Adaptive Licensing - Maximising Value

Applying adaptive licensing strategies can significantly increase the value of R&D projects. Although regulatory frameworks do not include adaptive pathways yet, some strategies already work within the existing regulations and regulators encourage pilot schemes. Thus, a new opportunity to optimise R&D portfolio value has arisen.

Since 2005 there have been several initiatives, mostly from regulators and academia, proposing adaptive approaches to drug licensing where the main goal is to enable earlier access to novel drugs for patients[1-13]. Although concrete ideas for adaptive regulatory pathways differ, they fundamentally harbour one of two elements; initial approval in a patient sub-setting or approval based on preliminary data. The key to both approaches is to establish a positive benefit-risk balance as early as possible in restricted settings, followed by an extension to an unrestricted license which is supported by more comprehensive data.

However, as regulatory implementation and pilot projects are lacking, uncertainty regarding regulatory and commercial viability is high. Therefore we have analysed what strategies are feasible within the current regulatory frameworks in the EU and the US and what commercial advantages they may bring. For the latter, we have applied a value-at-risk methodology which has been tailored to compare the commercial value and risk of different approval strategies.

Not Yet Implemented Into Regulatory Frameworks

Apart from existing accelerated approval pathways, which were developed to expedite market access for drugs addressing patient populations with a high unmet need, adaptive licensing pathways have not yet been integrated into regulatory frameworks. As the progressivity in adaptiveness ranges from simple sub-indication approaches to highly progressive approaches like initial approval on the basis of registry data, it becomes clear that there are currently different levels of regulatory feasibility. This range of strategies can be grouped into three categories: first, there are those which are already feasible within the current regulatory frameworks; second, those highly progressive strategies which require an amendment of current legislations; and finally, there are also 'in-between cases' where progressive strategies can be negotiated with regulators, given that proposals for adaptive licensing mostly come from regulators themselves and pilots are now officially encouraged by authorities in both the EU and US [8,16].

In our regulatory analysis, we have assessed the comprehensive list of adaptive licensing strategies provided in a 2012 article by Eichler *et al.*[10] in terms of current or future regulatory feasibility in the EU and the US. Highly progressive strategies have been categorised as 'not yet feasible', considering the current reservations of the European Commission and the US Government[8,17]. However, this does not mean that the relevant legislations are unlikely to change; it would seem reasonable to run pilots with less progressive approaches first and then subsequently to carefully evaluate the legal implications of more progressive approaches. Importantly, overall feasibility will depend on harmonisation of relevant regulations across major commercial regions, since regional variation of regulatory and clinical development requirements is often a no-go criterion for industry due to cost and/or complexity issues, leading to limited commercial value. This aspect should also be carefully considered when developing new adaptive licensing regulations – harmonisation across regions will be a key success criterion.

Two Strategies Feasible Today

The results of our analysis can be found in Table 1. The key result is the identification of two adaptive licensing strategies which are likely to be feasible in both regions today: the surrogate endpoint and the enriched subpopulation approaches. Although one might argue that both approaches are not entirely new, certain aspects of these strategies appear in a new light when applying the adaptiveness perspective. Surrogate endpoints have often been regarded with scepticism – in adaptive licensing they enable earlier patient access based on a sound initial benefit-risk assessment, supplemented by mandatory 'real-endpoint' evidence at a later point. Subpopulation approaches

