Avoiding the Fast Track Disconnect

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SHORTENING TIME TO MARKET FOR IMPORTANT NEW THERAPIES

Few people will disagree that striving to make effective new drugs in high unmet need indications reach the patient as soon as possible is a worthy aim. Many countries allow "early access" to drugs before approval, but administrative burden and additional costs that go with the strict follow-up of named patients constitute a serious hurdle for broad access. Therefore there was broad support when the U.S. Food and Drug Administration (FDA) introduced procedures such as "fast track," "accelerated approval," "breakthrough therapy," and "priority review." The European Medicines Agency (EMA), on the other side of the ocean, initiated "accelerated assessment" and "conditional approval" *(see Table 1).* Some of these procedures skim only a few months from the assessment time, however, all stakeholders are more interested by the gains that can be made when products are approved substantially faster. Adopting an accelerated approval approach in oncology, for example, in which drugs were evaluated based on surrogate endpoints, resulted in launches about four years sooner to the market than they would have been with regular approval.[1]

BENEFITS OF FASTER APPROVAL

Of course, the first thoughts go to the patient in need who may have access to valuable treatment options before it is too late. However, the corollary is that yet unknown safety aspects or failure to confirm efficacy in later studies may expose the patient to a harmful risk/benefit ratio. An illustrative example includes a leukemia drug that achieved fast approval by both the FDA and EMA, but within a year it was taken off the U.S. market and faced strong restrictions by the EMA. Moreover, there is more and more criticism about companies not fulfilling the obligations for further research in a timely fashion as this may be interpreted as a significant risk to public health.[2]

The benefit to the patient increases with time gained, but for many patients waiting a few months longer for a new therapy may not be that important. For the innovator company however, a few months may be important with regard to competitors and may prolong patent protected life. Additional months added to the end of the patent life may mean substantial additional sales. A company may also benefit from an authority-endorsed recognition of product value, which should support obtaining faster market access, possibly better prices with payers, and faster adoption by physicians.

However, companies also face substantial risks:

- The investment of upscaling of production and the marketing effort to create awareness for the new drug, the two most expensive activities after development cost, may not be recouped if issues are discovered and the treatment does not receive full approval.
- The upscaling of production can be more expensive as a company may need to ask third-party producers to fill the gap, e.g., many oncology companies had to involve a now closed third-party laboratory for their early sourcing of new products; a biopharmaceutical company had a significant challenge in sourcing the first fusion inhibitor for HIV.[3]
- The inability of the innovator to source the new product adequately may lead to treatment issues with patients and damage the company's image well beyond the launch period.
- The obligations that the innovator company will have to fulfil, e.g., Risk Evaluation and Mitigation Strategy (REMS) requirements and post-marketing surveillance (PMS), drive faster awareness and create real-world data, however, they also create substantial cost.
- Serious side effects that show during the sales of any drug, equal for fast tracked or standard drugs, always increase risks for legal consequences.

WHAT DOES FAST TRACK MEANS FOR MARKET ACCESS?

Products that achieve fast track in one way or another should all deliver therapeutic value in high unmet need indications. Hence, one would expect that the fast track designation will only exert some time pressure on the market access, pricing, and HEOR functions. Market access may already have produced a target value dossier and target value proposition at the end

CONCEPTS TO MAKE IMPORTANT DRUGS AVAILABLE AS SOON AS POSSIBLE TO THE PATIENT		
Concept	*Most important characteristic*	*Eligible products*
EMA		
Accelerated assessment	Review time is reduced from standard 210 days to 150 days	Expected to be of major public health interest from the point of view of therapeutic innovation
Conditional approval	Marketing authorization (MA) can be granted even while comprehensive clinical data have not been provided; to be renewed annually and with obligations (additional studies)	Products for seriously debilitating or life-threatening diseases or emergency threats; orphan drugs
Approval under exceptional circumstances	MA granted even while applicant will be unable to provide comprehensive clinical data; to be renewed every 5 years	Same as for conditional approval; lack of data acceptable because of: • Rarity of the disease • Present state of scientific knowledge • Ethical constraints
FDA		
Fast track	Rolling Review: company can submit completed sections of its Biological License Application (BLA) or New Drug Application (NDA) for review by FDA one by one	Drugs treating serious conditions and filling an unmet medical need
Breakthrough therapy	Fast track plus intensive guidance and organizational commitment	Drugs for treating a serious condition; preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)
Accelerated approval	Allows FDA to approve drugs based upon surrogate endpoints, without the need to wait for proof of full clinical benefit. Implies confirmatory trials after launch.	Drugs for serious conditions that fill an unmet medical need and have a positive effect on a surrogate or an intermediate clinical endpoint reasonably likely to predict clinical benefit
Priority review	Drug review time 6 months instead of the standard 10 months	Drugs showing significant improvements in safety or effectiveness, diagnosis, or prevention of serious conditions

