Legal Foundations of Adaptive Licensing
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In April 2012, MIT's Center for Biomedical Innovation and the European Medicines Agency (EMA) cosponsored a workshop on legal foundations of adaptive pharmaceuticals licensing. Past and present attorneys from the US Food and Drug Administration (FDA), the EMA, and Health Sciences Agency Singapore (HSA) found that existing statutes provided authority for adaptive licensing (AL). By contrast, an attorney from Health Canada identified gaps in authority. Reimbursement during initial phases of adaptive approaches to licensing was deemed consistent with existing statutes in all jurisdictions.

Background on adaptive licensing

In March 2012, Eichler *et al.* published "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" in this journal.[1] The article contrasted traditional binary approaches to drug licensing with adaptive approaches that emphasize stepwise learning under conditions of acknowledged uncertainty. It summarized recent comprehensive proposals for AL, discussed how proposals might be shaped to fit different therapeutic areas, and identified unresolved issues associated with design and implementation of AL. The article spurred debate over whether existing statutes and regulations provided authority for AL, with reference to elements of early and late stages.

Initial authorization. Traditional accelerated approval–conditional marketing authorizations (CMAs) provide early access to a limited number of drugs. AL would provide earlier access to more drugs in an initial authorization stage with novel measures to manage risks. Access to a drug would be limited to a restricted population, defined on the basis of knowledge about benefits and risks at the time of initial approval. Off-label use would be limited. Drugs would be labeled as initially authorized, and patients and physicians would be informed on knowns and unknowns about the drug. Reimbursement would be provided with rates as yet to be determined.

Evidence generation and learning. At present, the treatment experience of most nontrial patients does not contribute significantly to evidence generation. AL would make fuller use of all sources of information to update regulatory and treatment decisions. Evidence generation, particularly in later stages of the drug life cycle, would not be limited to conventional randomized controlled trials but would encompass a broader methodology spectrum, including pragmatic clinical trials, clustered randomized controlled trials, observational studies based on electronic medical records, registries, and other forms of active and passive surveillance.

Workshop findings

The workshop was organized to assess whether existing statutes in the European Union, United States, Canada, and Singapore provide adequate authority for AL. Conclusions included the following.

United States. Authority currently exists in statutes and regulations for all elements of AL, but regulators are not obligated to pursue AL approaches. Private and public payers may reimburse for drugs during initial authorization.

European Union. Authority can be identified with enactment of pharmacovigilance legislation in July 2012,

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and regulators have room to pursue AL approaches. Reimbursement for drugs remains a national rather than a European responsibility.

Canada. Regulators are seeking legislation to provide clearer authority for accelerated market entry and risk management, and for comprehensive AL. Health Canada and payers are studying the potential benefits of the proposed AL model, especially the use of on-market evidence.

Singapore. Authority currently exists for regulators to conduct all elements of AL. Patients and providers are free to use and to pay for drugs during periods of initial authorization.

National summaries

United States. Peter Barton Hutt, currently of Covington and Burling LLP and former chief counsel for the FDA, noted that there are two schools of thought regarding FDA authority. One school argues that under a restrictive reading of the Federal Food, Drug, and Cosmetic (FD&C) Act,[2] the FDA has limited discretion to adopt adaptive approaches to licensing. Hutt suggested that this view is too narrow and argued that the following four sections of the FD&C Act, taken together, provide the FDA with clear legal authority to engage in AL, a view shared with one of the reviewers of the manuscript of this article.

Section 506(b) authorizes the FDA to expedite the development, review, and approval of a "fast-track" drug that is intended for the treatment of a serious or life-threatening condition and that demonstrates the potential to address an unmet medical need. The terms "serious" and "unmet medical need" can both be broadly interpreted in the context of a subset of patients for whom a drug may have special benefit.

Sections 505(p) and 505-1 authorize the FDA to require the development and implementation of a risk-evaluation and -mitigation strategy (REMS) as a condition for approval of some new drugs so as to ensure that benefits outweigh risks. AL approaches can therefore include risk-mitigation strategies relevant to the drug being developed. Risk-mitigation strategies can be more restrictive at initial authorization and relaxed as more safety and effectiveness information becomes available.

Sections 505(o)(3) and 506(b)(2)(A) authorize the FDA to require postmarket studies and clinical trials as a condition of licensing. Thus, the FDA has the authority to require whatever testing is necessary to confirm the safety and effectiveness of the new drug during initial authorization and before the marketing of the drug is expanded.

Sections 505(b)(1)(F), 505(d), 505(o)(4), 505-1(e)(2) and (3), and 506(b)(2)(B) authorize the FDA to require whatever labeling is necessary to implement licensing of a new drug. As more information becomes available, the agency may require changes in labeling, e.g., expanding or contracting uses of the product and providing additional information regarding its safety and effectiveness.

