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Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

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Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals; discusses how proposals might be translated into practice, with illustrations in different therapeutic areas; and identifies unresolved issues to inform decisions on the design and implementation of AL.

INTRODUCTION

Public and political trust in the current drug development and approval process is frequently challenged by the controversy over timely access to new therapeutics, product withdrawals, and postapproval modifications to labels. Partly in response to consumer advocates and the medical community,^{1,2} and to advances in regulatory, bench, and clinical sciences, there have been increases in the amount of up-front data required to market a new drug. Current scientific and regulatory approaches to marketing authorization generally utilize randomized controlled trials (RCTs) to provide information on safety and efficacy, yet data on real-life comparative effectiveness are required to inform clinical decisions and those of payers.³ Taken together, these issues have led to more data being required during the initial development of a new product. To meet this demand, pharmaceutical firms have increased their investment both in research and development and in the number, size, duration, and design complexity of clinical trials. Yet, despite the near universal increase in effort and investment from all stakeholders in the health-care system, including regulators, the number of newly

approved drugs per year has remained flat. Costs of medicines are increasing, and there are few truly innovative treatments. As a result, the rising cost of incremental gains in health benefits is unsustainable within an environment of strained budgets.

Under the traditional regulatory paradigm, the life span of a drug is divided into two distinct phases: prelicensing and postlicensing. During the prelicensing phase, patients are exposed to a new drug only if they enroll in clinical trials with informed-consent procedures, meet specific enrollment criteria, and are randomized to the investigational product. The situation changes abruptly upon licensure. Often, this single event expands the exposure of a new drug from a relatively small number of highly selected trial subjects to millions of real-world patients who might not fit treatment eligibility requirements as specified in the label. At this point, drugs are generally perceived to be “safe and effective.” The unpredictability of the confounded real-world populations and usage combined with the unrealistic expectation of perpetual safety based on the extrapolation of limited data is not generally acknowledged in the current regulatory-decision framework. Such unrealistic expectations

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may indirectly discourage drug development by fueling demand for additional safety and efficacy data before licensing and fueling litigation after licensing. There is tension across satisfying the need for comprehensive information on benefits and risks, reducing barriers to innovation, and providing timely patient access. Under the current model of drug licensing, it is difficult to improve the terms of these trade-offs.

Within the traditional systems, efforts have been made to address many of the aforementioned development needs. US accelerated approval (AA) and EU conditional marketing authorization (CMA) allow earlier access to patients with unmet medication needs, as under these circumstances, patients, practitioners, and regulators are willing to take greater risks, including the risk of the unknown when it comes to ultimate efficacy and safety. US Risk Evaluation and Mitigation Strategies (REMS) and EU Risk Management Plans impose controls on approved drugs to manage known risks and explore unknown risks. Although these approaches have proven useful and will facilitate the implementation of adaptive licensing (AL) approaches, the vision of a more comprehensive and transformative framework will require expanded authorities for regulators and payers in some jurisdictions, more informed and interactive decision making by patients

and providers, and the continued development of new and emerging technologies to ensure an increase in the quality of knowledge communicated to all.

This article briefly summarizes recent proposals for AL, discusses how proposals may be translated into practice, and provides examples of how AL may be tailored to different indications. Finally, we discuss key issues that need to be resolved if AL is to become either a more commonly traveled road or the standard road to market for new drugs.

RECENT PROPOSALS FOR AL

Over the past five years, a wave of proposals for prospectively planned adaptive approaches to drug licensing has emerged under various labels, including staggered approval, managed entry, adaptive approval, and progressive authorization. These are summarized in [Table 1](#). These proposals vary in detail, but all are based on the premise that knowledge of drugs is not binary but continues to evolve over time. The single “magic moment” between nonapproval and approval is replaced with progressive management and reduction of uncertainty. Access to new therapies is based on a combination of data from RCTs and observational data describing the safety, efficacy, and effectiveness of drugs in real-world use and access control.

Table 1 Summary of proposals for adaptive approaches to drug licensing

| Proposal | Description |
|---|---|
| Health Canada Progressive Licensing Project (2005–present) ²⁸ | Life-cycle, evidence-based approach to licensing. 2007 workshops specified procedures for building knowledge about drugs in use; set standards for continued licensing; analyzed timing and length of reviews; and defined mechanisms for updating system. The proposed legislation expired on the Order Paper due to the dissolution of Parliament in 2008, but regulatory modernization efforts continue. |
| US Institutes of Medicine, Future of Drug Safety (2006) ²⁹ | Assumes impossibility of understanding effects of drugs at time of market entry and endorses: (i) aggressive assessment of drug effects through life cycle; (ii) public–private funding of postmarket assessments; (iii) overhaul of adverse events reporting; (iv) investments in pharmacoepidemiology; (v) FDA authority to demand postmarketing reports and conduct full 5-year reviews of new molecular entities. |
| European Medicines Agency, Road Map to 2015 (2010–present) ^{30,31} | Defines “staggered approval” approach for situations not covered by conditional marketing authorizations, with initial focus on restricted population of good responders, followed by modification as real-life data become available; AL should not lead to reducing evidentiary requirements for first-time marketing authorization. |
| Singapore Health Sciences Authority (2011) | Expressed commitment to explore AL for selected novel drugs. May enable patients and providers to have faster access to novel drugs without compromising safety through prospectively accumulating clinical data through active surveillance and to better understand heterogeneous responses to new drugs. |
| Woosley and Rice Rolling Approval (2005) ⁴ | Would accelerate licensing of drugs to patient subpopulations and, as safety is assured, remove restrictions until some drugs are cleared for over-the-counter use; indemnify firms for adverse effects if firms assume medical costs of treating adverse effects; create “behind-the-counter” status for some drugs with less control than via full prescription but more than over-the-counter therapies. |
| UK Athenaem Group (2010–present) ³² | Multistakeholder group examines the limits of the current model of drug licensing; argues for flexibility in licensing, enabling in appropriate cases early access by patients while additional data are collected. |
| MIT New Drug Development Paradigms (2010–present) | International multistakeholder collaborative developing approaches to AL, with work on evaluation of existing adaptive elements; on assessment of comprehensive proposals; and on development of methods for evaluating drug effects on natural (confounded) patient populations not included in current clinical trials. |
| Usdin and Flores Biocentury Provisional Approval (2010) ³³ | Propose FDA provisional approval where: (i) no current treatment exists or existing treatments need to be replaced; (ii) patients are enrolled in electronic registries for ongoing monitoring; (iii) benchmarks for policy changes, including shifting from provisional to general approval, are specified in advance; and (iv) patient groups are invited to provide input into such policy changes. |

AL, adaptive licensing; FDA, US Food and Drug Administration.