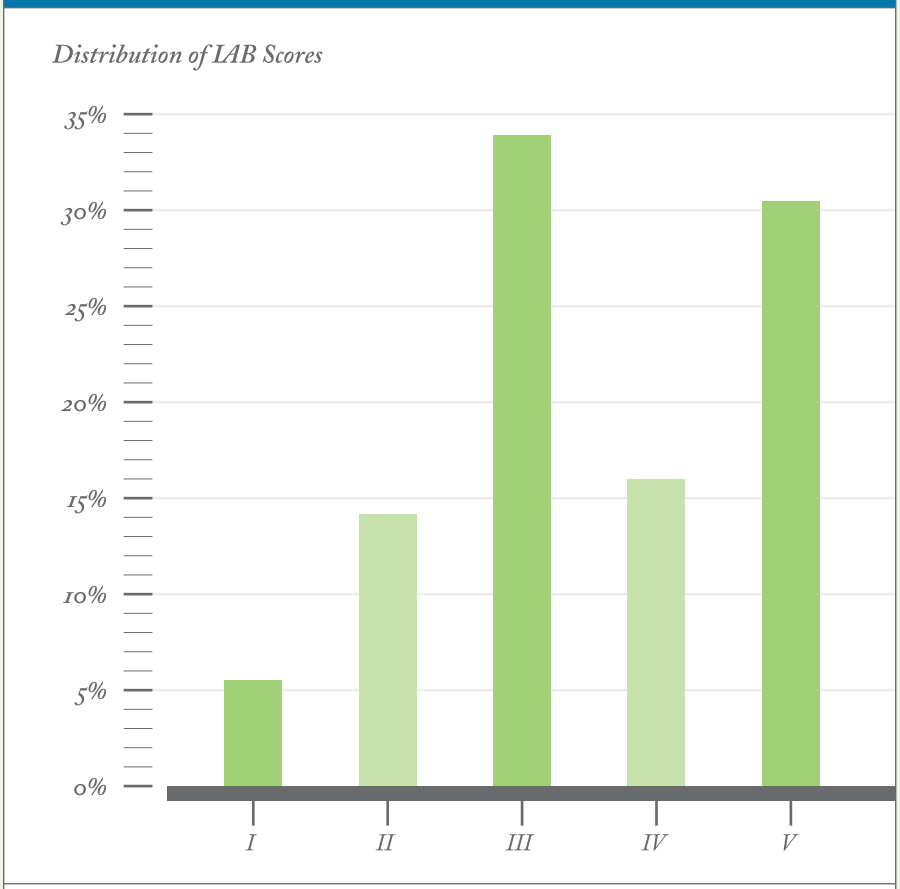
table 1

of Phase IIb, but global value dossier content, comparative effectiveness data, cost-effectiveness (CE) models, budget impact models, and the launch value proposition would normally be carefully developed and underpinned with the necessary data during the later phases of development. Hence, the faster approval will in essence create a void in this data package at the time the company will be discussing launch price and reimbursement. Would this not be compensated by the clear sign of product value given by the fast track designation?

To better understand how HTA bodies were assessing these fast tracked products at launch, we selected and studied the assessment process of 35 products that had accelerated approval, conditional approval, or any other sign of expedited approval process with the EMA. Typically these products were approved on Phase II data, or only one Phase III study, or while Phase III studies were still ongoing. Some of these products were simply lacking full clinical benefit data.

The French Transparency Commission (TC) has the most flexible attitude versus these "fast tracked" products *(see Figure 1)*. About half of the assessed products had an Improvement of Actual Benefit (IAB, ASMR) score of I-III, acknowledgement of their perceived therapeutic value. [Note the scale used for IAB scores for improvement of actual benefit: I (major); II (important); III (moderate); IV (minor); V (no improvement).] However, 11 products were deemed offering no therapeutic value versus existing standard of care. Lack of comparative data and perceived small effect size are mentioned frequently as main

DISTRIBUTION OF 36 TC SCORES FOR "FAST TRACK" PRODUCTS AT FIRST PASS



Note: The scale used for IAB scores for improvement of actual benefit: I (major); II (important); III (moderate); IV (minor); V (no improvement)

figure 1

reasons for the negative decisions, clearly showing the TC did not always follow EMA thinking.

The Scottish Medicines Consortium (SMC) is able to make evaluation decisions in the shortest timeframe. However, this advantage also means that companies have less time to prepare their dossier, which can result in sub-optimal submissions. Nine products were not recommended because the company did not submit a dossier to SMC. At first appraisal SMC accepted only seven products of the selection for use by NHS Scotland, and four of these were allowed for a smaller patient segment than specified in the label ("restricted"). Half of the products were not recommended for use, although four of these achieved this shortly thereafter by agreeing with a patient access scheme. The most important reason for not recommending a new product was related to cost effectiveness of the product (e.g., "the economic case was not demonstrated").

