 4. April 2019]; https://www.apple.com/researchkit/
[193] C. Farr; CNBC; [Online]; [Cited: 4. April 2019]; https://www.cnbc.com/2018/10/14/apple-is-donating-1000-watches-for-a-new-study-to-track-binge-eating.html
[194] Stanford Medicine; [Online]; [Cited: 4. April 2019]; https://news.stanford.edu/thedish/2017/07/04/center-for-digital-health-awards-first-seed-grants-1000-apple-watches-to-five-teams/
[195] Novartis; [Online]; [Cited: 4. April 2019]; https://www.novartis.com/news/media-releases/novartis-launches-focalview-app-providing-opportunity-patients-participate-ophthalmology-clinical-trials-from-home
[196] Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards/real-world-data

3.4 TECHNICAL PERSPECTIVE

PHARMACEUTICAL INDUSTRY & DIGITIZATION

In regards to digitisation in general, the chemicals and pharmaceutical industry lags behind other industries such as Information and Communication, Media, Finance and Insurance.[197] This may also be due to the general risk averse approaches manifested in the roots of the industry. However, many pharmaceutical organizations "in the private and public sector have already moved to the third wave of IT adoption – full digitisation of their entire enterprise, including digital products, channels, and processes, as well as advanced analytics that enable entirely new operating models".[198]

When looking at the general technological development the world is undergoing, a transition from client-server (the PC world) to cloud-mobile (the internet world) to decentralised connectivity technologies (the decentralised world) can be observed.[199]

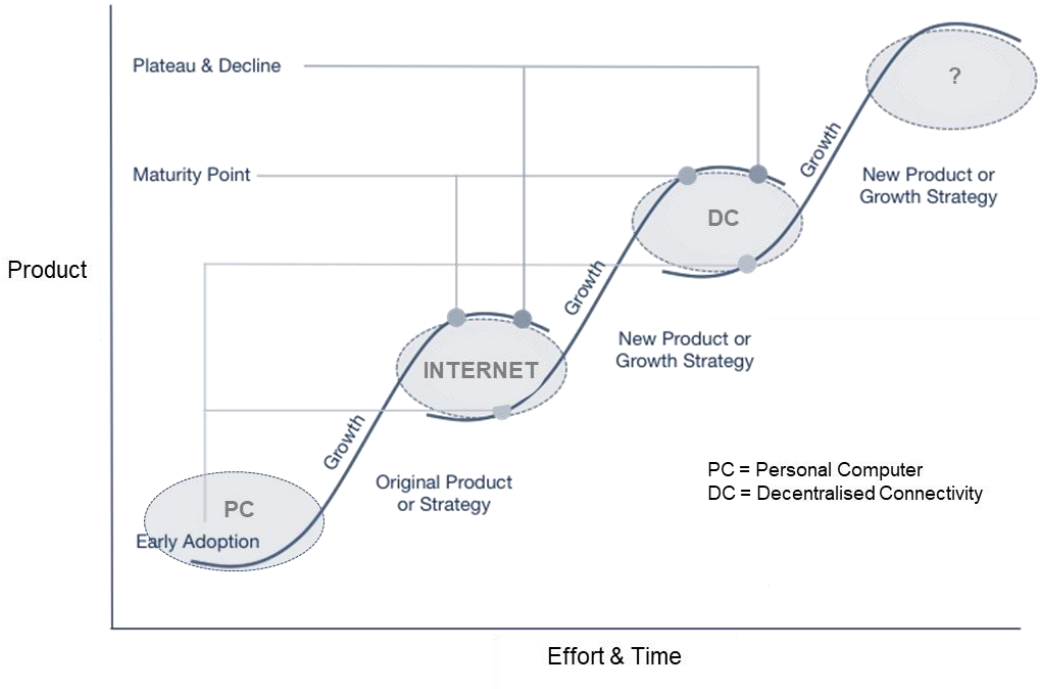

Figure 2 Technological Development S-Curves

[197] P. Gandhi, et. al.; Harvard Business Review; [Online]; [Cited: 4. April 2019]; https://hbr.org/2016/04/a-chart-that-shows-which-industries-are-the-most-digital-and-why
[198] S. Biesdorf, F. Niedermann; McKinsey; [Online]; [Cited: 4. April 2019]; https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/healthcares-digital-future
[199] J. Jobanputra; [Own Transcript]; MIT Conference Business of Blockchain, Boston, USA; 2017.

As displayed in figure 2, the overall development theoretically can be described in clearly defined s-curves. Today, pharmaceutical organisations tend to make use of all technology-worlds simultaneously.

While a historically grown amount of pharmaceutical companies' IT systems are client server based, pharmaceutical businesses tend to use more and more cloud solutions such as IBM Watson for insights in research and development data or during drug discovery.[200] Pharmaceutical companies also start employing decentralised solutions. SAP develops decentralised solutions for medicinal products distributers to handle product returns and cope with the challenge that these returns are actually original and also dealing with expired shelf-life.[201] The U.S. FDA is starting to use decentralised technology to improve the security of the drug supply chain.[202] It is very likely that the technological development will further transition from the hardware- to the internet- to the decentralised-world.

This whole technological development will be fuelled and made smarter by Artificial Intelligence (AI). Already today, healthcare actually is the top industry for AI equity deals, furthermore indicating the industry's convergence to the ever more digital age we live in.[203]

The question is how this technological development will impact the perspectives described above and what can be expected for digital information transfer standards between regulatory bodies and pharmaceutical companies with the new possibilities that the technological development gives at hand.