Table 1: Regulatory feasibility assessment of adaptive licensing strategies

Adaptive Strategy	Feasibility EMA	Feasibility FDA
Initial license based on surrogate endpoint	Not a new concept, considered feasible for surrogate endpoints with sufficient validity. Many accepted endpoints can be considered surrogate endpoints (e.g. occurrence of HPV-related lesions within 5 years after preventive HPV vaccination vs. long-term efficacy as a real endpoint). Covered by guidance for accelerated approval for high unmet need populations (EMA CMA, FDA AA).	
Initial license in enriched subpopulation	Subpopulation approval is generally feasible, advanced enrichment approaches are probably subject to negotiation with regulators	Draft guidance exists (14), i.e. FDA is generally willing to accept enriched trials
Initial licenses based on lower statistical hurdle	Not yet feasible. There are examples of drugs for rare conditions where this approach makes sense, but guidance/legislation that specify the lower hurdle does not exist	
Novel-novel combinations	Not yet feasible	Feasible, guidance exists (15)
Initial license based on non-randomized or non-controlled trials	Possible for accelerated approval for high unmet need populations (EMA CMA, FDA AA). However, unlikely to be feasible for "normal" adaptive licensing, since the level of evidence is significantly sub-standard	
Initial license based on (small) RCT, followed by full license supported by real-world data	Not yet feasible. Regulatory consideration of additional real-world data is problematic due to comparability questions; the feasibility of substitution of RCT evidence by real-world data is questionable	
Delinking of efficacy and safety populations	Not yet feasible. Lowering current PhIII safety standards and further shifting safety data generation into the post-approval phase appears legally questionable	
AA: Accelerated Approval, CMA: Conditional Marketing Authorisation		

Table 2: Input parameters for the obesity drug example case

Parameter	Standard licensing	Adaptive licensing
Discount rate	10%	Same
Loss of exclusivity	10 years market period	Same Loss of Exclusivity date as standard licensing (i.e. determined by patent, not data protection)
Probability of success	55% PhIII, 95% Reg	65% PhIII subpopulation, 95% adaptive licensing registration, 55% PhIII subpopulation + PhIII full population, 2 failure scenarios in adaptive licensing phase: safety failure after 2y and efficacy failure at end of PhIII full population, at efficacy failure drug stays on the market, but reaches only 30% of peak sales
Study costs & duration	€60m PhIII (3y)	€25mn PhIII subpopulation (1y), €60mn PhIII full population (3y)
Registry costs		€3mn
Registration costs	€2mn	€2mn first license, €1mn after PhIII full population
Launch costs	1y peak marketing spend, €50mn for failure after filing	1y peak marketing spend – 30% of which after adaptive licensing registration and 70% after PhIII full population, €11mn for failure after adaptive licensing filing or €25mn after PhIII full population efficacy failure
Marketing costs	22% of sales	Same
CoGS	10%, €30mn before launch (also incurring in case of license refusal)	10%, €20mn before launch (also incurring in case of license refusal), €20mn in case of PhIII full population efficacy failure (production for full launch preparation)
Peak Sales	€500mn	Same, 30% interim peak in adaptive license phase and 100% peak in full license phase

followed by a later extension of indication are not new either – what is new is the idea of (potentially multi-factorial) enrichment to initially focus on patient subsets where a drug can show a highly favourable benefit-risk balance. The FDA has recently published a draft guideline on this topic[14].

Tailored Valuation Methodology

In order to compare the commercial viability of adaptive licensing strategies versus the non-adaptive pathway, we have applied a simple decision tree and discounted cash flow model, which is the standard method for commercial assessment of pharmaceutical development projects. To better display the differences between the two strategies in terms of both scenario values and risk profile, we have used cumulative value-at-risk graphs, which display the different scenario value/risk combinations sorted by value in ascending order. These graphs show each strategy's unique value-at-risk profile. Increases/decreases of failure costs, scenario probabilities and success scenario values can be easily recognised by differences between the non-adaptive and adaptive graphs, allowing for a visual comparison between the two options, which facilitates decision making.

De-risking and Higher Revenues

In order to assess the commercial viability of the two currently feasible strategies, we created example cases for both. For the surrogate endpoint approach, we have chosen a disease-modifying osteoarthritis drug, where the short-term effect on cartilage structure can serve as a surrogate endpoint (the real endpoint being long-term structural and symptomatic efficacy). For the enriched subpopulation approach, we chose an obesity drug, where initial development in a high unmet need population with a very high body mass index could be an option. In these cases, adaptive licensing increased the eNPV by 37% (surrogate endpoint, increase from €278mn to €382mn) and 23% (subpopulation, increase from €426mn to €523mn) respectively. This benefit is driven by both de-risking (by lowering the lost investment for development failure scenarios) and increased revenues for the successful/market scenario. It is important to note that adaptive licensing did not have any negative effects on the value-at-risk profile in our example cases. Figure 1 displays the value-at-risk profiles for the subpopulation case; the input parameters for the underlying commercial model can be found in Table 2.