The following working definition of AL is proposed:

Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made.

GENERAL CONSIDERATIONS

AL may not be applied to all drugs in the same manner. For a product that is being used to treat a serious or life-threatening illness, the quantity of data required for an initial authorization might be considerably less than that required for a new product to treat a disease for which there are already ample treatments in the armamentarium (unless the product offers something clearly of advantage to the patients in terms of efficacy and/or safety). A successful AL pathway for any drug will also be dependent on the willingness of patients, health-care providers, payers, and regulators to accept a greater level of uncertainty in the expectation of a drug’s improved benefit and/or improved safety. It is unlikely that regulators, health-care providers, or patients would be inclined to accept the risk of increased uncertainty over the benefit–risk balance for a drug that does not offer the *a priori* promise of added clinical value for patients. The specifics of an AL pathway to market will likely vary on a case-by-case basis and are expected to be different from one product to the next and from one therapeutic area to the next. We present a few possible AL design features in **Table 2** and provide narrative

examples below. However, we speculate that all AL pathways will need to address the following considerations.

The evaluation of all drugs is not binary but a continuum

Per the aforementioned working definition, AL is designed to manage the entire life span of a drug, during which data continue to be generated on the product through various modalities, including active surveillance and additional studies after initial and “full” licensing; the artificial dichotomy of pre- vs. postlicensing stages (the “magic moment”) will be replaced by graded, more tightly managed, but more timely and potentially more cost-effective, market entry and market stability.

An acknowledgment of acceptable levels of uncertainty

At least during the initial licensing stage(s), AL is expected to involve a trade-off between earlier access for some patients vs. an increased level of acceptable uncertainty about benefits and risks, although the degree of uncertainty is expected to diminish with additional evidence generation. Greater willingness by patients, practitioners, and regulators to accept uncertainty is not to be equated with lack of scientific or methodological rigor. For example, an open-label, noninferiority study with soft end points may be no more convincing under AL than it would under the conventional licensing paradigm, whereas an increased nominal level of statistical significance (example 2) or use of an unvalidated surrogate marker (example 3) might be acceptable in some circumstances.

Rather than to shortcut development or to do it with less scientific rigor than in present practice, the aims of AL are to improve the quality of knowledge developed and the timeliness of knowledge generation, especially during the early stages of

Table 2 Examples of potential “design features” of AL pathways

| Aim | Initial license based on | Subsequent license based on | Comment |
|--|--|--|--|
| Reduce uncertainty around end point | (Not fully validated) surrogate end point | Clinical end point | Not a new concept; it is the basis for AA/CMA but may be used more frequently; there are challenges to enrolling postmarket RCTs |
| Broaden treatment-eligible population | Studies in enriched population with highest need based on benefit–risk | Studies in broader population | Currently common for oncology drugs but sees limited use in other therapeutic areas |
| Reduce statistical uncertainty | Superiority studies: greater than conventional significance level | Conventional significance level ($P < 0.05$) | For example, for a follow-on drug with safety advantage, drugs for rare conditions, long follow-up; may be challenging to do studies after the initial license for ethical reasons |
| | Noninferiority studies: wider than normal CI | Stringent CI | |
| Enable new–new combination development | Study showing improved efficacy (or risk profile) of combination vs. SOC | Full regulatory work-up to demonstrate the contribution of individual components | Allows initially for smaller (two-arm) trials, enabling shorter time to initial licensing |
| Reduce uncertainty around study design | Single-arm study; observational study; registry | RCT | Not a new concept; it has been the basis for AA/CMA for some cancer, orphan drugs |
| Ensure “real-world” effectiveness | Explanatory trial | Pragmatic RCT or observational study | Applicable to situations where real-life performance is in doubt |
| Address rare AEs | Trial powered for efficacy | Trial powered for defined AE (and, perhaps, in more confounded, real-world population) | Where there is a concern over a defined rare or difficult-to-detect AE; example: FDA diabetes drug guideline; “delinking” of the efficacy and safety populations; see text |

Different drug classes will probably require different regulatory pathways; elements from each of these pathways could also be combined for the AL of a single drug.

AA, accelerated approval; AE, adverse event; AL, adaptive licensing; CI, confidence interval; CMA, conditional marketing authorization; FDA, US Food and Drug Administration; RCT, randomized controlled trial; SOC, standard of care.

product development/knowledge generation, and, based on that improved knowledge, prospectively plan the marketing and the further development of knowledge about the product. Elements of AL should be flexible enough to handle various levels of efficacy and safety knowledge generated and the risk tolerances (both in terms of the known benefit–risk calculus and the risks inherent in lack of knowledge at any given point) in the community for the specific disease being treated.

Improved public communication and perception of safety and efficacy

Under an AL scenario, communication to the public and practitioners would necessarily place more emphasis on uncertainties, the evolving nature of knowledge about the product and its use, and the provisional nature of benefit–risk assessments. New models of information to patients might include, for example, postlicensure informed-consent sheets used after an initial license had been granted on limited information. It is expected that communication would not be a one-way street but that AL may lead to more participation of patients in defining acceptable thresholds of risk tolerance as well as acceptable levels of uncertainty for each drug considered for AL. This will require more formalized interaction during the decision-making process among patients, physicians, and pharmacists and, in the process, may reduce liability litigation in some instances. It will also need to accommodate differences in risk tolerance in different societies and thresholds that vary with time, sociopolitical factors, and experience of adverse events.