[200] IBM; [Online]; [Cited: 4. April 2019]; https://www.ibm.com/watson/health/business-need/healthcare-research/ https://www.ibm.com/products/watson-drug-discovery
[201] N. Morris; Ledger Insights; [Online]; [Cited: 4. April 2019]; https://www.ledgerinsights.com/sap-pharma-supply-chain/
[202] U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630942.htm
[203] CB Insights; [Online]; [Cited: 4. April 2019]; https://s3.amazonaws.com/cbi-research-portal-uploads/2018/05/10163951/healthcare-quarterly-deals-dollars_05-2018-1024x768.png

4 GENERAL DISCUSSION

"You will not find national solutions for global challenges".[204]

"In 20 years' time one global life science regulation and approval of drugs is possible".[205]

The following section will debate the findings of the thesis and summarize main aspects in a discussion, looking at regulator's possible shift in paradigm as well as emphasising on how important standardisation will be to advance global digital health regulatory affairs.

[204] Y. N. Harari; 21 Lessons for the 21st Century; 2018.
[205] World Health Organisation; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

4.1 PARADIGM SHIFT IN DIGITAL STANDARDS FOR GLOBAL HEALTH REGULATORY AFFAIRS

In simple terms, when all manufacturing, non-clinical and clinical information, as well as safety monitoring data and change requests end up in marketing authorisation applications or variation applications for assessment, why are regulators not globally harmonizing technical standards and procedures to access necessary data for all perspectives? Why does a harmonized standard not cover all aspects from first contact with the agency for research on potential drugs to (non)clinical trials and marketing application up to post-marketing quality, safety, and efficacy surveillance?

As todays' standards for information transfer between industry and agencies tend to have been created decades ago and have fragmentally been developed further from there in almost isolation – historically, a gap between disciplinarily and regionally separated systems in industry and agency have led to individual or disjoined data transmission understandings throughout the lifecycle of a medicine.

Today, mainly driven through technological advancements, more and more approaches tend to discover a disciplinarily and regionally unified view on data exchanges. An understanding for different periodicities for submissions and objectives of information tends to change today to a more real time view on quality, safety, and efficacy data – on demand.

"The days of the regulation guidance system as we know it today is coming to an end. Today, in the moment a guidance is published, it is outdated".[206] We tend to move towards a different regulatory framework in which collaboration stands over isolation. We tend to change towards looking at regulatory information differently, in a more flowing, real time, even permanent review throughout the product lifecycle. The role of a regulator will evidently change.

Most likely from a 'police-culture' checking in if components and aspects of product characteristics are adhering to protocol and demanding periodically additional information to prove compliance, to a self-regulating industry with monitoring regulators that collaborate and enable access to necessary treatments. [207]

The U.S. FDA enhanced its framework of evaluating real world data by the end of 2018, falling under the 21st Century Cures Act. Currently, focusing the efforts on supplemental products, U.S.

[206] T. Senderovitz; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.
[207] Deloitte; [Own Transcript]; Global Pharmaceutical Regulatory Affairs Summit, Berlin, Germany; 2018.

FDA strives for data driven comparatives for effectiveness and safety. The agency exchanges extensive trial data with insurance companies and industry to learn from each other and promote change. The principle shift, however, remains that the collaboration data approach needs to be plausible, hence a (business) case must exist, as standards do not change because of real-time data alone.[208]

Nevertheless, the potential of real-time (big) data for decision making in industry, regulatory, academia and for patients is undeniable. The way regulators gather and review data from industry will change. However, there are a few main barriers for real-time (big) data to unleash its potential for decision making:

i. Data access. Which algorithms and tools help to gather data? How can data be accessed in narratives and paper format and from multiple sources of truth?
ii. Data quality and validity. How is data integrity ensured? How can disunited standards and multiple sources of truth be connected in an interoperable way? How can data and source of data (e.g. wearables or machine learning/AI software) be validated?
iii. Privacy and governance. How is access to data regulated from institutional access until anonymization on a private level? Which are the controlling data access systems?
iv. Analytical methods and acceptability. How is information generated that regulates how data is being provided and how different sources of data interplay and are maintained? How will data access be accepted from various stakeholders?

With ever more individual devices and thus data sources being used by humans (and by objects, the so called Internet of Things (IoT)) – long term, most likely the individual (potential) patient will be in the centre of data creation and decision on what data to provide to which organization for which cause. Today, there are 17 billion connected devices in the world.[209] Four billion people are online, with more than three billion people using social media platforms regularly. Most social media users (90 percent) access platforms via mobile devices.[210] An average person spends four hours a day on a smartphone.[211] The number of connected devices and humans using these

[208] U.S. Food and Drug Administration; Implementing The 21st Century Cures Act: A 2018 Update From FDA And NIH; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/NewsEvents/Testimony/ucm614607.htm
[209] K. L. Lueth; State of the IoT 2018: Number of IoT devices now at 7B – Market accelerating; IoT Analytics; [Online]; [Cited: 4. April 2019]; https://iot-analytics.com/state-of-the-iot-update-q1-q2-2018-number-of-iot-devices-now-7b/
[210] S. Kemp; Digital in 2018: World's Internet Users Pass The 4 Billion Mark; we are social; [Online]; [Cited: 4. April 2019]; https://wearesocial.com/blog/2018/01/global-digital-report-2018.
[211] M. Curtin; Are You on Your Phone Too Much? The Average Person Spends This Many Hours on it Every Day; Inc.; [Online]; [Cited: 4. April 2019]; https://www.inc.com/melanie-curtin/are-you-on-your-phone-too-much-average-person-spends-this-many-hours-on-it-every-day.html

devices is expected to increase further. The more individual the data creation might get, the more prominent the topic of privacy and governance will become – if not one of the most central subjects today already.

