



The promise and perils of biotech in personalized healthcare: Can new regulatory pathways protect the vulnerable?

Giovanni De Grandis, Irina Brass and Arthur Petersen discuss critical questions for regulatory innovation in personalized healthcare

The coming of age of personalized therapies

In the last decades the hottest areas of medical innovation have been the fields of targeted therapies and personalized medicine – medical treatments tailored to the specific molecular features of patients or diseases. Monoclonal antibodies are the prime example of successful targeted therapies, while genuinely personalized treatments have not been as forthcoming as expected. The greatest promise in this area comes from cellular and genetic therapies, which have the potential to be curative by stopping the causal chain leading to disease, or by regenerating cells or tissues that have genetic defects or have been damaged, or by enhancing bodily functions, like the immune system capacity to fight disease. This latter is the mechanism of action of CAR-T cells: the class of treatment that has recently been hailed as the coming of age for cellular therapies and advanced biological treatments in general. Until the summer of 2017, only a few advanced biological therapies had made it to the market, and none has been a commercial success or has had a significant impact in terms of patients treated. In Europe, for instance, by the end of 2017 more than 500 clinical trials had led to only 18 marketing applications and 9 authorized products, 4 of which were later withdrawn from market. All in all, 111 patients had been treated with those products. But when in 2017 the Food and Drug Administration (FDA) in the USA licensed the first two CAR-T cell therapies (Kymriah and Yescarta) – followed by the European Medicines Agency in 2018 – observers thought that this was a turning point and that treatments with a clear potential for commercial success and medical impact had finally hit the market. While initially approved for the treatment of some forms of leukaemia, it is expected that their therapeutic indications will expand and that new products will address an increasing range of tumours.

However, advanced therapies like CAR-T cells bring new challenges for the regulation and financing of healthcare products. For instance, while CAR-T cells can save the life of patients not responding to other therapies, they also have severe side effects, so that both the FDA and the European Medicines Agency (EMA) have required risk-management plans and enhanced post-marketing surveillance. More strikingly, these products have hefty prices: in the USA Kymriah and Yescarta cost \$475,000 and \$373,000 per patient respectively, which have triggered criticism and raised questions about rationing and financial sustainability.

The new regulatory landscape and its critics

Both CAR-T cells products have achieved market authorization on both sides of the Atlantic through some special regulatory pathways designed to assist companies with their development plans and to speed up the process of clinical evidence collection and regulatory review of the application. Both the FDA and the EMA have currently a portfolio of facilitated pathways which are the result of an important change in the role and mission of these regulatory agencies. Traditionally, the goal of pharmaceutical regulations has been to ensure the *safety, quality and effectiveness* of the products that are authorized for commercialization. But in the last decades, regulatory agencies have taken a broader mission, which next to their traditional function includes facilitating *faster and broader access* to innovative products for patients with serious medical needs, as well as the promotion of *medical innovation*.

This broadening of their mission has important consequences. While before the vulnerable group they were protecting was of patients receiving drugs, now they are also trying to help patients for which existing treatments are of no use or who may benefit from experimental drugs but may not wait until they achieve marketing authorization. Remarkably, the new mission of promoting early access and innovation forces rethinking of established regulatory practices. Ensuring safety, quality and effectiveness is time-consuming and imposes high costs on developers, and it delays market entry of innovative products and deters companies from developing products unless they have the potential for huge profits. Therefore, regulators have had to streamline the regulatory procedures and ease their requirements, in order to speed up the process and incentivize companies. The result is that the new regulatory focus on unmet medical needs creates trade-offs with the traditional values of safety, quality and effectiveness.

Unsurprisingly, the new facilitated pathways designed to promote faster access and innovation have been subjected to a number of criticisms. The robustness of the evidence that is accepted by facilitated pathways has been questioned: smaller and shorter trials, and sometimes reliance on only one phase 2 trial – as in the case of the 2 CAR-T cells therapies – is not considered sufficient to establish effectiveness and detect less common adverse events. Similarly, the use of surrogate endpoints instead of meaningful clinical endpoints has led to the approval of drugs that were later shown to be ineffective. The safety of the process has also raised concerns. First,

some studies have shown that strict review deadlines lead to decisions made under time pressure, which in turn are associated with higher incidences of post-marketing safety issues. Moreover, small trials on targeted populations provide limited information on the risks of wider use and thus make off-label use (notoriously difficult to discipline) rife with uncertainties and dangers. Another concern is the ability of these facilitated pathways to achieve their goals. Faster market authorization does not immediately translate into faster or wider patient access. Even advocates of facilitated pathways have acknowledged that achieving their goals needs a broader system approach that involves Health Technology Assessment bodies, payers, providers and clinicians. Finally, scepticism has been manifested about the capacity of regulatory agencies to make up for higher uncertainty at time of approval with enhanced collection of post-marketing data. Critics have pointed out that so far compliance with the performance of post-marketing studies and the implementation of lifecycle evaluation has been poor, and that things are unlikely to change as long as industry lacks incentives and healthcare systems lack resources for their fulfilment.

The new vulnerable

The new and extended mission of regulatory agencies in the medicinal domain is having significant impact on different vulnerable groups through reshuffling risks and benefits. Clearly, patients with serious unmet medical needs (i.e. not getting any really effective treatment for life-threatening or severe diseases) are given much more attention than before, and arguably future patients could also benefit from the emphasis on innovation. For the target population addressed by new therapies there is a lower risk to miss their therapeutic benefits, but increased uncertainty about side effects and durability of benefits. Future generations face a similar trade-off; they are likely to see more therapeutic options if facili-

tated pathways manage to promote innovation. However, not all innovation is valuable and unless ineffective products are removed from the market they will run the risk of missing the best therapies and mis-allocating their resources. Finally, new regulatory pathways redistribute risks between different patients' groups. This is where they generate new vulnerable groups. Given that healthcare budgets cannot be indefinitely expanded, providing hyper-expensive therapies comes with the risk that public healthcare systems and private insurers will have to introduce coverage cuts elsewhere. This means that some patients will be at risk of losing (full) coverage of effective treatments. Furthermore, if the innovative and hyper-expensive treatments are introduced on the basis of less evidence about their effectiveness, then the allocation process will become less consistent and fair: a given level of uncertainty would be acceptable for some products, but not for others. In light of these impacts on different vulnerable groups, it seems that the benefit and the justifiability of facilitated regulatory pathways is conditional on regulators building their capacity to acquire high quality post-marketing evidence and withdraw from the market products that fail to confirm their value.

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