

SCIENCE & SOCIETY

Drug discovery in renal disease —towards a more efficient framework

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Abstract | The time and cost involved in bringing new drugs to the market hamper their approval. This problem is especially apparent in the case of renal diseases. Efficient drug research requires an *a priori* understanding of disease pathophysiology, target validation, rational and efficient drug discovery strategies and early testing of the physiological and pharmacological effects of the new agent in humans. Drug development initiated by academia benefits from international research networks and relies on internationally acceptable high-quality nonclinical data packages and bulk investigational drugs. Academics should, therefore, better understand pharmaceutical practice regulations and novel, efficient drug-development strategies. Many researchers remain unfamiliar with these areas and should collaborate with regulatory authorities to discover and validate surrogate markers for use in drug development, and to efficiently and effectively maximize the benefits and minimize the adverse effects of new drugs. The Japanese government and regulatory authorities have implemented a framework to encourage such collaborations; extension of this framework beyond its current reach is envisaged.

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Introduction

The number of newly approved drugs continues to decrease over time^{1–3} as a result of the attrition of tested novel molecules, the increasing time needed to market new agents and their potential clinical risks—all of which entail rising costs. Moreover, despite the large number of affected patients, very few drugs have been developed to treat kidney disease.⁴ As of 22 January 2014, a total of 4,726 trials (2,837 in North America and 1,290 in Europe) of investigational new drug applications were registered in the ClinicalTrials.gov registry of federally and privately supported clinical trials conducted around the world.⁵ However, only 13 of these trials related to diabetic nephropathy, a major cause of CKD.

A lack of experimental animals that mimic human kidney disease, as well as the difficulty in extrapolating findings from animals to humans, has hampered

progress. Indeed, the development of bardoxolone methyl, an antioxidant inflammation modulator that acts through induction of the Keap1–Nrf2 pathway,⁶ perhaps illustrates this point best. The BEACON placebo-controlled phase III trial of bardoxolone methyl in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease (CKD) was terminated early due to serious cardiovascular events (that is, heart failure) in the treatment group.⁷ Such events were not reported in preclinical animal studies;⁸ however, no perfect animal model of human diabetic kidney disease currently exists.⁹ Analogues of bardoxolone methyl were shown to worsen diabetic nephropathy in a rat model of type 2 diabetic kidney disease, but the reported adverse effect (liver dysfunction) has not been observed in human trials. Innovation in kidney disease therapies is further hampered by a lack of validated surrogate end points that can be used in clinical trials as an alternative to well-accepted but difficult to reach robust end points that require long

follow-up times, such as doubling of serum creatinine levels or progression to end-stage renal disease (ESRD).

The discovery and clinical development of new drugs is a lengthy and very costly process; an estimated 10–17 years and US\$0.8–1.7 billion are required to bring a therapeutic agent to the market.^{1,3,10} Several years are needed before clinical studies are undertaken in humans. Traditionally, early, phase I clinical studies focus on the pharmacological characteristics of an agent in humans (including pharmacokinetics and pharmacodynamics), whereas efficacy in humans is tested only in proof-of-concept phase II trials (Figure 1).

The main causes of drug attrition have changed over time. In 1991, poor pharmacokinetic properties were implicated in approximately 40% of cases of drug attrition but this decreased to <10% of cases during the subsequent decade.^{1,11} Currently, the main reason for drug attrition is a lack of efficacy in humans. Attrition rates are, therefore, highest (approximately 60%) during phase II trials.¹² To reduce the time and costs involved in drug discovery and approval, an *a priori* understanding of the pathophysiology of the relevant disease, target validation, rational and efficient drug discovery, and early testing of the physiological and pharmacological effects of the agent in humans are required.

In this Review, we discuss the current status of drug development, the remaining challenges and the need for closer collaboration between academia, industry and regulatory authorities. We also describe the current Japanese framework that was implemented to facilitate such collaboration.

Guidelines for drug development

The FDA has paid special attention to the revision of drug development and regulatory processes¹³ and has highlighted the importance of translational research to develop new concepts and tools to efficiently select drug candidates at an early stage of clinical development.¹ In Europe, the Committee for Medicinal Products for Human Use has offered similar guidance for exploratory early clinical studies,¹⁴ which have no therapeutic intent, and are not intended to examine clinical tolerability, but

Competing interests

The authors declare no competing interests.

