COMMENTARY

ELSI Implications of Prioritizing Biological Therapies in Times of COVID-19

Louise C. Druedahl, Audrey Lebret, and Timo Minssen

In their recent paper, Bladt et al.[1] focus on the delicate question of whether the four principles of biomedical ethics identified by Tom L. Beauchamp and James F. Childress[2] are reflected in the process of prioritization of financial resources in the Danish heath care system. They focus on biological treatment and multiple sclerosis, conducting a study based on eight semi-structured interviews.

Since ethical challenges are often intertwined with legal and social implications, we would like to use this opportunity to add some perspectives from the legal and regulatory sciences that we regard as particularly relevant in the ongoing SARS-Cov-2 pandemic. There is no doubt that COVID-19 will have a substantial impact on access to biologics and biosimilar uptake, as well as on the related ethical, legal, and social dimensions of prioritization decisions. This holds especially true for Denmark and European markets, where governments are expected to cover most of the pharmaceutical needs of their citizens and where the crisis has been leading to an important reduction of available resources.[3] Thus, we would like to make four key comments relating to (1) broader ethico-legal dimensions of prioritizations in Europe, (2) human rights law and (3) regulatory aspects of access, diversification, vulnerability and systemic trust, and (4) additional challenges posed by COVID-19.

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Firstly, the issue of prioritization of scarce resources is not a new issue, but it becomes particularly critical in times of crisis. Several studies point towards different ways of rationing health resources.[4] For example, Persad, Wertheimer, and Emanuel published interesting work on the ethics and allocation of very scarce medical interventions, such as organs and vaccines, arguing that there are no "value-free medical criteria for allocation."[5] In this context, biomedical ethics principles offer relevant guidelines to discuss such prioritization. Bladt et al's. choice to use the four principles of biomedical ethics is justified by relying on a study that concluded Denmark was aligned with those principles.[6] It is true that the content of those principles have a universal scope, but Bladt et al. admit that their weights can differ. However, since their study focuses on Denmark, it could be interesting to place those principles in a European context by referring in particular to the "four ethical principles" common of European bioethics: autonomy, dignity, integrity and vulnerability.[7] Beyond terminology, there are certainly overlaps between those principles. Yet, the principle of dignity, constantly referenced in Europe, is much less present in the American ethico-legal debate. Besides, Bladt et al ignore the principle of solidarity, although quite important in the Danish context. In this regard, we welcome that the authors' empirical study allowed the persons interviewed to formulate other principles than those set out in their original framework. Indeed, it is important to note that one of the essential elements of the right to health according to international law is that it is both culturally appropriate and respectful of medical ethics.[8]

Second, Bladt et al. focus on principles of bioethics and moral obligations which is both understandable to limit the scope of the study and consistent with

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the authors' research question. However, they do not account for law, although studies on prioritization of health resources would benefit from engaging with state obligations under human rights law. Denmark is bound by several international and European legal instruments on bioethics, health, or more broadly, the protection of vulnerable people.[9] Denmark must respect, protect, and fulfill human rights in biomedicine, which makes it not only a relevant, but a mandatory source to assess its policies. While it will not solve all health dilemmas, the World Health Organization encourages a human rights-based approach to health. Human rights law requires states to ensure equitable access and non-discrimination in health care. Human rights treaties and courts also give states some discretion when it comes to manage scarce resources and establish criteria of allocation.[10] This also applies to limit compassionate use of experimental drugs, an issue that was at the center of the seminal Charlie Gard case. In that case, the UK authorities denied to the parents of a baby with severe brain damage a right to maintain life support and to access to experimental treatment available in the US. In conformity with its prior jurisprudence, the European Court of Human Rights found the application inadmissible and upheld the UK judicial decision.[11] The polarization of the debate surrounding those findings,[12] demonstrates the divergence of conceptions on access to experimental treatments and prioritization of resources.

Third, an additional part of prioritization of resources is to look into diversifying the available treatments and increasing access to affordable medicines to decrease the need for such prioritization. One such means was the introduction of biosimilars to often costly originator biologics.[13] While market challenges for these products still exist,[14] biosimilars need to be used to fulfill the aim of their regulatory introduction. The reluctance to use these products by treating physicians as described by Bladt et al. indicate that there is a regulatory issue at stake even in a country such as Denmark with high biosimilar uptake.[15] Physician skepticism towards these follow-on products have been reported extensively and is present among about two-thirds of physicians according to a recent review.[16] Thus, the high standard of biosimilars in the European Union seemingly remains untranslated into trust and certainty amongst physicians. A risk associated with physician skepticism is its influence on patients and their willingness to use these products. A study found that 21% of patients were more willing to switch to biosimilars if the information was positively framed[17] and concerns among patients relate to uncertainty of differences in safety or efficacy compared to the originator.[18] For increasing access to medicines via biosimilars, physicians must be able to counsel patients with their concerns as attempt to facilitate positive non-medical switches and limit negative patient expectations (also known as the nocebo effect).[19] This is especially important in countries such as Denmark with almost mandatory switches due to tender procurement and prescription guidelines.[20] However, overall, these considerations assume that the given patients can access biological medicines. In dire cases, and especially in a time of crisis such as COVID-19, some patients may be left more vulnerable and face increasing social consequences if medicines

Finally, and notwithstanding the past impressive successes of the Danish regulatory framework for biologics and biosimilars' uptake, we believe that the remaining lack of certainty in biosimilars might become an increasingly important issue that is aggravated by COVID-19. The push towards more use of follow-on products is likely to intensify as a means to drive cost reductions in strained health systems. This will also enhance public pressure on pharmaceutical pricing and fuel the related controversies over the current frameworks for intellectual property rights, trade secrets, pharmaceutical regulation and competition law. We therefore assume that COVID-19 will substantially influence the perceptions, approaches, and regulatory options with regard to physician-led switching and pharmacist-led substitution of biosimilars and originator biologics.

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are not introduced to a market due to their prices, a possibility raised by participants in the study by Bladt et al. To stabilize biosimilar uptake, more effective initiatives are needed to facilitate physician trust in these products — which will be communicated to patients — and such initiatives are tasks likely to end up on desks in governments and medicines authorities.

Finally, and notwithstanding the past impressive successes of the Danish regulatory framework for biologics and biosimilars' uptake,[21] we believe that the remaining lack of certainty in biosimilars might become an increasingly important issue that is aggravated by COVID-19. The push towards more use of follow-on products is likely to intensify as a means to drive cost reductions in strained health systems.[22] This will also enhance public pressure on pharmaceutical pricing and fuel the related controversies over the current frameworks for intellectual property rights, trade secrets, pharmaceutical regulation and competition law. We therefore assume that COVID-19 will substantially influence the perceptions, approaches, and regulatory options with regard to physician-led switching and pharmacist-led substitution of biosimilars and originator biologics.

Since there is much ado about something in the biosimilar space, we see a strong need for further interdisciplinary ethical, legal, and social research in this area.

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