However, at a certain point, and if technologically implementable, patients may realise the value from their healthcare data being shared securely as part of an ever-learning healthcare system and healthcare providers might leverage patient data to improve health and wellness for their patients with improved clinical and financial outcomes through collaboration possibilities. At a point, conventional EHRs could be replaced in a way that makes patient data accessible 'as a service' and improved health IT deployment alongside the medicinal product lifecycle may include identity schemes, data storage and automatic technological validation mechanisms that could execute against shared data infrastructures – securely accessible by relevant stakeholders.[212] In any case, regulators tend to be pretty sure that machines will "never" make regulatory decisions themselves.[213]

[212] C. Brodersen, et. al.; Blockchain: Securing a New Health Interoperability Experience; [Online]; [Cited: 4. April 2019]; https://pdfs.semanticscholar.org/8b24/dc9cffeca8cc276d3102f8ae17467c7343b0.pdf
[213] T. Senderovitz; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

4.2 IMPORTANCE OF HOMOGENISING CURRENT STANDARDS AS WELL AS CURRENT STANDARDISATION INITIATIVES

Benefit-risk assessments today tend to be a snapshot, which is likely to shift from industry providing information periodically to regulators accessing and evaluating data on demand – and validating ways data is created – by the industry and or patients directly. For that, digital health regulatory affairs will most likely change from a document to a data world. However, since the approval of new drugs was required by the Federal Food, Drug and Cosmetic Act of 1938; following the sulfanilamide disaster, the healthcare sector's data has historically not grown structurally. Legacy information in a mixture of paper, electronic narrative texts and electronic information will have to transform to digitally interoperable data. Nevertheless, in reality today, most parts of the regulatory system worldwide are underdeveloped.[214] Many regions of the global regulatory system are not electronic yet.[215] Therefore, it will be important to follow a phased approach and not change radically to entire new ways of data transition – as the legacy data and multiple sources of truth will hunt the stakeholders otherwise.[216]

From the analysis of this thesis it seems most plausible to first start with a broader implementation of proven standards such as eCTD and help its application in more regions and disciplines. As captured above, the eCTD "does not apply to the electronic submission of pre-marketing authorisation (MA) information such as scientific advice, clinical trial applications, Orphan drug designations, PIP submissions and related submission correspondence as well as dossier content explicitly excluded from the commonly maintained electronic dossier".[217] This should be re-evaluated as it would work towards making digital standards more homogeneous and increasing efficiencies, both for industry and agencies. Same applies for eCTA, PSMF, and many other communication steps that can or cannot use eCTD. As a further example, the EMA, the Heads of Medicines Agency (HMA) and the European Commission (EC) are currently working on an electronic version of the product information - ePI. The product information (mostly SmPC and PL) are a central part of the marketing authorisation. However, PI tends to not be a standardized

[214] J.L Valverde.; E. Pisani; The Globalisation of the Pharmaceutical Industry, 2016; [Online]; [Cited: 3 April 2019] https://www.ifpma.org/wp-content/uploads/2016/11/The-Globalisation-of-the-Pharmaceutical-Industry-Monograph.pdf.
[215] J. Archer; A. Nixon; U. Vollmer; Practical Experience & Proposal for eCTD Implementation Regulatory Information and & Technology Expert Group; [Oral Presentation]; EFPIA; 2017.
[216] P. Middag; [Own Transcript]; Global Pharmaceutical Regulatory Affairs Summit, Berlin, Germany; 2018.
[217] European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf

part of eCTD. Now, the ePI shall follow a common electronic standard (XML, controlled vocabularies, and SPOR data).[218] It would be advisable to use proven standards, such as eCTD, to gain efficiencies in terms of data processing and not create yet another structure, adding further complexities regarding maintenance and cross-disciplinary/-regionally transfer of information.

It is important that as many other regulatory regions as possible apply a common standard for exchange on quality, safety and efficacy data. The thesis shows that eCTD is a good candidate to be adopted by regions, as it is rolled out in more than 40 regions globally. Being stricter about the usage of eCTD - not leaving alternatives to other formats such as individual file formats (e.g. eCTA or NeeS) will drive digital accessibility to information and possible cross discipline and multi-regional information exchange. It may also be advisable to look into standardized cross regional processes for the usage of eCTD, making electronic dossiers as compact and transferrable to other regions as possible. Regional differences such as accepting eCTD dossiers for multiple strengths but to require different eCTD dossiers for multiple dosage forms – while in other regions an eCTD dossier will cover all dosage forms and strengths of a product – must be eliminated as these cause unnecessary administrative overhead. Processes for mutual recognizing and or learning evaluation standards from each other will help as well. How can not only clinical studies and manufacturing inspections but also orphan drug designations and more comparable evaluation principles from one region be accepted by more regions? How can processes, such as fast track status and rolling review (both U.S. FDA) and exceptional circumstances (EMA) be harmonised across regions? How can information requirements in different phases of a lifecycle be brought to the same understanding (IND vs. CTA)? To prepare health regulatory affairs for the digital era optimally, it must be as easy as to copy and paste data from the one discipline and region to the other.

Secondly, once existing standards are more homogenous cross disciplinary and regionally, they should be further developed to transition from a document to a data world. Currently, there are important standardisation initiatives further evolving existing standards. “The objective of the Regulated Product Submission [RPS / eCTD 4.0] message is to define one message structure that can be used for all regulated products” – worldwide.[219] The RPS / eCTD 4.0 will follow the current eCTD v.3.2.2 structure and complement the format with e.g. re-using documents

[218] B. Ginnow; Bundesverband der Pharmazeutischen Industrie e.V.; [Online]; [Cited: 4. April 2019]; https://mediaclipping.bpi.de/landingpage.jsp?params=EEOOO5Y7JvS8Xb5AwcNSJ0i6EOO8V2XhfH0z2rfGBNfoWgxCrnABrhizgVqkJ1QIfqsuWyNyeiaUyhteSY1SvkF4D9uEq7KIXu%2BN1RjJoLI%3D%20628