Greater adherence to use in treatment-eligible populations and the importance of label conditions

Drugs are normally authorized for a well-defined “label-scenario,” which most often includes a circumscribed treatment-eligible population (for example, patients with cartilage defects of grade III or IV) or restricted therapeutic setting (for example, second line: “carcinoma after failure of prior platinum-containing regimen”). Yet the population defined in the label often does not match well with the population treated postauthorization; newly approved drugs are often prescribed off-label and administered to patients with few, if any, restrictions⁴ and little regard for the label. Disregard or insufficient understanding of the label has given rise to safety issues under the current licensing paradigm⁵ and would defeat the intent of AL, at least during the initial licensing period when new medicines should be reserved for specific patients who need them the most and are therefore willing to accept a higher degree of uncertainty. Appropriate targeting to the label population will need to be a high priority under any AL scenario.

Increased need for prescription controls and support

It follows that, at least after the initial approval, systematic restrictions and monitoring of prescribing may be required to prevent off-label use. Restrictions on prescribers are not an entirely new concept and are an integral part of some current REMS/Risk Management Plan programs. For example, the US Food and Drug Administration’s (FDA’s) REMS program

includes Elements to Assure Safe Use.⁶ As part of REMS/Elements to Assure Safe Use, the FDA has the authority to apply restrictions on distribution that could require advanced certification for prescribers and pharmacists, dispensing of medication in authorized pharmacies, and requirements for enrollment into patient registries. The overall aim of these programs is to ensure proper administration and education on risks and to maximize the likelihood that only the patient population for which the product was approved receives the drug. That is not to say that under AL all off-label use needs to be avoided. In some indications, such as oncology, off-label use may provide a learning opportunity about a new drug’s role in combination therapies. However, full documentation of the patient experience under off-label conditions and the availability of the information for future rounds of assessment would be a key goal under AL. Interventions to ensure appropriate drug utilization may include support for patient concordance. Poor patient concordance impairs benefit–risk assessment, which, under AL, might lead to a false-negative outcome during subsequent rounds of regulatory assessment. Hence, companies and health-care providers will likely be incentivized to develop, implement, and assess concordance-enhancing measures, thus benefiting public health. One such potential measure available in the United States is medication therapy management, which involves pharmacists actively engaged in identifying, preventing, and resolving drug therapy problems in collaboration with prescribers and other providers on the health-care team. Medication therapy management could provide the controls and documentation needed to implement AL (<http://www.pharmacist.com/mtm/corelements2>).

Surveillance and evidence generation

Under the current licensing scenario, the treatment experience of most non-trial patients does not contribute significantly to evidence generation for the majority of drugs. Under AL, learning about a drug’s benefits and risks, and changing its regulatory status in a planned manner based on that new knowledge, is a more continuous process that informs repeated rounds of assessment, making fuller use of all sources of information. Evidence generation, particularly in the later stages of the drug life span, would not be limited to conventional RCTs but is expected to encompass the full methodology spectrum, including RCTs, pragmatic clinical trials, clustered RCTs, observational studies based on electronic medical records, registries, and other forms of both active and passive surveillance. Innovative methods for generation of hypotheses about unanticipated benefits and risks, such as pattern-recognition methods based on advanced computational learning, may be applied to analysis of observational data. It is hoped that more intelligent surveillance methods would not only detect safety signals earlier but, ideally, also identify markers associated with specific adverse events, identify actions that could prevent them, or generate signals to help identify characteristics of subpopulations that achieve the greatest benefit. The goal of continuing evidence generation is progressive reduction of uncertainty coupled with increased information to patients and

practitioners so that the best-informed individual treatment decisions can be made. After one initial and one (or more) subsequent cycle(s) of data collection, analysis, and adjustment of the intended treatment population, the drug may be considered “fully authorized.” In reality, full authorization is in name only, because continued surveillance may reveal rare adverse events or other information that could lead to further adjustments to the drug label and/or treated population. A true AL scheme is continuous throughout the life span of the drug, although data generation needed for later-stage authorizations/modifications may be based largely on analysis of observational data or on RCTs for use in other therapeutic settings. The collection and analysis of observational data supporting clinical studies following an initial authorization would be performed by the drug’s sponsor or by contractors working on behalf of the sponsor, as occurs today, or could be shared with pharmacists and other members of the health-care system. However, improvements in health information technology that address connectivity and information exchange among providers, payers, pharmacists, and other members of the health-care team are needed to better support this surveillance process (<http://www.pharmacyhit.org>). Although much of the infrastructure for the collection of postmarketing data collection as well as the data themselves may already exist in the form of electronic medical records and medical claims systems used by health-care organizations, insurers, and other parties, closer collaboration among regulators, manufacturers, providers, and payers is needed.

Comparison of AL approaches with AA/CMA and tiered-claims development

The US AA and the EU CMA are licensing pathways that share many features with the more comprehensive AL proposals and some of the proposals can likely be implemented under existing regulations and statutes. However, AL is envisioned as the ultimate replacement for the current development and authorization process/model, and as such would be applicable to most new products. Nonetheless, all AL frameworks envisage that a two- (or more) stage licensing path should be more broadly applied than is currently the case under AA/CMA, which is applicable to only a small subset of product development, i.e., situations that involve serious and life-threatening conditions for which there are few therapeutic choices.

With AL, a comprehensive development and licensing plan is agreed on in advance by the sponsor, regulators, and payers. In theory, sponsors and regulators develop such a plan for AA/CMA, but payers are not generally included in the discussions. The AL approach should facilitate more open and timely dialog and cooperation between sponsors, regulators, and payers. Restriction on utilization, including utilization monitoring, is also a key feature of AL but not always of AA/CMA, as is a stronger emphasis on communicating the higher than usual level of uncertainty to patients and providers.

With some drugs, e.g., oncology agents, “tiered-claims” development has become almost a standard. This is also an adaptive way of market introduction, in which the target population in the drug label is progressively broadened, e.g., from second- to

first-line treatment, or across biologically similar tumor types. For some drugs, AL may follow a similar path but, in addition, aims to include elements discussed above.

Incremental vs. transformative approaches to AL

Some AL scenarios may be considered mere incremental steps from current AA/CMA scenarios (see also examples below). At the other end of the spectrum, there are proposals for more transformative changes to the licensing model.