NICE assessed less than half of the products in the selection and did not recommend half of these. Four other products were recommended only after the companies agreed to lower cost through a patient access scheme.

Because many products were launched before AMNOG (Act on the Reform of the Market for Medical Products), the German HTA body IQWiG (Institute for Quality and Efficiency in Healthcare) reviewed only 12 of the products from the selection. Five assessments resulted in the negative outcome "benefit not quantifiable/benefit not established." Four products received "significant benefit"; and three received the appraisal "small incremental benefit."

In conclusion, payers seem very critical of the products that have had an expedited approval process by EMA. They seem leery of offering positive recommendations when in their view there is insufficient proof of the value of the product. Payers fail to follow suit for many products where regulatory authorities feel it is important for these to reach the patients quickly.

SOME EXAMPLES OF THE HTA—EMA DISCONNECT

A quick review of just six examples illustrates a clear disconnect between HTA and EMA evaluations. An orphan drug for the treatment of chronic lymphocytic leukemia received conditional approval from the EMA on January 6th, 2010. In June 2010, NICE was "unable to recommend cancer drug in draft guidance owing to lack of robust data." The TC concluded in October 2010 an IAB score of V (no improvement) explaining "the effect size is difficult to assess because of the methodology used, an interim analysis of a subgroup of patients in a non-comparative study and historical comparison with the results of a retrospective study." SMC did not recommend use in August 2010 because the manufacturer did not present a sufficiently robust economic analysis.

After Marketing Authorization (MA) in July 2011 for a multiple sclerosis (MS) treatment, the TC decided in April 2012 for IAB V because "the gain was minimal and was only observed in a sub-group of patients; the identification of these patients as "responder" after two weeks of treatment has yet to be validated. The changes observed in secondary endpoints were not clinically relevant." SMC did not recommend the product because of the lack of submission of a dossier. IQWiG concluded in July 2011 that an incremental benefit could not be established due to incomplete documentation.

A treatment for Pompe Disease received the score "important" (IAB II) in September 2006 from the TC. However, SMC decided not to recommend the product in March 2007.

At first pass, the TC assessed an antifungal agent as just offering another therapeutic option without proof of incremental benefit, whereas one year later with additional data, the conclusion was revised to moderate benefit. SMC, however, accepted to fund the product at first pass.

A few months after approval in 2007 of an orphan drug for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), the TC decided to award the IAB score "important actual benefit." SMC repeatedly decided not to recommend the product as there was no proof of cost-effectiveness, whereas NICE challenged how the company could explain the high cost of the product.

HTA bodies do not always come to the same conclusions for these "fast tracked" products. As a result patients may not have access to a new "fast tracked" product if they are living in the "wrong" country. Payers might avoid this inequity of access by accepting novel concepts for reimbursement, such as reimbursement with obligations for evidence development.

WHAT CAN A COMPANY DO TO AVOID THE FAST TRACK DISCONNECT?

It is clear that with most payers a company cannot rely on a priority treatment for a fast tracked product. Hence the challenge will be to deliver the necessary substantiation of product value even while timelines are shorter and data are lacking.

If a product has a remote or clear chance for rapid approval, a company should prepare a back-up approach in case fast track would be achieved, including:

- Identifying minimum of resource use measurements and patient-reported outcomes (PRO) data in Phase II (if there is any chance of fast track on Phase II data)
- Develop target value dossier and target value proposition during Phase II
- Be ready for quick price finding
- Develop some simple CE and budget impact models
- Prepare for a fast, market access strategy development process
  - Plan the activities in case of fast track
  - Pre-define suppliers and partners, and set up a fast procurement process
- Ensure you have people and resources available for the work (may be external)

Once the fast track decision is made, good preparation will enable the company to implement an efficient market access process. Moreover, at approval there are other strategies to mitigate the evidence gap:

- Mitigation of lack of comparative data with indirect comparisons
- Utilization of REMS and PMS opportunities for real-world data

When companies request pricing and reimbursement for their fast tracked product, they should be aware of the dilemma payers are facing, including the uncertainty of product value and certainty of budget shortage, when making their determinations. Payers would like to approve these products as soon as they feel they will deliver value for money. Hence, offering options up front that handle uncertainty—such as patient access schemes, conditional reimbursement, conditional pricing—may help overcome the disconnect.

Finally, in a time where most companies are struggling to show any positive differentiation for their new products, they should be happy if the product is fast tracked. It definitely beats having a me-too.

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