[219] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/ectd/Business%20View%20on%20eCTD%20v4%20rev.pptx

submitted previously, change information (e.g. display name or document title) easily, to group documents within a CTD section in a consistent way across regions, fix the order of documents within a CTD section, identify submission content (e.g., datasets) for additional processing. Also, "eCTD 4.0 can make it possible to indicate that submitted content has received agency assessment, and what the outcome was. Such information could save further review and assessment work. […] A digital management tool for the electronic regulatory information in the eCTD format will be a prerequisite for using RPS / eCTD 4.0", as this prepares to shift from a one-way to a two-way communication with having the agency to also communicate back using the format. [220]

From there on, further digitization initiatives; such as the FDA proposal for structured data for the CMC Module 3 of the eCTD standard will most likely help transition proven standards to a data world – by transforming narrative texts to data. [221]

The structured data for CMC Module 3 of the eCTD standard initiative give room for assuming that Module 2, Module 4 and Module 5 of the eCTD could be considered to be turned from narratives into even more data elements as well. In total there are around 2500 nodes in a full eCTD. Turning all nodes into data endpoints is comparatively small, when measured against Google, Amazon, Facebook, Apple (GAFA), or Baidu, Alibaba and Tencent (BAT) data processing standards – but will be an immense step forward for health regulatory affairs. However, the most important piece of the CMC Module 3 proposal from FDA is to integrate it with other standardisation experts such as ICH, and align the proposal with the main data initiative in the field; ISO IDMP.[222]

IDMP will most likely become the global structure standard for data processing in health regulatory affairs. The moment the controlled vocabularies for SPOR are implemented, it is expected that the standard will boost ways in which industry and agencies communicate via data elements on a global scale – in a way the industry has not experienced before. Existing data transfer mechanisms such as SPL and xEVPRM will most likely merge into IDMP. At best, the existing proven (more narrative text) standards, such as eCTD, will be further developed until then, to integrate tightly with IDMP as well.

[220] European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/ectd/Business%20View%20on%20eCTD%20v4%20rev.pptx
[221] IDMP1; [Online]; [Cited: 4. April 2019]; https://www.idmp1.com/download/8713/
[222] IDMP1; [Online]; [Cited: 4. April 2019]; https://www.idmp1.com/download/8713/

Lastly, further developed digital health regulatory affairs data standards must be integrated long-term with other data standards used in the healthcare sector, such as FHIR and CDISC in real time – when e.g. making more and more use of health data created in consumer wearables, to ensure data transmission between all industry stakeholders throughout the lifecycle of a medicinal product is efficient. Hence, the digital health regulatory affairs data standards must also possess the ability to adapt to a more complex regulatory context such as product development, supply chain, and safety monitoring.

In any case, any data processing initiative, which misses to understand and look at what is actually already there – in terms of proven and promising standards; and failing to integrate existing proven standards as well as align with most promising initiatives globally, will not only create further complexities and inefficiencies, but most likely will be doomed to fail – wasting scarce healthcare resources in a quest to improve global health.

LIST OF ABBREVIATIONS

ACTD	ASEAN Common Technical Dossier
ADHD	Attention-Deficit/Hyperactivity Disorder
ADR Database	Adverse Reaction Database
AE	Adverse Event
AF	Application Form
AI	Artificial Intelligence
ASMF	Active Substance Master File
BAH	Bundesverband der Arzneimittel-Hersteller e.V. German Medicines Manufacture's Association
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte / Federal Institute for Drugs and Medical Devices
CD	Compact Disc
CDA	Clinical Document Architecture
CDISC	Clinical Data Interchange Standards Consortium
CEDIT	Comité d'Evaluation et de Diffusion des Innovations Technologiques Committee for Evaluation and Dissemination of Innovative Technologies
CESP	Common European Submission Portal
CMC	Chemistry, Manufacturing and Controls
CSF	Case Report File
CSR	Clincal Safety Report
CTA	Clinical Trial Application
CTAD	Clinical Trial Application Dossier
CTD	Common Technical Document
DMF	Drug Master File
DSUR	Development Safety Update Report

DTD	Document Type Definitions
DVD	Digital Video Disc
EAHP	European Association of Hospital Pharmacists
EAHP	European Association of Hospital Pharmacists
EC	European Commission
eCTA	Electronic Clinical Trial Application
eCTD	Electronic Common Technical Document (v.3.2.2)
EDMF	European Drug Master File
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Records
EKG	Electrocardiogram (also ECG)
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
ePI	Electronic Product Information
eTMF	Electronic Trial Master File
EU	European Union
EVCTM	EudraVigilance Clinical Trial Module
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
GBT	WHO Global Benchmarking Tool
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GDP	Gross Domestic Product

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
HL7	Health Level 7
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
IB	Investigator Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IoT	Internet of Things
IRB	Institutional Review Board
ISO	International Organisation for Standardisation
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder - typically a pharmaceutical company
MedDra	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
NeeS	Non-eCTD electronic Submission
OECD	Organisation for Economic Co-operation and Development
PAES	Post-Authorisation Efficacy Study
PAM	Post-Authorisation Measure
PASS	Post-Authorisation Safety Study

PDCO	Paediatric Committee
PC	Personal Computer
PDF	Portable Document Format
PEI	Paul-Ehrlich-Institute
PI	Product Information
PIP	Paediatric Investigational Plan
PL	Patient Information Leaflet
PMF	Plasma Master File
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QMS	Quality Management System
RMP	Risk Management Plan
RPS / eCTD 4.0	Regulated Product Submission
SDTM	Study Data Tabulation Model
SEND	Standard for the Exchange of Non-Clinical Data
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOP	Standard Operating Procedure
SPC	Supplementary Protection Certificate
SPL	Structured Product Labelling
SPOR	Substances, Products, Organisations, Referential Master Data
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
US	United States
USD	United States Dollar

USR	Urgent Safety Restriction
WHO	World Health Organisation
xEVMPD	Extended EudraVigilance Medicinal Product Database
xEVPRM	Extended EudraVigilance Product Report Message
XML	Extensible Markup Language

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REFERENCES

BOOKS

E. Topol; The Creative Destruction of Medicine - How the Digital Revolution Will Create Better Health Care; 2012.

K. U. Heitmann; Standard für elektronische Dokumente im Gesundheitswesen – die Clinical Document Architecture Release 2.; 2005.

