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Editorial

IS THIS THE REAL LIFE? IS THIS JUST FANTASY?

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When the late Freddie Mercury penned these words (1), perhaps he had in mind bringing innovative medicines and devices to patients more quickly.

The development pathway for these technologies is long and costly. Stakeholders agree, in principle, that efforts are needed to reduce the time it takes for patients to be able to access innovative treatments with appropriate subsidy or coverage. Accelerated or adaptive pathways that cover the process from regulatory submission to subsidized access appear to offer possibilities to make this happen. But "is this the real life or is this just fantasy?"

Following completion of randomized controlled trials to assess efficacy and safety in expanding numbers of patients a dossier is compiled for review by regulators. If they are satisfied that the product meets appropriate standards, the result is marketing authorization. While the product can now be prescribed, in practice for many patients to obtain access it may require a coverage or reimbursement determination. In many countries, this requires further review by some form of health technology assessment (HTA) process. These combined processes can take up to 10 years for an individual medicine, depending on the nature of the regulatory, HTA, pricing and reimbursement processes in place.

Multiple stakeholders (patients, carers, clinicians, and manufacturers) have expressed frustration with the time involved in this process, prompting consideration of accelerated processes—especially when current treatments are inadequate and "unmet" clinical need is high. In the regulatory environment, this is not news. In the United States, for example, multiple pathways exist for accelerated regulatory processes when new technologies may offer substantial advantages over currently available treatments. (e.g., Breakthrough designation, Fast Track approval) (2). Earlier this year, the European Medicines Agency announced it is willing to discuss accelerated regulatory processes if manufacturers consider the product and clinical indication warranted this (3).

It is becoming clear from the U.S. experience that it is possible to accelerate regulatory review processes, as several new medicines have recently received market authorization under the Breakthrough Product program (and other programs), although the gains are often months rather than years. However, several experts in this area have begun viewing the whole development, review and approval process as more dynamic. For example, the MIT NEWDIGS initiative (4) is suggesting a more iterative and *adaptive* approach, where a new medicine may be approved for a subset of patients at the earliest opportunity based on the evidence available. Further ongoing and adaptive clinical trials then feed into iterative reviews and expansion of the product label, resulting in use in a wider patient population. In early versions of this proposal the focus had been largely on the regulatory process and associated expansion of the product label. As Eichler and co-workers put it in 2012 (5), there are multiple competing goals related to accelerated regulatory approval, faster patient access, and simultaneous, continuing development of evidence. They suggest adaptive pathways are the answer to reconciling these competing goals.

More recently, attention has focused on the lag between regulatory approval and reimbursement or coverage decisions. In fact, the delays in the HTA and reimbursement process are often greater than those in the regulatory process. One obstacle to a fast result from HTA processes (leading to timely reimbursement) is the extent to which the evidence presented to support the value proposition is deemed to be "uncertain". Experience suggests HTA agencies place a value on the robustness of the evidence. Various forums and mechanisms have discussed and experimented with "early advice", to improve the ability of the Phase III trial/s to provide the evidence of value that HTA agencies and payers now expect. This is important, because efforts to speed up the overall medicines development process potentially could run the risk that the evidence of value is insufficient, creating more uncertainty for HTA agencies and payers despite the collective desire to speed patient access.

In addition, many companies are now working to accelerate their research and development processes and multiple strategies have been identified. One risk continues to be that accelerated development and regulatory assessment processes might combine to deliver less than optimal evidence of value, thus preventing the HTA agency / payer from doing their part in enabling faster access for patients. Without careful consideration of the implications and strategies to deal with them, it is possible that the vision of fast appropriately subsidized access to innovative technologies could remain a fantasy for some time. For these reasons, the HTAi Policy Forum decided to focus this year on the broader topic of "Adaptive Approaches

to Technology Management" (see Husereau et al. in this issue).

Several potential scenarios exist for managing this uncertainty. The HTA literature and practice contain examples of "coverage with evidence development" and "managed entry schemes," where initial, limited reimbursement or coverage decisions are made in the presence of uncertainty regarding the evidence of value. These are actually often "salvage" strategies used after rejection of a technology by an HTA agency or payer. Under that scenario considerable delays can still occur before subsidized access occurs. What is potentially different about adaptive approaches to HTA is a proactive plan for assessment, pricing and reimbursement aligned with the evidence available at first regulatory approval and able to be expanded as the evidence of value grows. Potentially all parties could benefit from this approach.

Other challenges beyond uncertainty also need to be more fully considered and strategies developed to address them, if such a vision is to become a workable reality. Regulatory and HTA agencies have different mandates, evidence requirements, decision models and processes. A greater consensus on appropriate methods and approaches for generating the necessary evidence of value under these circumstances is needed, while preserving the separation of these mandates.

Sources of evidence may need to expand to include observational studies, adaptive trial designs, and patient registries. All have been used, but there is a lack of consensus on "best practice" in regard to optimal data collection, analysis and interpretation. More discussion is also needed on who pays for what in regard to further data collection. It should be acknowledged that further additions to the cost of technology development will also constrain industry's ability for flexible pricing. Operationalizing the relationship between evidence of value and reward is another challenge. Some HTA systems are directly connected to the negotiation of prices. In theory, it should be possible to make a product available to patients at the earliest opportunity, with a price appropriate to the evidence of value available. Price would continue to be reviewed at points when additional evidence is presented. Both price and patient population could be adjusted to ensure that the most appropriate patients receive the new technology. In some cases, this will be a narrower population. Of course, strategies need to be considered to deal with the possibility that the promised value is not substantiated by the further evidence. Options for this are available including limiting subsidized access to patients where most value is experienced. However, industry currently lacks confidence that such increased recognition of value will be rewarded; there are few if any examples of this applying to pharmaceuticals. Industry is, therefore, reluctant to start the early, proactive discussions needed to put such processes in place for a specific technology.

The Policy Forum discussion reported in this issue is a promising beginning to a very important dialogue. To succeed in bringing desired innovative technologies to patients who need these, stakeholders must continue to collaborate on finding ways forward. The NEWDIGS collaboration published modeling efforts exploring the impact on patient populations and revenues associated with various adaptive scenarios (6). This is to be applauded and encouraged. Above all, the various partners must build a climate of trust around these discussions, where each can be frank about risks as well as benefits and be prepared to take some risks in committing selected new technologies to such processes. While the benefit-risk balance must remain a focus, there is scope for genuine collaboration on selected technologies that could make the fantasy of faster, subsidized access by patients a reality.

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