For these two strategies, a positive effect on the commercial viability could be expected. One reason is that the adaptive approach allows for an earlier launch, which brings additional, earlier sales. In addition, the initial surrogate endpoint or subpopulation study is less expensive than the later full-blown study, while being a good indicator for success of the full-blown development. This has a de-risking effect on the programme. However, this does not mean that adaptive licensing should now be blindly applied wherever possible; commercial viability will still need to be assessed in detail for every individual case. The methodology we have applied provides a valuable tool for this purpose. A good example for a factor that can easily "break the case" is data protection. If data protection is the mechanism guaranteeing market exclusivity, the clock already starts to run during the initial approval period for the adaptive licensing case. Considering this, extending data protection by one to three years for adaptive licensing cases would be a "quick fix" by authorities for incentivising adaptive licensing.

Another important factor which can significantly impact the value of adaptive scenarios is reimbursement. For the enriched subpopulation example, we did not assume any reimbursement issues, since clear efficacy evidence in the subpopulation, which is required for approval, entails effectiveness. For the surrogate endpoint example, we assumed a 40% risk sharing scheme (i.e. 40% payback of revenues to payers if real endpoint study fails) to reflect the uncertainty regarding efficacy, and thereby effectiveness, during the initial surrogate endpoint license phase. Reimbursement conditions for cases with uncertainty regarding effectiveness may, however, vary widely, also between different countries and payers, and are a risk factor of adaptive licensing strategies.

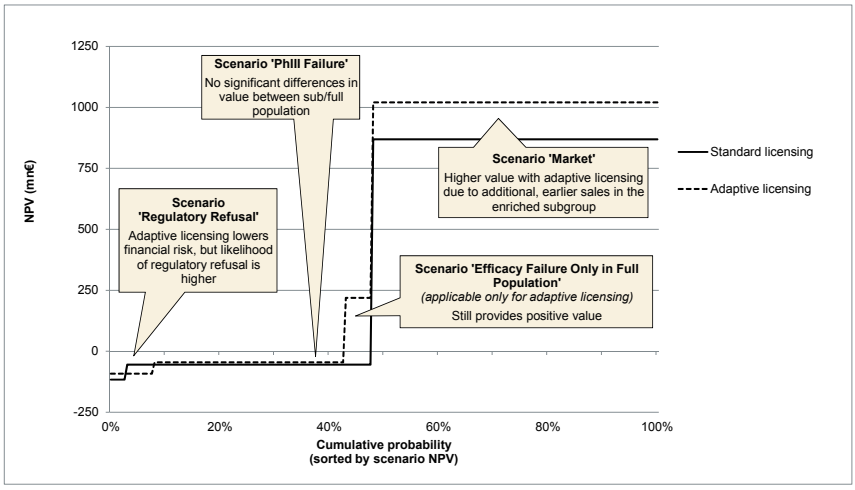

Figure 1: Value-at-risk profile comparison for the obesity drug example case

Time to Act

In conclusion, adaptive licensing is not a theoretical exercise, but an attractive opportunity that can be applied to medicines currently in the pipeline. The commercial advantage of adaptive licensing strategies can be significant, and can easily be assessed with standard toolsets. However, from a regulatory standpoint, adaptive strategies are currently limited to the two 'semi-progressive' surrogate endpoint and enriched subgroup approaches. As specific regulatory guidance is not in place yet, close cooperation with regulators is a must. This should not be a hurdle, since both EU and US government bodies are interested in pilot projects[8,16]. Thus, pharmaceutical companies should start to act now and assess what adaptive licensing opportunities are applicable to their projects and how they can increase the value of their portfolio.

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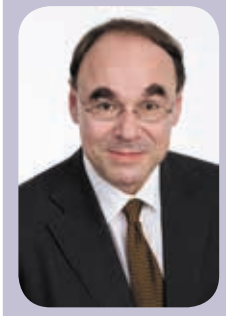

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