

Adaptive licensing: creating a safe haven for discussions

The concept of adaptive licensing as a means of making innovative medicines available faster is generating much excitement, but some drug companies are worried about how this emerging approach might be implemented. *Lynn Baird* and *Gigi Hirsch* say their concerns can be overcome.

The perceived merits and weaknesses of an adaptive licensing approach for approving medicines are being widely discussed around the world.

Stakeholders are almost universally enthusiastic about exploring adaptive licensing (also known as staggered approval, progressive licensing, etc) as a means of making innovative medicines available to patients in need in a more timely manner^{1,2}. Nevertheless, some stakeholders have expressed concerns and skepticism about how the emerging approach might be implemented³⁻⁵.

The willingness of stakeholders to engage in creatively overcoming these concerns is a prerequisite for moving adaptive licensing forward. An announcement is pending by the European Medicines Agency about the creation of a "Safe Harbour"* environment for potential adaptive licensing pilots that will deliver just such an opportunity. The intention of the Safe Harbour is to enable sponsors to meet with the EMA and informally share ideas about the design of potential adaptive licensing pilot programs⁶.

However, some pharmaceutical companies have already expressed concerns over how this Safe Harbour environment might work and what the implications of it might be for them. Their concerns relate to such things as:

- (1) the ability/willingness of stakeholder groups to step out of their traditional roles;
- (2) the potential regulatory consequences of such a meeting if a decision (sponsor and/or regulator) is made to abandon the pursuit of an adaptive approach; and
- (3) uncertainty about the dynamics of the multi-stakeholder meeting.

The Massachusetts Institute of Technology's NEW Drug ParadigmS (NEWDIGS) initiative is a multi-stakeholder collaboration that is working to define what an adaptive development and licensing program might look like. The NEWDIGS experiences over the last several years in its multi-stakeholder "scenario design" sessions may help address some of the concerns that are being voiced.

NEWDIGS mission and goals

The NEWDIGS initiative, hosted by MIT's Center for Biomedical Innovation, involves representatives from regulatory agencies from around the world (the EMA, the US Food and Drug Administration, Health Canada, Singapore's Health Sciences Authority, and the UK Medicines and Healthcare products

Regulatory Agency), European and US payer and health technology assessment (HTA) organizations, pharmaceutical companies, patients, providers, and academic researchers. The initiative was started in 2010 with the goal of catalyzing the evolution of global regulation from the current binary "go/no go" model to a more adaptive approach involving a progressive reduction of uncertainty over the lifetime of the product.

A neutral, "safe haven" environment is critical for fostering new kinds of interactions and candid dialogue among stakeholders

Due to the highly complex and interconnected issues involved in medicines regulation, NEWDIGS took a systems approach to this challenge, as defined by the following elements:

- (1) key stakeholders would be engaged in the process in order to ensure the alignment of inter-dependent benefit-risk tradeoffs; and
- (2) processes, technologies, policies, and people would need to be co-ordinated in order to achieve the collaboration necessary to affect implementation.

The creation of a neutral, "safe haven" environment is critical for fostering new kinds of interactions and candid dialogue among the stakeholders. The MIT Center for Biomedical Innovation serves as a neutral intermediary when issues arise relating to competition and potential conflicts of interest. GlaxoSmithKline is one of the companies that has been actively involved in NEWDIGS. According to GSK senior vice president & acting head of rare diseases Tony Hoos: "NEWDIGS has an ambitious agenda and novel approach that we believe will help enable timely delivery of new medicines to the patients that need them."

Early in the initiative, NEWDIGS decided to use case-based (product-specific) adaptive design exercises (scenario design sessions) in order to explore the elements of adaptive licensing and to move it from a noble concept to a sustainable reality. A potential by-product of this approach is the identification of actual compounds that could become potential candidates for real-world pilot projects, such as those contemplated by the EMA.

Evolution of NEWDIGS scenario design session methodology

The initial scenario design discussions were conceptual in nature with limited learnings since product details about which to design an adaptive development plan were lacking. To help address this issue, a "call for assets" was issued to the NEWDIGS pharma partners, with the idea of focusing the adaptive licensing design discussions around a medicine currently under development. Shortly thereafter the first asset was presented in a scenario design session. The company's development team for the asset was charged with presenting their traditional development plans for the asset in a multi-stakeholder, pre-competitive forum along with a proposal for an "adaptive approach" for the same product. Then, as a collaborative group activity, the adaptive licensing plan was critiqued and refined taking into account the needs of each stakeholder group.

Early discussions focused primarily around regulator and pharma perspectives. Over time, the perspectives of various payers and HTA officials have been incorporated, though this has been challenging due to the many significant differences in their approaches across regulatory jurisdictions. Participation of providers and patients has been tailored to the specific asset being discussed.

In order to allay the sponsor's concerns about exposing themselves and their product to this unique development environment in an extremely competitive industry, guiding principles and procedures were established for the conduct of each session. All workshop attendees not covered by governmental confidentiality were required to sign an asset-specific confidential disclosure agreement. Attendees from a pharmaceutical company having a directly competing product could be asked to "sit out" a session at the discretion of the asset owner. (This option has been used on occasion but has tended to occur less frequently as trust among stakeholders increased and the value of the multi-stakeholder discussions was recognized over time.)