K. U. Heitmann; The Clinical Document Architecture (CDA); 2003.

M. Putzeist; Marketing authorization of new medicines in the EU: towards evidence-based improvement, Thesis Utrecht University; 2013.

N. Eckstein; Arzneimittel - Entwicklung und Zulassung: Für Studium und Praxis; 2018.

P. H. Diamandis, S. Kotler; Abundance: The Future Is Better Than You Think; 2012.

P. Janmano/U. Chaichanawirote/C. Kongkaew.; Analysis of medication consultation networks and reporting medication errors: a mixed methods study; BMC Health; 2018.

R. Becker; Dem Arzneistoff eine Chance – die Arzneiform; In: D. Fischer, J, Breitenbach (Hrsg.); Die Pharmaindustrie; 2010.

R. H. Dolin,et. al.; The HL7 Clinical Document Architecture; 2001.

T. Jung; Menschen, Prozesse, Material – die Produktion; In: D. Fischer, Jörg Breitenbach (Hrsg.); Die Pharmaindustrie; 2010.

W. Youyou/M. Kosinski/D. Stillwell; Computers judge personalities better than humans; Proceedings of the National Academy of Sciences; 2015.

Y. N. Harari; 21 Lessons for the 21st Century; 2018.

Y. N. Harari; Homo deus: a brief history of tomorrow; 2016.

ORAL PRESENTATIONS / OWN TRANSCRIPTS

Deloitte; [Own Transcript]; Global Pharmaceutical Regulatory Affairs Summit, Berlin, Germany; 2018.

G. Neuwirther; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

J. Archer; A. Nixon; U. Vollmer; Practical Experience & Proposal for eCTD Implementation Regulatory Information and & Technology Expert Group; [Oral Presentation]; EFPIA; 2017.

J. Heun; [Own Transcript]; Master of Drug Regulatory Affairs, Bonn, Germany; 2018.

J. Jobanputra; [Own Transcript]; MIT Conference Business of Blockchain, Boston, USA; 2017.

M. Wegner; [Own Transcript]; Master of Drug Regulatory Affairs, Bonn, Germany; 2018.

N. Brun; [Own Transcript]; DIA Europe Conference, Basel, Switzerland; 2018.

P. Middag; [Own Transcript]; Global Pharmaceutical Regulatory Affairs Summit, Berlin, Germany; 2018.

R. Schwarzer; HTA in German-speaking countries. Switzerland + Austria; [Oral Presentation]; 12th Annual Meeting of DNEbM; EbM & Individualized Medicine; Berlin, Germany; 2011.

T. Salmonson; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

T. Senderovitz; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

World Health Organisation; [Own Transcript]; TOPRA Annual Symposium, Stockholm, Sweden; 2018.

X. Qin; [Own Transcript]; DIA Europe Conference, Basel, Switzerland; 2018.

ONLINE

(EC) No 1234/2008; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf

08/ENTR/CT/09 Revision 4; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/application-form2009_en.pdf

A. Regalado; Technology Review; [Online]; [Cited: 3 April 2019]; https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/.

A. Singh/S. Singh; The Connection Between Academia and Industry; [Online]; [Cited: 4. April 2019]; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3369181/.

Apple Inc.; [Online]; [Cited: 4. April 2019]; https://developer.apple.com/documentation/healthkit/samples/accessing_health_records

Apple Inc.; [Online]; [Cited: 4. April 2019]; https://www.apple.com/healthcare/health-records/

Apple Inc.; [Online]; [Cited: 4. April 2019]; https://www.apple.com/researchkit/

B. Cobert; Drug Safety Update Reports (DSURs) [Online]; [Cited: 4. April 2019]; https://www.c3isolutions.com/blog/drug-safety-update-reports-dsurs/

B. Ginnow; Bundesverband der Pharmazeutischen Industrie e.V.; [Online]; [Cited: 4. April 2019]; https://mediaclipping.bpi.de/landingpage.jsp?params=EEOOO5Y7JvS8Xb5AwcNSJ0i6EOO8V2XhfH0z2rfGBNfoWgxCrnABrhizgVqkJ1QIfqsuWyNyeiaUyhteSY1SvkF4D9uEq7KIXu%2BN1RjJoLI%3D%20628

B. Lehman; The Pharmaceutical Industry and the Patent System. International Intellectual Property Institute [Online] [Cited: 3 April 2019] https://users.wfu.edu/mcfallta/DIR0/pharma_patents.pdf.

Biopharma Excellence GmbH; [Online]; [Cited: 4. April 2019]; http://www.biopharma-excellence.com/news/2018/3/2/from-impd-to-ind-same-but-different

Boehringer Ingelheim, Glaxo-Smith Kline, Image Solutions Inc, Lundbeck Inc, Merck, Pfizer, sanofi-aventis, Takeda, and ePharmaCMC; [Online]; [Cited: 4. April 2019]; http://www.triphasepharmasolutions.com/Resources/Industry%20Book%20of%20Knowlege%20Quality%20Overall%20Summary%20(QOS)%20in%20eCTD%20format.pdf.