Leslie Norwalk, former acting administrator of the Centers for Medicare and Medicaid Services, suggested that under initial authorization, reimbursement could take place under Medicare Part A for hospital-administered prescription drugs, Part B for physician-administered prescription drugs, and Part D for self-administered prescription drugs. Medicaid can restrict initial access to the subset of patients with the most favorable benefit/risk profiles, whereas Medicare does not. Norwalk cautioned that, although legal authority to reimburse AL products exists, changing Medicare coverage would require political acceptance from providers and patients as well as the FDA.

European Union. Vincenzo Salvatore, currently professor of EU law at the University of Insubria, and former head of legal service for the EMA, observed that pharmacovigilance legislation (namely, EU Regulation 1235/2010 and corresponding EU Directive 2010/84/EU, ref. 3) provides grounds for authority for AL approaches. Before its enactment, CMA provided an early-access pathway, and risk-management plans provided a mechanism for limiting use in instances where clearly defined risks were identified. Salvatore noted that the EMA had interpreted the scope of appropriate application of these mechanisms narrowly. For example, modifications of CMAs were considered acceptable only if made in accordance with previously agreed development plans. Formal standards for eligibility for CMA, including the definition of exceptional circumstances, were not modified in the new legislation. Rather, the new pharmacovigilance legislation supports an adaptive licensing approach by expanding EMA authority to request postmarketing evaluation of efficacy in addition to safety.

The pharmacovigilance legislation set forth a new approach to postmarket monitoring with the explicit goal of improving management of uncertainty at the time of initial drug authorization. The legislation authorized tighter controls on prescriptions, more extensive reliance on patient registries, and improved monitoring of compliance by health-care providers, national professional organizations, and pharmaceutical sponsors. The legislation improved pharmacovigilance by requiring adherence to good pharmacovigilance practices guidelines, creation of a pharmacovigilance master file system, stronger risk-management plans, and performance of noninterventional post-authorization safety studies. The legislation also reinforced existing authority to impose restrictions on prescriptions should public health issues be detected. The directive, though not the regulation, expanded pharmacovigilance to encompass effectiveness as well as safety testing.

Stephen Hocking, head of the Public Health Law Department of DACBeachcroft, provided an assessment of payer issues in the context of the UK National Health Service and the National Center for Health and Clinical Excellence (NICE). NICE's role is to appraise benefits and costs to make recommendations to the UK National Health Service. NICE favors value-based analysis based on systematic data and could support reimbursement during the initial authorization phase of AL.

Canada. David Lee, director of the Office of Legislative and Regulatory Modernization of Health Canada, reviewed provisions for approval, postmarketing surveillance, and license withdrawal of Canada's Food and Drug Act. Health Canada's pioneering interest in AL approaches arose because of challenges to its ability to offer a pathway to conventional accelerated access. Initial attempts at providing early access to drugs on the basis of unmet medical needs proved confusing when provincial payers refused to provide reimbursement. Ongoing discussions and pilots have increased reimbursement potential. However, the courts further limited the authority and flexibility of regulators to require the collection of on-market evidence in a generic competition case. Health Canada has proposed a comprehensive package of adaptive reforms for "progressive authorization" of pharmaceuticals that included provisions for accelerated access.[4] In 2008, Parliament was dissolved before the bill was fully considered. Nevertheless, Health Canada is continuing to develop proposals that will accommodate the AL model.

Singapore. Ambrose Chia, senior legal counsel of the HSA, indicated that the organization is authorized to implement AL approaches in Singapore. The HSA has considerable discretion in setting evidentiary standards, monitoring use, and modifying license terms and conditions. Chia suggested that the HSA has the latitude to impose conditions "as long as they are fair and reasonable."

Conclusions

Conventional wisdom holds that the absence of legal authority poses a fundamental barrier to development of AL approaches. This generalization currently holds in Canada but does not hold in the United States, the European Union, or Singapore. Canada and Singapore represent polar opposites, with Health Canada tightly constrained by existing statutes whereas the HSA has significant freedom within limits of what is fair and reasonable. Authority to engage in AL exists in both the United States and the European Union, but the legal bases of authority differ. In the United States, existing statutes provide broader discretion than has been used in practice. The FDA has authority to move toward AL under existing provisions for fast-track and for REMS. In the European Union, new pharmacovigilance legislation authorizes and obligates the EMA to move toward AL approaches under a redefined standard approval pathway with the potential to expand pharmacovigilance to encompass effectiveness as well as safety testing.

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CONFLICT OF INTEREST

A.C., S.H., and D.L. are representing the positions of their employer organizations. P.B.H., L.N., and V.S. are writing in their current private capacities and not as representatives of the US Food and Drug Administration, the Centers for Medicare and Medicaid Services, and European Medicines Agency, respectively.

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