One of the more transformational AL approaches proposed is the “delinking” of the populations in which the fundamental efficacy hypothesis and the overall safety hypothesis are tested. Under the current development scenario, as well as some of the AL scenarios, the same test population of unconfounded patients is generally used for both. Although this population is, of course, the appropriate population for testing an initial efficacy hypothesis, the patients are expensive, difficult to find, and, ultimately, an inappropriate population in which to test the product’s safety. In this AL example, the early determination of efficacy is in an RCT in a small and unconfounded patient population that also yields a preliminary safety data point. Lack of efficacy or the identification of a significant safety problem at this point would terminate product development. In comparison to conventional current development schemes, this has the potential to allow a quicker assessment of efficacy, a quicker go/no-go decision point regarding safety hypothesis testing, and savings in both time and money in the use of smaller numbers of the most expensive and difficult-to-find patients in which to test safety hypotheses.

Further assessment of safety would take place in a more abundant and less costly confounded patient population. Safety testing could also be done in large, simple RCTs enrolling real-world patients in which there would be relaxed inclusion/exclusion criteria allowing inclusion of subjects with other diseases so that safety is determined in a population much more representative of the ultimate intended population for the product. These studies would be prospectively planned as to when interim analyses would be made so that a decision on any initial authorization could be made while the trial then continued to gather additional data. It is envisioned that there would be agreement to continue the safety RCTs that were started before the initial authorization, and there would be initiative on a robust active surveillance program in the population for whom it is intended and with whom it is used in this initial authorization period, with close monitoring for adverse events, efficacy, compliance/adherence, and unanticipated benefits.

The *sine qua non* of such a transformative AL scenario is the concept of initial licensing for use in a restricted population by a restricted number/group of physicians based on the issues that surround a given product and the level of knowledge generation at the point in the product’s life when an initial authorization would be undertaken. Any such initial authorization would be accompanied by increased information to patients and physicians about what is and what is not known regarding the product at that time, and any distribution under an initial authorization scheme would try to ensure no off-label use during this period. Such communication vehicles

might include the authority to require product packaging/labeling as “initially authorized” and to prohibit (or to require and enforce company agreement not to engage in) general consumer advertisements during the initial authorization marketing period. In addition, it could be envisioned that the amount charged/paid for products during the initial marketing period would vary with the amount charged/paid after full authorization, again reflecting the level of knowledge about the product at that time and the value that it is shown to be bringing to the patient and the health-care system. One final element envisioned for some AL scenarios might be a prohibition on product liability suits, except for gross negligence, during the initial marketing period—again, consistent with a progressive learning model about the product and a model in which those prescribing it and taking it during this initial marketing period would be better and more realistically informed as to the state of knowledge (or lack thereof) about the product during this period of continued learning.

AL SCENARIOS: ONE SIZE DOES NOT FIT ALL

Most critical for the concept of AL is the design of the drug development plan and its alignment with repeated steps of regulatory evaluation and action, as well as with appropriate drug utilization and monitoring in the market, as new knowledge is acquired in the most timely and robust manner. The successful introduction of a new drug under AL requires an evolution of knowledge generation about its risks and benefits and an understanding of the risk tolerance in the community that will be using the product. The goal of each authorization step is to minimize uncertainty about benefits and risks and to ensure that patients and practitioners understand what is and what is not known about the product. The pathways along that knowledge growth curve will probably be unique to each drug or class of drugs, and one size is not expected to fit all. An element critical to the success of any AL approach is the prospective agreement by the sponsor, regulators, and payers on the evidence (of both efficacy and safety) needed at each stage of development and authorization. It is not practical to fully sketch out all possible development and licensing pathways, but we provide some examples of “design scenarios” for different drug classes in [Table 2](#). Many AL scenarios will see progressive widening of the label population, although AL also allows for narrowing or no modification to the label population, as knowledge about the product grows. The pace of growing or shrinking usage across subpopulations or risk strata will not be the same for all drugs. In the remainder of this section, we provide concrete examples of what an AL pathway might look like for a few drug classes. Examples 1–4 represent AL pathways that expand on existing procedures and control elements, and example 5 represents a more transformative pathway. What is common among the examples is an attempt to strike a compromise between timely access for at least some patients and development of sufficient evidence for reliable benefit–risk assessment across a much broader population. The potential benefits for companies would be an earlier revenue stream than under a conventional licensing pathway and less expensive and shorter clinical trials.

Example 1: adaptation around treatment-eligible subpopulations with initial restrictions (weight-loss drug)

Obesity is a chronic condition associated with significant morbidity and mortality. The increasing prevalence of obesity generates an urgent need for safe and effective interventions. The postmarketing utilization of antiobesity medicines has been problematic and characterized by heavy marketing, inappropriate prescribing, and poor patient concordance. This has resulted in withdrawals from the market after reports of safety problems and lower-than-expected efficacy⁷ despite evaluation in relatively large clinical trials. Appropriate utilization and/or a higher quality of data from clinical trials might have prevented this outcome.

An AL scenario of novel antiobesity drugs could focus initially on demonstrating benefit–risk in a narrowly defined, highly enriched patient population; patients would be selected for high medical need (at the high end of the body mass index spectrum and presence of risk factors), for expected high responsiveness to beneficial effects and low susceptibility to adverse effects (to the extent that this can be predicted from the pharmacological mode of action), for higher-than-average expected treatment concordance (e.g., by way of placebo run-in phase), and for tightly controlled management (dedicated centers, concordance-enhancing measures, excluding primary-care settings). The sample size of the confirmatory placebo-controlled RCTs required under this scenario is probably smaller than under conventional conditions, owing to the higher signal-to-noise ratio. If results are favorable, an initial license would be granted with a number of caveats: (i) the license and subsequent usage reflects RCT conditions more closely than today, in regard to patient-selection criteria and treatment settings; (ii) the treatment experience—benefits and harms—will be recorded by way of registry or suitable electronic medical records and contribute to the evolving knowledge base of the drug; (iii) prescribers have to be specifically qualified and can demonstrably ensure required treatment conditions as laid out in the license, including close patient follow-up and monitoring. In parallel, RCTs would continue to be conducted in different (wider) patient subpopulations with fewer restrictions; after the initial license, RCTs may be placebo- or active-controlled. If results from these studies and observational experience gained from real-life use were favorable, the license would be widened and prescribing conditions relaxed. [Figure 1](#) shows a graphic comparison of the time course of evidence generation and patient accrual under traditional and AL scenarios. This example also highlights the importance of clear-cut criteria for treatment eligibility after the initial license: obesity and cardiovascular risk factors represent a continuum that, in the absence of unequivocal criteria, may put prescribers in a difficult position when patients request access to the drug.