Federal Institute for Drugs and Medical Devices; [Online]; [Cited: 4. April 2019]; https://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/news/ElectronicSubmission.html

C. Brodersen, et. al.; Blockchain: Securing a New Health Interoperability Experience; [Online]; [Cited: 4. April 2019]; https://pdfs.semanticscholar.org/8b24/dc9cffeca8cc276d3102f8ae17467c7343b0.pdf

CB Insights; [Online]; [Cited: 4. April 2019]; https://s3.amazonaws.com/cbi-research-portal-uploads/2018/05/10163951/healthcare-quarterly-deals-dollars_05-2018-1024x768.png

CHMP/QWP/227/02 Rev 3/Corr; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-active-substance-master-file-procedure-revision-3_en.pdf

Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards

Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards/data-exchange/dataset-xml

Clinical Data Interchange Standards Consortium; [Online]; [Cited: 4. April 2019]; https://www.cdisc.org/standards/real-world-data

CMDh/097/2000/Rev5; [Online]; [Cited: 4. April 2019]; http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/USR/CMDh_097_2000_Rev5_2017_02-clean.pdf

CPMP/BWP/4663/03; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/guideline-requirements-plasma-master-file-pmf-certification_en.pdf

CPMP/ICH/3945/03; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

D. Roland; Pfizer Adds to Big Pharma's Gene-Therapy Deal Streak; [Online]; [Cited: 4. April 2019]; https://www.wsj.com/articles/pfizer-adds-to-big-pharmas-gene-therapy-deal-streak-11553081391.

Datapharm Communications Limited; [Online]; [Cited: 4. April 2019]; https://www.medicines.org.uk/emc/product/1159/pil

DIRECTIVE 2001/20/EC; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

DIRECTIVE 2005/28/EC; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf.

DIRECTIVE 2011/62/EU; [Online]; [Cited: 4. April 2019]; https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF

Document 31992R1768; EUR-Lex; [Online]; [Cited: 3 April 2019]; https://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX:31992R1768.

E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide – Data Elements and Message Specification; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm275638.pdf

E2BM Data Elements for Transmission Of Individual Case Safety Reports; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073092.pdf

EMA/119871/2012 Rev 1*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-iii-pharmacovigilance-inspections_en.pdf

EMA/159776/2013; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/electronic-submission-article-572-data-questions-answers_en.pdf

EMA/42176/2014 Rev. 1, Corr.*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/functional-specifications-european-union-eu-portal-eu-database-be-audited_en.pdf

EMA/52449/2015 v9.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/psur/docs/PSUR%20Repository%20user%20guide%20for%20MAH%20submissions.pdf

EMA/732656/2015; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/introduction-iso-identification-medicinal-products-spor-programme_en.pdf

EMA/816573/2011 Rev 2*; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

EMA/90915/2016 Version 1.2; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en.pdf

EMA/CHMP/ICH/135/1995; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/ich-e-6-r1-guideline-good-clinical-practice-step-5_en.pdf.

EMA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf

EMA/INS/GCP/636736/2012; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-good-clinical-practice-compliance-relation-trial-master-files-paper/electronic-management-audit-inspection-clinical-trials_en.pdf

EMEA/180079/2005; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-application-so-called-sunset-clause-centrally-authorised-medicinal-products_en.pdf

EMEA/512725/2009 V1.0; [Online]; [Cited 4. April 2019]; http://esubmission.ema.europa.eu/doc/eCTD%20Plasma%20Master%20File%20Guidance%20-%20FINAL.pdf.

EMEA/CHMP/ICH/309348/2008; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/ich-e-2-f-development-safety-update-report-step-3_en.pdf

EMEA/CVMP/134/02 Rev 1; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/scientific-guideline/guideline-active-substance-master-file-procedure-revision-1_en.pdf.

EU Module 1 eCTD Specification Version 3.0.2; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eumodule1/docs/EU%20M1%20eCTD%20Spec%20v3.0.2-corr-HHMG-20170502.pdf

EudraCT; Clinical trial application menu; [Online]; [Cited: 4. April 2019]; https://eudract.ema.europa.eu/help/Default.htm#eudract/cta_menu_ov.htm

EudraVigilance Components & Functionality Introduction; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/presentation/presentation-eudravigilance-components-functionality-introduction-training-module-phv-m2_en.pdf

European Commission; Volume 2B Notice to Applicants Medicinal products for human use; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf.

European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/central_repository.HTML

European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eaf/

European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/ectd/Business%20View%20on%20eCTD%20v4%20rev.pptx

European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/esubmission.html

European Medicines Agency; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html

Stanford Medicine; [Online]; [Cited: 4. April 2019]; https://news.stanford.edu/thedish/2017/07/04/center-for-digital-health-awards-first-seed-grants-1000-apple-watches-to-five-teams/

C. Farr; CNBC; [Online]; [Cited: 4. April 2019]; https://www.cnbc.com/2018/10/14/apple-is-donating-1000-watches-for-a-new-study-to-track-binge-eating.html

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit.

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/glossary/eudravigilance

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-templates

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/data-submission-authorised-medicines-article-57

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/notifying-change-marketing-status

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plan-rmp-questions-answers

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-procedural-qa/transfer-marketing-authorisation-questions-answers

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/renewal-annual-re-assessment-marketing-authorisation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/renewal-annual-re-assessment-marketing-authorisation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-designation/questions-answers-orphan-designation-application

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/news/eu-us-mutual-recognition-inspections-medicines-manufacturers-enters-operational-phase

Novartis; [Online]; [Cited: 4. April 2019]; https://www.novartis.com/news/media-releases/novartis-launches-focalview-app-providing-opportunity-patients-participate-ophthalmology-clinical-trials-from-home

European Medicines Agency; [Online]; [Cited: 4. April 2019];https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-designation/questions-answers-orphan-designation-application

European Medicines Agency; Annual Report 2017; [Online]; [Cited: 3 April 2019]. https://www.ema.europa.eu/en/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf

European Medicines Agency; Annual Report 2017; [Online]; [Cited: 3 April 2019]. https://www.ema.europa.eu/en/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf.

European Medicines Agency; Electronic Active Substance Master Files (eASMF) [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/eASMF/index.htm.

European Medicines Agency; PSUR Repository; [Online]; [Cited: 4. April 2019]; https://psur-repo.ema.europa.eu/psur-ui/prepare/submission.html

European Medicines Agency; SPOR data management services; [Online]; [Cited: 4. April 2019]; https://spor.ema.europa.eu/sporwi/

World Health Organisation; Global Benchmarking Tool; [Online]; [Cited: 3 April 2019]; https://www.who.int/medicines/regulation/benchmarking_tool/en/.