The following guiding principles steered each session:

- (1) the thoughts and perspectives that workshop participants expressed were their own; participants represent a knowledgeable stakeholder group and not their employer organization;

- (2) no binding decisions were to be made during the session. It was a time to learn and explore; and
- (3) specific comments and learnings from the sessions could be shared. However, specific comments could only be attributed to a stakeholder group and not to any specific individual or affiliated organization, in keeping with the Chatham House Rule on providing anonymity to speakers.

There was no expectation or assumption at initial sessions that an asset would progress to an adaptive licensing pilot. Assets were accepted for presentation after the sponsors submitted a brief questionnaire or "asset nomination form" that was reviewed by NEWDIGS staff. Assets were accepted solely for the purpose of focusing the discussions and advancing an understanding of adaptive licensing. Presentations were generally 45-60 minutes in length, followed by a facilitated discussion of approximately the same amount of time. Stakeholder feedback was oral, although it was also captured informally in the workshop summary.

Over time, the processes used for asset selection have evolved and become more structured and selective. More recently, the asset nomination form was refined and expanded to include information about whether other accelerated access pathways might be available for this particular asset, and thereby making an adaptive licensing approach unnecessary. With that change, all completed forms were reviewed by the core regulator group in order to assure that selected assets were likely appropriate for an adaptive approach. Following the workshop, written consensus regulatory feedback was provided to the sponsor within two weeks of the workshop.

At the beginning of 2013, the asset nomination form was again refined to include information relevant to payers. Similar to the pre-review by the regulators, a pre-review of completed forms by a core payer group has now been included to assure that the asset is a viable candidate for adaptive licensing from their perspective. Following the workshop, written consensus feedback from the payers has also been provided to sponsors. In order to accommodate the expanded focus of the scenario design sessions, the length of the combined presentation and facilitated discussion for each asset has been increased to three-and-a-half hours.

Deliverables and accomplishments

The value and/or success of the NEWDIGS work on adaptive licensing can be measured through the learnings from these sessions that have/are being communicated to the broader global community in the form of publications⁷⁻¹⁰, invitations to speak at industry conferences as

well as from the metrics of the scenario design sessions (see below).

Since 2011, 13 assets from nine therapeutic areas have been submitted by sponsors for discussion at scenario design sessions. These assets were submitted by nine biopharma companies. Two companies each have submitted three assets, one of which was GSK.

Development teams have universally expressed that the discussion and feedback they received were extremely useful and the experience had pushed their thinking in invaluable ways. According to Dr Hoos: "All stakeholders were focused on helping the team define the optimal development approach. This created a sense of shared goals and collaboration I haven't seen elsewhere."

The sponsor feedback was independent of whether a decision was made to pursue an adaptive approach. Six assets were discussed at two or more scenario design sessions. One asset was not presented since during the pre-screening process it was not considered an acceptable candidate for adaptive licensing. Six of the 12 assets were determined not to be viable adaptive licensing candidates due to prior regulatory advice, suitability of an existing accelerated access pathway, and/or absence of a suitable surrogate marker. An adaptive approach was not pursued for four candidates due to business decisions. The remaining two assets are considered potential candidates for adaptive licensing pilots, although both are quite early in development. It is hoped that one or both of these assets will find its way to the EMA when the agency issues its call to sponsors to take part in an adaptive licensing pilot; the call is expected to be issued soon.

Conclusions

The NEWDIGS systems approach to adaptive licensing has been instrumental in catalyzing the global discussion about adaptive licensing, both positive and negative, as determined by the increased frequency of the topic in academic and other industry-associated publications and its recognition in senior level policy documents¹¹. Much of the collective understanding of the elements of adaptive licensing has been the result of the outputs from NEWDIGS scenario design sessions. A similar exercise, ie developing adaptive licensing case studies, was undertaken earlier this year by a working group at the EMA¹². On the basis of its work, the EMA is now poised to initiate multi-stakeholder consultations with sponsors to see if this idea can be moved forward to the next step, ie the initiation of real-world adaptive licensing pilots.

The NEWDIGS work on adaptive licensing suggests that regulatory change cannot be driven by regulators alone. The complexities and uncertainties of translational science will

increasingly require a safe environment, such as the one developed by NEWDIGS, for exploring and aligning benefit-risk tradeoffs among stakeholders¹³. Looking forward, the collaboration environment and structured methodology used by NEWDIGS provides a prototype that can be adapted to address other challenges. In addition, NEWDIGS is uniquely positioned to play an influential role in the education of the next generation of healthcare leaders, being at the intersection of academia, government, and industry.

**"Safe Harbour" is a legal term defined in the US as "Provision in an agreement, law, or regulation that affords protection from liability or penalty under specified circumstances or if certain conditions are met" and is distinct from the safe haven environment provided during the NEWDIGS workshops.*

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