Example 2: adaptation around statistical uncertainty (drugs for rare conditions)

Many of the 7,000 or so rare diseases identified are chronically debilitating, life-threatening, or life-limiting and represent a substantial unmet medical need.⁸ Conducting traditionally

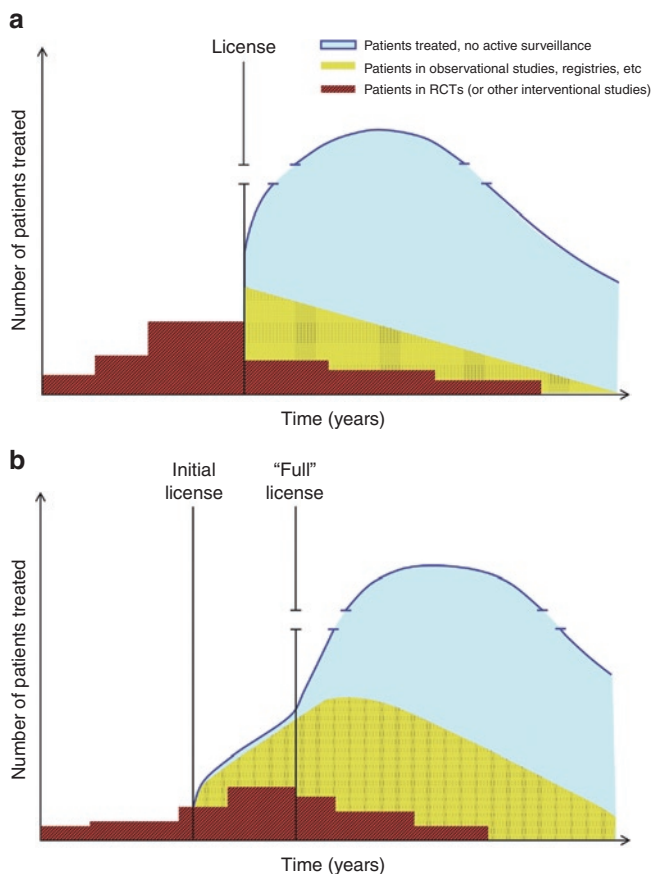


Figure 1 Time course of evidence generation and accrual rates of patients treated with a new drug under the current and adaptive licensing (AL) scenarios. The schematic representation is modeled on example 1 (weight-loss drug) but is broadly applicable to other AL scenarios. Note that axes are not to scale. **(a)** Current scenario; before the license, nearly all patients treated with the new drug are formally enrolled in randomized controlled trials (RCTs) or other types of interventional studies. Once the license is granted, the treated population expands rapidly. For the majority of drugs, the treatment experience of most patients does not contribute to evidence generation; some patients (or all patients for a small number of drugs) may be enrolled in registries or other forms of observational studies (active surveillance). RCTs are initiated or continued to explore new indications or potentially as part of a risk evaluation and mitigation strategy or risk management plan. **(b)** AL scenario; the number of patients in prelicensing RCTs may be smaller and the initial license may be granted earlier than under the current scenario. After the initial license, the number of treated patients grows more slowly, owing to prescribing restrictions. Nearly all patients who are not enrolled in ongoing or new RCTs would be captured by some form of observational study, contributing to real-world (effectiveness) information. Following the delivery of pre-agreed milestones, a “full license” may be granted after which requirements for active surveillance and RCTs are gradually eased. Note that repeat cycles of evaluation and modification of the label may occur unscheduled or in line with an agreed-on late-stage development plan (not shown in graph).

powered RCTs may be nearly impossible in some very rare conditions because the small number of eligible patients would stretch recruitment periods over many years. Flexible regulatory pathways may be the only feasible approach to balancing early access with adequate level of certainty about benefits and risks, and some orphan drugs have been successfully brought to market by way of AA/CMA.

Under an AL scenario for very rare conditions, an initial license might be granted based on an uncontrolled study or, where possible, on a placebo-controlled trial planned to show superiority at a significance level higher than the conventional 5% two-sided significance that would usually be required. Patients receiving the treatment under the initial license would be made aware of the heightened uncertainty about the benefits and risks through patient-consent procedures. Given the very high costs of some of these drugs, it is critical that the development and licensing plans be the result of a collaborative effort among sponsors, regulators, and payers and include consideration of affordability and potential risk-sharing schemes.

Evidence generation after the initial license will be challenging in these conditions as patients would probably be reluctant to enroll in controlled trials, even if institutional review board/ethics committee approval can be obtained, as participation in such studies immediately loses its appeal once the drug becomes available in the treatment setting. In specific cases, randomized active-controlled trials might be feasible, albeit, again, with an inflated nominal significance level. In the majority of cases, however, no proven alternative treatments will be available and subsequent knowledge generation will have to rely on observational data confirming or refuting point estimates of clinical outcomes derived from the initial study (studies). **Figure 2** graphically illustrates this approach.

An alternative AL scenario can be envisaged for heterogeneous rare diseases. Conditions such as congenital ichthyosis, cystic fibrosis, or Duchenne muscular dystrophy have many different phenotypes based on different gene mutations. Hence, genome-specific therapies, such as oligonucleotide-based drugs, will need to be targeted to often very small genetic subpopulations. It will not be feasible to run a full-scale clinical development for each member of a “family” of targeted molecules.⁸ An AL scenario might involve an initial development and license as described above for one particular subpopulation; this would establish proof of clinical activity and benefit. Subsequent licenses for additional in-class molecules for subpopulations that arise from similarly caused and correctable preexisting mutations would be based on small case series, provided that biological pathways are sufficiently similar to allow for extrapolation across subpopulations.