Good Clinical Practice Network; [Online]; [Cited: 4. April 2019]; https://dev.ichgcp.net/75-appendix-2/.

Good Clinical Practice Network; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf

Good Clinical Practice; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf.

H.V. Perlmutter; D. Heenan; Cooperate to Compete Globally; [Online]; [Cited: 4. April 2019]; https://hbr.org/1986/03/cooperate-to-compete-globally

European Medicines Agency; Harmonised Technical Guidance for eCTD Submissions in the EU Version 3.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf.

European Medicines Agency; Harmonised Technical Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU V.4.0; [Online]; [Cited: 4. April 2019]; http://esubmission.ema.europa.eu/tiges/docs/NeeS%20eGuidance%20Document%20v4%200_final%20for%20publication%20Nov%202013.pdf

Heads of Medicines Agencies; Common European Submission Portal; [Online]; [Cited: 4. April 2019]; https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f

Health and ancestry service; 23andMe, Inc.; [Online]; [Cited: 3 April 2019] https://www.23andme.com/dna-health-ancestry/.

Health Canada; [Online]; [Cited 4. April 2019]; https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-ectd-pilot-clinical-trial-regulatory-activities.html

Health Level 7; [Online]; [Cited: 4. April 2019]; http://hl7.de/themen/hl7-cda-clinical-document-architecture/

Health Level 7; [Online]; [Cited: 4. April 2019]; https://www.hl7.org/fhir/ehr-fm.html

Health Products Regulatory Authority; [Online]; [Cited: 4. April 2019]; https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0001-guide-to-clinical-trial-applications-v12.pdf?sfvrsn=50.

I. Rager; MAA pre-submission issues and EMA meeting opportunities; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/documents/presentation/presentation-marketing-authorisation-application-pre-submission-issues-european-medicines-agency_en.pdf

IBM; [Online]; [Cited: 4. April 2019]; https://www.ibm.com/watson/health/business-need/healthcare-research/ https://www.ibm.com/products/watson-drug-discovery

ICH; M4 : The Common Technical Document; [Online]; [Cited: 4. April 2019]; https://www.ich.org/products/ctd.html

ICH; Structure And Content Of Clinical Study Reports E3; [Online]; [Cited: 4. April 2019]; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

IDMP1; [Online]; [Cited: 4. April 2019]; https://www.idmp1.com/download/8713/

IDMP1; [Online]; [Cited: 4. April 2019]; https://www.idmp1.com/wiki/spl/

INFORMATION 2010/C 82/01; [Online]; [Cited: 4. April 2019]; https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF.

INFORMATION 2011/C 172/01; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf.

J.A. Di Masi/H.G. Grabowski, R.W. Hansen; Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs, Journal of Health Economics; [Online]; [Cited: 4 April 2019]; https://www.ncbi.nlm.nih.gov/pubmed/26928437.

J.L Valverde.; E. Pisani; The Globalisation of the Pharmaceutical Industry, 2016; [Online]; [Cited: 3 April 2019] https://www.ifpma.org/wp-content/uploads/2016/11/The-Globalisation-of-the-Pharmaceutical-Industry-Monograph.pdf.

Johns Hopkins; Study Suggests Medical Errors Now Third Leading Cause of Death in the U.S.; [Online]; [Cited: 4. April 2019]; https://www.hopkinsmedicine.org/news/media/releases/study_suggests_medical_errors_now_third_leading_cause_of_death_in_the_us

K. Breithaupt-Grögler; Neue Regelung Neue Regelung des SUSAR des SUSAR-Reporting Reporting in der GCP in der GCPVerordnung; [Online]; [Cited: 4. April 2019]; https://www.agah.eu/uploads/tx_news/Breithaupt-Groegler_Kerstin_Neue_Regelung_des_SUSAR-Reporting.pdf.

K. D. Barnard, et al.; Journal of Diabetes Science and Technology; [Online]; [Cited: 3 April 2019]; https://www.eversensediabetes.com/wp-content/uploads/2018/07/Acceptability-of-Implantable-Continuous-Glucose-Monitoring-Sensor-1.pdf.

K. L. Lueth; State of the IoT 2018: Number of IoT devices now at 7B – Market accelerating; IoT Analytics; [Online]; [Cited: 4. April 2019]; https://iot-analytics.com/state-of-the-iot-update-q1-q2-2018-number-of-iot-devices-now-7b/

L. Garrison, Ph.D; An Introduction to Health Technology Assessment in the U.S. and Canada; [Online]; [Cited: 4. April 2019]; http://globalmedicines.org/wordpress/wp-content/uploads/2014/01/Garrison-HTA-US-CAN-July-5-2011-FINAL-7-5.pdf?1478792404

L. Garrison, Ph.D; An Introduction to Health Technology Assessment in the U.S. and Canada; [Online]; [Cited: 4. April 2019]; http://globalmedicines.org/wordpress/wp-content/uploads/2014/01/Garrison-HTA-US-CAN-July-5-2011-FINAL-7-5.pdf?1478792404

M. Curtin; Are You on Your Phone Too Much? The Average Person Spends This Many Hours on it Every Day; Inc.; [Online]; [Cited: 4. April 2019]; https://www.inc.com/melanie-curtin/are-you-on-your-phone-too-much-average-person-spends-this-many-hours-on-it-every-day.html

M. Roser/H. Ritchie; Our World in Data. [Online] [Cited: 3 April 2019] https://ourworldindata.org/burden-of-disease.

Medical Dictionary for Regulatory Activities; [Online]; [Cited: 4. April 2019]; https://www.meddra.org/how-to-use/support-documentation/english