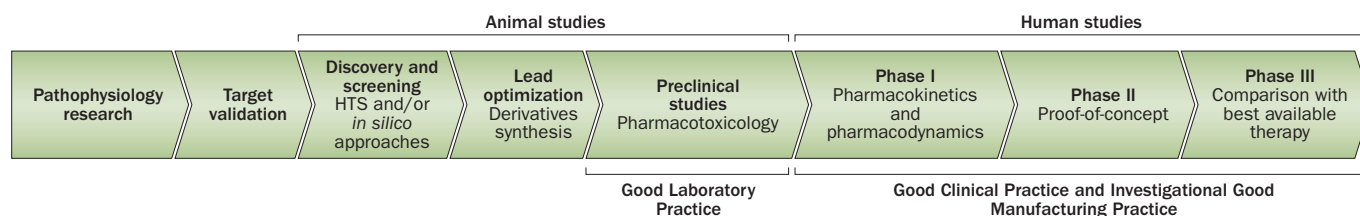


Figure 1 | Procedures for drug discovery and clinical development. Research into disease pathophysiology enables identification and validation of target molecules. Numerous lead compounds are then identified using HTS or *in silico* approaches, such as structure based drug design, and a programme of structural optimization is launched. The physical and toxicological properties of the various compounds are tested in animals before selection of the candidate compound for clinical trials. Phase I trials focus on the pharmacokinetics and pharmacodynamics of the agent in humans, whereas efficacy is tested only in proof-of-concept phase II trials. Phase III trials are used to compare the efficacy of the new agent with that of the best available treatment. All procedures must be conducted according to pharmaceutical regulations (that is, Good Clinical Practice, Good Laboratory Practice and Good Manufacturing Practice). Abbreviation: HTS, high-throughput screening.

can be used mainly to investigate a variety of parameters such as pharmacokinetics and pharmacodynamics. On 11 June 2009, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use issued new guidance on 'exploratory clinical trials' and recommended the use of various validated biomarkers and molecular imaging technologies, such as positron emission tomography.¹⁵ These techniques might enable early assessment of the distribution of drugs within the kidney and of their physiological and pharmacological effects. Trial participants can be patients from selected populations or healthy individuals, and the amount and type of non-clinical supporting data that is required is dependent on the extent of the proposed exposure to the new agent. Undoubtedly, use of biomarkers (Box 1) and new imaging methods (Box 2) would lower costs and, therefore, enable a greater number of promising compounds for the treatment of kidney diseases to be investigated than at present, increasing the likelihood of eventual approval.

The role of academia

Currently, researchers in academia can undertake the entire research and development process for new drugs, from pathophysiological investigation to discovery of target molecules, identification of candidate compounds (using *in silico* approaches; Box 3), lead optimization, preclinical studies and exploratory clinical trials. They should select promising compounds that are active in human physiology and pharmacology, and provide the pharmaceutical industries with useful data for further full-scale development of novel drugs. Fortunately, academic researchers have access not only to basic science and technologies but also to various contracting research organizations.

With proper efforts, universities might progress from target validation to identification of candidate compounds, Good Manufacturing Practice (GMP) synthesis and formulation, nonclinical Good Laboratory Practice (GLP) studies and phase I and phase II Good Clinical Practice (GCP) studies in humans. With government support, researchers have a solid infrastructure for drug discovery. However, a cost-effective drug-discovery framework is necessary to enable high-quality materials and data to be obtained within the context of limited budgets, labour and time.

International research networks

In contrast to research in industry, which is not fundamentally based on open innovation and is closed in nature, drug development initiated in academic institutions benefits from many international research networks. If high-quality material (produced according to GMP guidelines) and GLP safety data are available, clinical trials might be conducted, in principle, through these international networks. Making materials and data available as open resources would facilitate this undertaking. Several initiatives have been launched to aid this process, including the Oxford University Structural Genomics Consortium, which aims to solve the structures of human proteins of medical relevance and place them into the public domain without restriction.¹⁶

Key to the goal of conducting clinical trials through international networks is the provision of internationally acceptable, high-quality nonclinical data packages and bulk investigational drugs for clinical trials. We are currently developing a new orally active, low-molecular-weight inhibitor of plasminogen activator inhibitor (PAI-1), which might offer a novel therapeutic strategy in renal and cardiovascular diseases.¹⁷ In addition to antithrombotic action,^{18,19}

this drug stimulates regeneration of bone marrow²⁰ and blood vessels,²¹ attenuates vascular senescence,²² and has antifibrotic,^{18,23} and anti-inflammatory²⁴ effects in experimental animals. This unapproved agent originates from a hit compound discovered through *in silico* techniques based on the structure of the human PAI-1 protein.¹⁸ After structural optimization, which involved the synthesis of ~540 new lead compounds, a single compound was selected for clinical development. GMP synthesis and formulation and a panel of GLP toxicological studies have been completed and, in the spring of 2013, an investigator-driven phase I clinical trial in 32 healthy men was initiated in Japan.²⁵ We are now planning an investigator-driven Phase II trial to evaluate the effect of the drug on bone marrow proliferation in myeloablated