Example 3: adaptation around end points with surrogate markers

The time and cost to drug approval can be decreased substantially by using surrogate end points rather than clinical end points as a basis for licensing. This would also potentially stimulate the development of more drugs for more conditions.⁹ However, surrogate end points have had a mixed record of predicting clinical benefit. Surrogates have predicted clinical outcomes, e.g., renal pathology markers for Fabry disease,¹⁰ but have also resulted in devastating outcomes, such as favorable electrocardiogram surrogate markers being associated with excess mortality in patients treated with certain antiarrhythmic agents.¹¹ Unsurprisingly, there is strenuous debate over

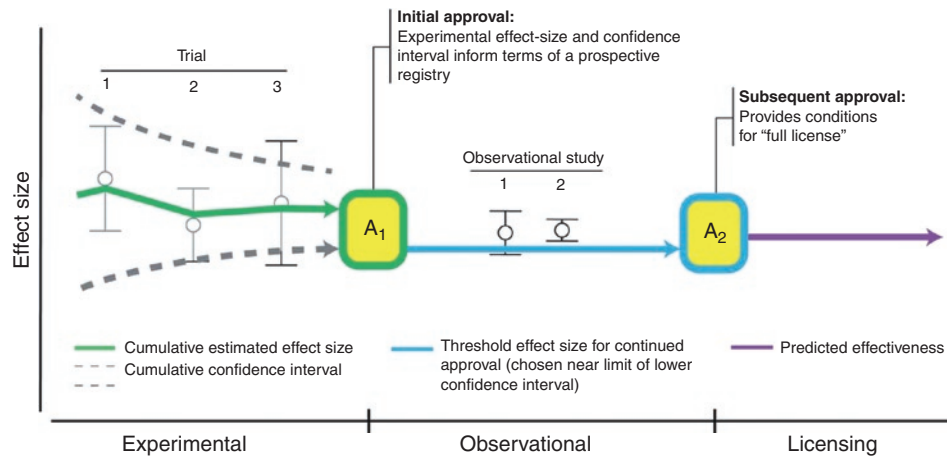


Figure 2 The threshold approach to evidence generation when randomized controlled trials (RCTs) are not practically or ethically feasible after an initial license. The threshold approach to adaptive licensing might lend itself to situations in which conventional, adequately powered RCTs are difficult to perform before licensing and nearly impossible after an (initial) license is granted; this may apply to orphan conditions for which no proven alternative treatment exists. Under this pathway, the sponsor would initially conduct one (or possibly more) small RCTs. If successful, an initial license may be granted on the basis of this limited information. Subsequent uncontrolled observational studies would aim to show that the treatment outcome under real-life conditions (e.g., mortality, time to event) remains above a pre-agreed threshold. The threshold value itself is based on the point estimate and confidence interval obtained from the initial RCTs, and prior knowledge of outcome with, for example, best supportive care. If efficacy were thus confirmed, the drug could transition to a “full” license. Note that the concept might also be applied to safety, e.g., to demonstrate that the drug does not produce an incidence of greater than x of a life-threatening adverse effect such as progressive multifocal leukoencephalopathy (not shown in graph).

the acceptability of surrogate end points, and some argue that only patient-important clinical end points should be considered an acceptable basis for drug approval.^{12,13} One approach might be to grant an initial license based on a convincing effect on a surrogate end point while further studies are conducted to confirm an effect on the relevant clinical end point. The FDA’s AA pathway is based on this approach,¹⁴ and many HIV therapies and several cancer drugs have been authorized under this model. However, AA has been limited to a few therapeutic areas. The concept might lend itself to selected drugs for cardiovascular or metabolic conditions, for which RCTs to demonstrate clinical benefit, e.g., on micro- or macrovascular complications of diabetes, might take an inordinate amount of time. The debate is expected to center on which surrogate end points are considered “reasonably likely to predict a real clinical benefit”¹⁴ for a wider circle of therapeutic indications and what needs to be done to validate the end point as predictive of clinical benefit.

As with most AL scenarios, patients and health-care providers would need to be explicitly informed about the limited evidence base during the initial licensing stage. Apart from ensuring the license holder’s commitment to continue the evidence-generation process, the key challenge is that, for ethical and practical reasons outlined above, initial licensing may close the window of opportunity for performing placebo-controlled randomized trials. Hence, randomized confirmatory trials should begin to enroll as early as possible, potentially before the conclusion of the initial trial.¹⁵ However, in many instances, additional evidence generation to explore the drug’s effect on clinical end points may have to rely on prospective observational studies and/or active-controlled RCTs.

Example 4: adaptation around combination treatments (oncology)

Advances in cell biology and genomics have led to ever more selectively targeted drugs. However, there is growing realization that, for some pathologies, selective modulation of only one target may not suffice to achieve a better outcome and more durable clinical response. For example, a combination of two (or more) targeted compounds may be required to prevent development of resistance when treating tumors or infectious diseases. It is therefore widely expected that a growing number of targeted molecules will be codeveloped as “new–new” combination drugs.¹⁶

Although new–new combinations may have the potential to address conditions of high unmet medical need, the concurrent development will probably provide less information about the safety and efficacy of the individual drugs at a higher cost. For ethical reasons, it may not be possible to conduct parallel-group comparisons in which the combination is compared with the individual compounds and with standard of care. The FDA has recently provided guidance on how the evidentiary standard for licensing of new–new combinations can be tailored to individual cases.¹⁷

We argue that the concept of AL may lend itself to some new–new codevelopment programs. For example, “if phase 2 data do not provide sufficient evidence of the contribution of each component of a two drug combination, but provide strong evidence that the combination is superior to one of the components, the guidance recommends that a phase 3 trial comparing the combination to the more active component alone and standard of care may be needed to demonstrate that the less active component contributes to the activity of the combination.”¹⁷ Under an AL paradigm, an initial license might be based

on favorable results from a smaller two-arm trial comparing the combination to standard of care. This would enable earlier patient access to a potentially beneficial treatment option when patient recruitment is a rate-limiting step for initial authorization. During the subsequent stage, and if deemed necessary to mitigate toxicity, contribution of individual components could be assessed, e.g., by way of trials with randomized withdrawal of one component or randomized variation of dose ratios. The challenge of developing labeling information for the two different combination drugs is acknowledged, and in some cases, and where feasible, this would argue for developing the combination as a fixed combination product.

