Personalised medicine and drug development

Valorisation

Although personalised medicine has not yet fulfilled its expectations, the advances in biology and genetics will lead to an increasing number of personalised medicines in the future. The analysis performed in chapters 2 and 3 will help with adapting the current environment in order to facilitate the implementation of personalised treatments. It is important to identify the aspects that need to be adapted and the areas of healthcare that need to change for its implementation. The literacy aspect discussed in chapter 2, 3 and 8, and the proposal to adapt the current curricula is paramount for the future and represent an immediate need. Universities should already be considering this. The newly created academic office at the EMA can help with this aspect and influence universities to change their curricula.

The research performed under the Coordination & Support Action (CSA) PerMed has already been implemented into a Strategic Research and Innovation Agenda (SRIA) that has guided the creation of the International Consortium for Personalised Medicine (IC PerMed) and its action plan recently published under the title "Actionable research and support activities identified by the International Consortium for Personalised Medicine" (March 2017). IC PerMed had it's first workshop with experts and funders in June 2017 in Milan. The SWOT and gap and needs analysis presented in chapters 2 and 3 are helping national funding agencies to identify the most urgent areas of research for the implementation of personalized medicine and guide their research funding activities.

It is clear from today's perspective, that the question formulated in chapter 4 and the main conclusions drawn were and are really relevant: since 2015, when the article was published, all stakeholders have gained interest in conditional approvals. This is evident from the adaptive pathways pilot, the IMI project Adapt-Smart and the agendas from the STAMP[23] meetings, between others. The EMA 10 year report on conditional marketing authorisations even states "*High interest in the conditional marketing authorisations and its relevance in the context of timely access to medicines have also led to it being discussed in various fora, including the European Commission Expert Group (…) ("STAMP"), and being referred to in conclusions of the Council of the European Union on strengthening the balance in the pharmaceutical systems in the EU and its Member States[5]"* (EMA, January 2017). What is left now is to encourage the right use of these promising tools that aim for timely patient access to promising medicines; and to enter discussions with "down-stream" stakeholders to seek their acceptance of conditional approvals. Furthermore, the tool box for evidence generation needs to be developed, including the use of RWD so that it fits to the requirements and expectations of all stakeholders and decision makers, as discussed in chapter 8. Chapters 2 and 3 claim new regulatory tools are needed, however, after evaluating the available

[23] European Commission Expert Group on Safe and Timely Access to Medicines for Patients

tools in Chapter 4, we reject this conclusion and claim that the tools are already available, they just have to be used correctly.

Stakeholders are also becoming interested in Managed Entry Agreements (MEAs). The future application of this P&R tool is very promising; however, there are some technical aspects that need to be improved in order to facilitate and extend their use. Methods based on data analytics, Electronic Health Records (EHRs) and Artificial Intelligence (AI) need to be developed in order to reduce the resources needed to implement them both on the side of the payer and the developer. Once these methods are available, game theory, as discussed in chapter 7, could be used to model the different scenarios and find the most appropriate model that maximises the utilities of all stakeholders; having in mind not only the effect on price, profit and innovation, but considering the bigger picture of net impact on welfare of this and future generations (Sood, De Vries, Gutierrez, Lakdawalla, & Goldman, 2009). MEAs could help to apply adaptive pricing and adaptive value proposition that would fit perfectly with the adaptive licensing proposals such as conditional approvals.

Chapter 6 lays all the possibilities for the application of big data in health care and drug development. The advances in this area will bring huge improvements into the healthcare market, if applied correctly. Patients should become more empowered to gather their data and create patient-owned data collections in order to ensure that the ethical concerns in health-data sampling and storing are addressed correctly and to the benefit of the patient. As already done in Belgium and Italy, the government could engage in creating the infrastructure for these type of registries. Going further than they already do, this infrastructure could be given to the patient organizations in order to create patient-centred registries that are owned by the patients and can be sold to the developers who need it.

Following the conclusion of chapter 7, one of the big applications of this work is to apply game theory to all stages of the drug development process, where rationale decision-making is needed. Going over the needs of drug development, game theory could also be applied broadly in healthcare. Experts in game theory can use the presented framework to create models and games that help companies and decision makers to maximise their utilities and improve the whole healthcare sector.

It is clear to the author that this thesis is very descriptive and what is needed now is to find useful applications to the topics described. But sufficient ideas and proposals have been framed to start with small steps that lead in the future to global structural changes. Only like this, patients and citizens will be able to enjoy the full promises of personalised medicine and flexible regulatory tools.

Table 0-1. List of publications and citations (up to 24.07.2017). Grey shadowed articles are part of the PhD thesis.

Article	Citations
Leyens L, Reumann M, Malats N, Brand A. Use of big data for drug development and for public and personal health and care. Genet Epidemiol. 2017 Jan;41(1):51-60. doi: 10.1002/gepi.22012. Epub 2016 Nov 21. PubMed PMID: 27873357.	1
Vozikis A, Cooper DN, Mitropoulou C, Kambouris ME, Brand A, Dolzan V, Fortina P, Innocenti F, Lee MT, **Leyens L**, Macek M Jr, Al-Mulla F, Prainsack B, Squassina A, Taruscio D, van Schaik RH, Vayena E, Williams MS, Patrinos GP. Test Pricing and Reimbursement in Genomic Medicine: Towards a General Strategy. Public Health Genomics. 2016;19(6):352-363. doi: 10.1159/000449152. Epub 2016 Sep 28. PubMed PMID: 27676083.	4
Leyens L, Brand A. Early Patient Access to Medicines: Health Technology Assessment Bodies Need to Catch Up with New Marketing Authorization Methods. Public Health Genomics. 2016;19(3):187-91. doi: 10.1159/000446537. Epub 2016 Jun 1. PubMed PMID: 27238553; PubMed Central PMCID: PMC5296921.	4
Negrouk A, Horgan D, Gorini A, Cutica I, **Leyens L**, Schee genannt Halfmann S, Pravettoni G. Clinical Trials, Data Protection and Patient Empowerment in the Era of the New EU Regulations. Public Health Genomics. 2015;18(6):386-95. doi: 10.1159/000441561. Epub 2015 Nov 14. PubMed PMID: 26565798.	2
Syme R, Carleton B, **Leyens L,** Richer E. Integrating Personalized Medicine in the Canadian Environment: Efforts Facilitating Oncology Clinical Research. Public Health Genomics. 2015;18(6):372-80. doi: 10.1159/000441560. Epub 2015 Nov 14. PubMed PMID: 26565702.	1
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Leyens L, Horgan D, Lal JA, Steinhausen K, Satyamoorthy K, Brand A. Working towards personalization in medicine: Main obstacles to reaching this vision from today's perspective. Personalized Medicine. 2014; 11(7):641-649 · November 2014. DOI: 10.2217/PME.14.55	6
Zaitseva L, Cherepanov P, **Leyens L**, Wilson SJ, Rasaiyaah J, Fassati A. HIV-1 exploits importin 7 to maximize nuclear import of its DNA genome. Retrovirology. 2009 Feb 4;6:11. doi: 10.1186/1742-4690-6-11. PubMed PMID: 19193229; PubMed Central PMCID: PMC2660290.	52