N. Morris; Ledger Insights; [Online]; [Cited: 4. April 2019]; https://www.ledgerinsights.com/sap-pharma-supply-chain/

O. Fasanya; Draft presentation: Summary of product Characteristics; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/presentation/presentation-summary-product-characteristics_en.pdf

OASIS; [Online]; [Cited: 4. April 2019]; https://www.oasis-open.org/news/announcements/electronic-trial-master-file-etmf-specification-v1-0-published-by-the-etmf-tc

OCDE/GD(95)114; [Online]; [Cited: 4. April 2019]; https://mobil.bfr.bund.de/cm/349/oecd_principles_glp_09.pdf

P. Gandhi, et. al.; Harvard Business Review; [Online]; [Cited: 4. April 2019]; https://hbr.org/2016/04/a-chart-that-shows-which-industries-are-the-most-digital-and-why

Patient Information Leaflet: Information For the User Sertraline Hydrochloride 50 & 100 Mg Tablets; [Online]; [Cited: 4. April 2019]; https://www.medicines.org.uk/emc/files/pil.8517.pdf.

PDF 32000-1:2008; [Online]; [Cited: 4. April 2019]; https://www.adobe.com/content/dam/acom/en/devnet/pdf/pdfs/PDF32000_2008.pdf

Pharmaceutical Technology; Verdict Media Limited; [Online]; [Cited: 3 April 2019]; https://www.pharmaceutical-technology.com/projects/ucsf-robotic-pharmacy-san-francisco/.

ICH; Post-Approval Safety Data Management: Definitions and Standards For Expedited Reporting E2D; [Online]; [Cited: 4. April 2019]; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf.

ICH; Structure And Content Of Clinical Study Reports E3; [Online]; [Cited: 4. April 2019]; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

Heads of Medicines Agency; Questions and Answers to the Annual Safety Report Frequently asked questions regarding the Development Safety Update Report (DSUR) [Online]; [Cited: 4. April 2019]; http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2011_12_22_Q___A_DSUR.pdf.

R. Postigo, et. al.; EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection; [Online]; [Cited: 4. April 2019]; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5990579/

R. Y. Wee; Biggest Pharmaceutical Markets In The World By Country; [Online]; [Cited: 4. April 2019]; https://www.worldatlas.com/articles/countries-with-the-biggest-global-pharmaceutical-markets-in-the-world.html.

Regulation (EC) No 726/2004. European Parliament and of the Council; [Online]; [Cited: 3 April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf.

S. Biesdorf, F. Niedermann; McKinsey; [Online]; [Cited: 4. April 2019]; https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/healthcares-digital-future

S. Kemp; Digital in 2018: World’s Internet Users Pass The 4 Billion Mark; we are social; [Online]; [Cited: 4. April 2019]; https://wearesocial.com/blog/2018/01/global-digital-report-2018.

EMA/100194/2018; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/documents/other/eudravigilance-operational-plan-milestones-2018-2020_en.pdf

European Medicines Agency; [Online]; [Cited: 4. April 2019]; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/submission-dates/procedural-timetables

Section 8 of ICH GCP and Section 3 of the Volume 10 TMF Guidance; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf

SecurPharm; [Online]; [Cited: 4. April 2019]; https://www.securpharm.de/

Senseonics Announces FDA Approval to Expand Eversense® CGM Certification to Nurse Practitioners and Physician Assistants; Press Release; BusinessWire; [Online]; [Cited: 3 April 2019]; https://www.businesswire.com/news/home/20181106006086/en.

Statista; Revenue of the worldwide pharmaceutical market from 2001 to 2017 (in billion U.S. dollars); [Online]; [Cited: 4. April 2019]; https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001/.

The ASEAN Secretariat Jakarta; ASEAN COMMON TECHNICAL DOSSIER; [Online]; [Cited 4. April 2019]; https://asean.org/storage/2017/03/68.-December-2016-ACTD.pdf

The Flu Trends Team; Google LLC; [Online]; [Cited: 3 April 2019]; https://ai.googleblog.com/2015/08/the-next-chapter-for-flu-trends.html.

The Lancet. Elsevier Inc. [Online] [Cited: 3 April 2019] https://www.sciencedaily.com/releases/2015/06/150608081753.htm.

The Medical Futurist; [Online]; [Cited: 4. April 2019]; https://medicalfuturist.com/china-digital-health

U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/forindustry/datastandards/stabilitydatastandard/default.htm

U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630942.htm

U.S. Food and Drug Administration; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/Safety/MedWatch/ucm168422.htm

U.S. Food and Drug Administration; Drug Master Files: Guidelines; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm

U.S. Food and Drug Administration; Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations [Online]; [Cited: 3 April 2019];

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM631786.pdf

U.S. Food and Drug Administration; Implementing The 21st Century Cures Act: A 2018 Update From FDA And NIH; [Online]; [Cited: 4. April 2019]; https://www.fda.gov/NewsEvents/Testimony/ucm614607.htm

VOLUME 2A Procedures for Marketing Authorization Chapter 1 Marketing Authorisation; [Online]; [Cited: 4. April 2019]; https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf

The Organization for Professionals in Regulatory Affairs (TOPRA); What is regulatory affairs?; [Online]; [Cited: 3 April 2019]; https://www.topra.org/TOPRA_Member/Careers/What_is_regulatory_affairs_/TOPRA/TOPRA_Member/What_is_regulatory_affairs.aspx?hkey=83f01672-bc7f-41ed-b6fe-672acf7791cd.

World Health Organisation; [Online]; [Cited: 4. April 2019]; https://www.who.int/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified

World Health Organisation; Current health expenditure as a percentage of gross domestic product (GDP); [Online]; [Cited: 4. April 2019]; https://www.who.int/gho/health_financing/health_expenditure/en/.

World Health Organisation; VigiBase; [Online]; [Cited: 4. April 2019]; https://www.who-umc.org/vigibase/vigibase/

STATUTORY DECLARATION

I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

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