Example 5: adaptation around demonstration of initial effects followed by more comprehensive efficacy and safety evaluation (antimicrobial agent)

Infections with multidrug-resistant bacteria are a growing public health concern (although the numbers of patients are not large in comparison to patients infected at the same body site with non-multidrug-resistant bacteria). There is an acknowledged dearth of new antimicrobial agents in development, which is due to many factors, including the traditional pharmaceutical business model that foresees broad usage in the population for treating infections at many different body sites. Unfortunately, this approach to antimicrobial development has also led to the increase in frequency of infections with multiply resistant bacteria. One way to encourage efficient development of new agents could be an AL scenario in which the sponsor would first demonstrate clinically relevant antibacterial activity of the agent by way of providing *in vitro* demonstration of antimicrobial activity, validated animal model evidence of activity, and/or human pharmacokinetic/pharmacodynamic studies demonstrating a concentration–time profile of the active drug in the target body compartment that would reasonably predict clinical benefit. In addition, data would be collected from an RCT of patients with one of the diseases caused by the target multiresistant organism, including those infected with both multiresistant and sensitive strains of the target organism based on an understanding that the number of patients having multidrug-resistant microbial infections, for which the new agent is expected to offer the greatest benefit, would be low. An initial authorization would be granted (with restrictions on real-world usage) to minimize emergence of drug resistance while the sponsor would pursue wider assessment of efficacy in patients demonstrated to be infected with multiresistant organisms in a larger number of indications and a fuller safety profile from an RCT to obtain the subsequent full authorization.

As these examples suggest, the details of AL may need to be adjusted to fit different therapeutic areas and clinical settings. Further research is needed to specify suitable criteria for determining which specific elements of licensing might be appropriate to which circumstances.

THE PROMISES AND CHALLENGES OF AL

AL has the potential to benefit a number of health-care stakeholders, whether adopted in its more conservative or

transformative embodiments as follows. AL may in some cases reduce time to full market approval. In others, AL may reduce the time to access by those who need it most while delaying general market access. AL should not be expected to reduce overall attrition rates during drug development (e.g., due to target failure) but may reduce the overall cost of development by allowing better-informed decisions on product viability to be made earlier in the development process. In addition, AL should reduce expensive late-stage attrition and postmarket withdrawals. Earlier and better-informed product viability decisions added together should address many of the root causes of the overall high costs of product development and sustained return. However, the adoption of AL of any embodiment also comes with challenges that must be addressed; these are discussed below.

The current framework of drug licensing rests on the perception that regulators should require drug companies to conduct the entire scope of work to fully establish safety and efficacy before licensing.⁴ This, to much of the public, implies 100% benefit and 0% risk for each patient taking the drug. In reality, this is impossible under any licensing system, given that no drug is 100% safe and effective. The notion of AL may give rise to the perception that regulators are lowering the initial entrance barriers and allowing untested drugs on the market. This is not supported by recent evidence.¹⁸ One of the main purposes of the AL scheme is to get more robust and more relevant data earlier and throughout product development. Any attempt to move toward a more adaptive approach would have to be complemented by appropriate communications to key stakeholders and assurance that the appropriate post-initial authorization capabilities exist for ongoing monitoring of medical products for which AL has been applied.

Under the paradigm of AL, all stakeholders will need to accept that initial approval is not just early but also conditional. Hence, a clear commitment is required from industry to conduct “stage $n + 1$ studies” after the initial licensing stage(s). The willingness of industry to conduct postlicensing studies under the current system has been called into question, and the rules of engagement will need to be clear and transparent to all if regulators, industry, and other stakeholders transition to an AL approach. The early and continuing dialog between sponsor, regulators, and payers and the ongoing review of data may reduce the development misalignments between marketing and reimbursement decisions as well as the postmarketing execution challenges faced by sponsors of traditional licensing programs.

In a survey of the status of open commitments for postmarketing studies requested by the FDA, Avorn¹⁹ reported that more than half of the studies were not yet started, behind schedule, or terminated before completion. Although it has been clarified by the FDA that this is not synonymous in all cases with failure to fulfill commitments,²⁰ and a more recent study of industry compliance paints a more favorable picture,²¹ the article by Avorn has highlighted a critical issue: what is the appropriate regulatory action to take in the event that promised studies are not performed or expected data do not become available? Taking no action and leaving the marketing authorization unchanged

would undermine the system, whereas revocation or restriction of the license, based simply on a lack of new data, will be difficult to argue before patients and health-care providers, particularly in the case of a potentially lifesaving drug.

Even if manufacturers were committed to doing post-initial authorization studies, this does not necessarily mean that they are feasible. First, in the ethical underpinning of RCTs, the notion of “equipoise” implies that physicians can ethically randomly assign patients to different treatment arms only in a state of true professional uncertainty about their relative therapeutic merits. If equipoise exists, no participant in an RCT is knowingly given inferior treatment.²² However, once a new drug has been assessed by regulatory experts and given an initial license, it may be argued that uncertainty is greatly diminished, and “loss of equipoise” may render some RCTs ethically unacceptable. Initial licensing under an adaptive scenario may close a window of opportunity to gather more randomized data on a given drug. Second, patients may be less willing to enroll in an RCT of a new drug once it has been granted an initial license and they can get direct access to it.

The pre- and post-initial authorization collection of clinical data might be navigated by astute planning of the development and licensing pathways and will require a new level of cooperation among industry, regulators, and payers. Different licensing stages could focus on different patient (sub)populations or different comparator treatment arms (e.g., initial licensing studies: placebo-controlled; subsequent studies: active-controlled). In addition, RCT information may be complemented by results from observational studies that are not subject to the equipoise requirement. It will be important, however, to flesh out the entire road map to market right from inception, with awareness of practical constraints to evidence generation.

For most drugs, treatment access also involves a subsequent decision on coverage (reimbursement) of an authorized drug by third-party payers such as Medicare in the United States or national health services in the European Union, followed by a prescriber's decision to select a drug for treatment and a patient's agreement to treatment. Gatekeepers to treatment access therefore include not only regulators but also payers, physician prescribers, and other health-care providers. To be successful, AL would require some alignment between the regulatory, payer, and prescriber decisions. Under the current system, the lack of alignment has led to payers unwilling to cover new treatments when they consider the evidence basis to be insufficient to justify the cost.

To prevent such misalignments, the current prelicensing interaction between regulators and sponsors may need to include payers in order to enable an early development program that meets the information needs of both regulators and payers. There is preliminary experience of “tripartite scientific advice” procedures, in which all three parties attempt to agree on a clinical development plan, including target populations, study end points, and comparators,²³ and coordinated review processes of regulators and government payers have been proposed.²⁴ Similar considerations apply to the stage after initial licensing; “coverage with evidence development” is the payers' analog to the regulators' concept of AL.^{25–27} Ideally, the studies agreed on

with regulators under an AL plan should match the “evidence-development” plan agreed on with payers. Harmonization of the development plan across sponsors, regulators, and payers could also be one way to ensure that sponsors continue to monitor their AL products once released into a wider market and to meet payer demands for data on the effectiveness of drugs in use.

To date, there are only a small number of drugs with regulatory restrictions on prescribers; most restrictions are imposed by payers to manage access, improve benefits, and mitigate risks. Under a few current REMS/Risk Management Plans, a drug may be prescribed only by specialists in a given field or by physicians who have undergone specific training and/or who take part in proactive surveillance programs. We have mentioned that AL would probably entail wider use of restrictions and surveillance of prescribing. Some prescribers and health-care providers may view AL as an opportunity for differentiation and competitive advantage, but others may be inclined to oppose restrictions of their freedom to practice. Acceptance by health-care professionals will likely be a challenge to introducing AL on a wider scale. Here again, communication to stakeholders will be important to ensure success of the new paradigm. Cooperation of payers may also be essential to create disincentives for off-label use.

Finally, if the goal of AL is to ensure well-managed and well-informed entry into the market, the impact on the revenue stream for drug developers will need to be evaluated. Under the current system, developers have to recoup their costs and make a return on investment during the finite period between market entry and expiration of patent or exclusivity periods, which motivates them to seek broad licenses and fast market uptake. New reward and incentive structures may be needed to counterbalance the rapid, “all-population” promotion and uptake that is common for products licensed under traditional paradigms. Hence, the incentive structures, including the terms and durations of patents and exclusivity periods, may need to be re-examined in some situations to allow successful implementation of AL. Appropriate incentives, as well as requirements, could build on the experiences gained with orphan and pediatric drug legislation but might also include some form of liability protection and/or tying of market exclusivity periods to appropriateness of prescribing or prespecified health outcomes.

The basic elements of AL are outlined here, but, admittedly, the prospect of developing a comprehensive AL model, along with its testing and validation, will require significant coordination among stakeholders. Elements and technologies that support a new adaptive drug licensing paradigm (e.g., biomarkers and surrogate end points, infrastructure for proactive drug safety monitoring, electronic medical records, new clinical trial designs in which safety and efficacy are decoupled to optimize study designs for optimal knowledge generation, and tools to enable appropriate utilization of new drugs) have been implemented as isolated efforts across the industry and various health-care environments. Precedents for AL, such as REMS, Risk Management Plans, and AA/CMA, have also been employed. But there has not yet been a coordinated effort to integrate, evaluate, and refine these approaches from a “systems” perspective.

Successful transition to any of the broad range of AL perspectives may best be accomplished by demonstration of the feasibility, challenges, and benefits of each to different stakeholders by way of pilot projects. This would include retrospective modeling of “what-if” scenarios for drugs that have been authorized in the recent past and under the current paradigm. Such retrospective studies may provide a basis for assessing the effects of AL on the timing and cost of development and on the quality of information on the safety, efficacy, and effectiveness of drugs in use. However, to make headway, the AL approach will need to be prospectively tested on drugs currently in development for which an AL scenario is agreed on by the sponsor, at least one regulatory authority, and relevant payers. Completion of a series of demonstration projects would allow for analysis and aggregation of the experience with the ultimate goal of facilitating the incorporation of “validated models” into the established system of drug regulation. Collection of prospective data from demonstration projects is believed to be essential to effecting timely changes because it should provide actual examples of what has worked and what has not.

To address this need, the Massachusetts Institute of Technology along with global regulators, pharmaceutical companies, health-care providers, payers, and other stakeholders have joined forces in a collaboration called the New Drug Development Paradigms (NEWDIGS) initiative. Under NEWDIGS, new ideas and models for drug development are currently being tested in live demonstration projects using product pipeline candidates contributed by research-based pharmaceutical companies. One module of NEWDIGS activities is focused on AL. The collaboration’s approach is to systematically evaluate different pathways of AL through iterative simulations and demonstration projects in a “microenvironment” in which all stakeholders participate and agree to adapt policies to accommodate the model; this approach has the potential to facilitate the sustainable but targeted growth of AL. Academic research teams at the Massachusetts Institute of Technology provide an impartial means of analyzing the outcomes and refining the models. A critical feature of the collaboration is that it provides a neutral and transparent “safe haven” environment for industry, regulators, payers, and health-care professionals in an academic setting that allows stakeholders to empirically evaluate various adaptive policy design elements. In addition, academic research teams are focused on advancing our ability to better leverage emerging data to inform decisions made by key stakeholders throughout the product life cycle. Currently identified research projects include modeling of adaptive vs. traditional licensing paradigms to compare economic outcomes for various stakeholders and using real-time, computational learning to rapidly and continuously monitor product safety.

CONCLUSIONS

The current standard pathway to market access is ill-suited to enable timely, well-informed patient access, stimulate drug development, and simultaneously ensure routine collection and evaluation of all relevant information on benefits and risks. Although these competing goals are quite challenging, we propose that an adaptive route to market that comprises successive licensing steps, more forthright communication

about unavoidable uncertainty and knowledge gaps, progressive reduction of uncertainty, and alignment of drug utilization with current knowledge will mitigate some of the current disconnects between industry, regulators, and their different stakeholders and engender public and political trust in the regulatory system.

However, conditions are in place to move from theory to practice, and this is best achieved by way of pilot projects, some of which are in the design phase. As with many things in drug development, skeptics will say, “Show me the data.” We hope to do so in the near future. AL requires a different approach from the dichotomous unapproved/approved current paradigm; involvement and buy-in of patients, providers, and payers is required.

There are considerable challenges and benefits to fully implementing AL as the common pathway for drug approval. Overall, there seems to be sufficient merit in the current ideas to allow pilots to go forward to try to generate the data to determine whether AL offers a more favorable alternative to the current licensing paradigm that maximizes the benefits of drug development and science-based regulation for patients and public health.

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CONFLICT OF INTEREST

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