Box 1 | Biomarkers

Biomarkers have the potential to facilitate drug discovery and clinical development in renal disease by enabling monitoring of kidney safety and evaluation of drug-induced nephrotoxicity.⁴⁴ Currently, diagnosis of nephrotoxicity is obtained using measurement of blood urea nitrogen or serum creatinine levels. However, these levels are nonspecific measures of renal function and are raised only after substantial deterioration has occurred. An urgent need exists to identify novel, early biomarkers of kidney damage for use in preclinical and clinical studies. Several potential biomarkers have been investigated; for example, urinary kidney injury molecule-1 has been identified as an early marker of proximal tubule injury in rats⁴⁵ and urinary type IV collagen has been suggested as a marker of glomerular damage in patients with glomerulonephritis.⁴⁶ The FDA and European Medicines Agency have approved a number of renal biomarkers for use in rodent drug-toxicity studies⁴⁷ but these have not yet been validated in humans.

Box 2 | Molecular imaging

Molecular imaging techniques provide valuable data for drug discovery and clinical development.⁴⁸ Direct measurement of the effect of a drug in the human body should shorten the timeline for drug development and lower its costs. Molecular imaging probes, developed to target specific molecular pathways *in vivo*, enable visualization of the phenotypic expression of key molecular targets associated with disease processes. Using these probes, early biochemical and physiological abnormalities can be identified prior to the occurrence of late structural changes that can be visualized using standard anatomic imaging techniques. Direct assessment of the sequential events involved in renal pathophysiology is difficult to obtain from analyses of blood or urine samples. Some of these events, such as renal tissue hypoxia, can now be assessed using molecular imaging techniques. For example, blood oxygen level-dependent MRI can be used to directly and quickly evaluate alterations in renal oxygen levels after an intervention.⁴⁹ Molecular imaging probes (such as 18F-fluoromisonidazole and 18F-FRP-170) taken up by hypoxic cells should prove to be even more sophisticated tools.^{50,51} Indeed, such probes have been used to detect ischaemic myocardium⁵² and renal hypoxia in rat models.^{53,54} Labelled probes might also be used to identify other disorders associated with kidney injury (such as, oxidative stress, inflammation and fibrosis) and, therefore, enable a faster process of drug discovery and approval in kidney diseases.

Box 3 | *In silico* approaches

After validation of a target molecule using biochemical, cell-based and experimental animal approaches, industry conventionally launches high-throughput studies using large chemical libraries. Academic researchers, by contrast, often use less-costly *in silico* (computer-aided) approaches to identify candidate compounds. The availability of protein tertiary structure information enables target localization and efficient computational identification of candidate compounds, SBDD or fragment-based drug design.^{55–57} Integration of detailed protein structural information, computational chemistry, medicinal chemistry and informatics enables virtual screening of new agents.^{18,58} As well as drug discovery, design and optimization, SBDD is essential to elucidate the pharmacological mechanisms of new agents.⁵⁹ This technique enabled the development of various drugs in current use in renal diseases, including direct renin inhibitors and tyrosine kinase inhibitors.

Abbreviation: SBDD, structure-based drug discovery.

patients undergoing chemotherapy and/or radiotherapy for haematological malignancies. If shown to be safe and efficacious in these patients, we plan to offer the drug to a large number of Japanese and foreign academic networks for clinical evaluation in thrombotic, inflammatory or fibrotic diseases. In addition, clinical development of the drug is underway in the USA in collaboration with Northwestern University, and a meeting has been organized with the FDA to discuss the feasibility of using our Japanese GLP data and GMP materials in US trials.

Many academic researchers, unfortunately, are unfamiliar with the latest regulations on pharmaceutical practices and novel, efficient strategies for preclinical

and clinical drug development. Scientists must collaborate with regulatory authorities for progress—to build-up experience and results. New drug development might then extend globally beyond its current reach. Initiatives to help facilitate communication between scientists and regulatory authorities include the International Society of Nephrology (ISN) Nexus symposium, ‘New era of drug discovery and clinical trials in kidney disease’, which will be held in Bergamo, Italy, in April 2014.²⁶ In the future, major pharmaceutical companies are likely to remain at the centre of drug discovery in developed countries, whereas in developing countries academia might be able to drive development in accordance with national health policies.

Remaining challenges

Noncommunicable diseases

Drug development remains challenging even for large pharmaceutical companies. Aging populations and changes in disease patterns are important issues in developing countries as well as in the developed world. The WHO has focused its efforts on non-communicable diseases (NCDs) in developing countries and currently recognizes cancer, cardiovascular disease, diabetes and chronic respiratory disease as key NCDs.²⁷ These diseases account for 60% of deaths worldwide, and 80% of deaths in low and middle-income countries.²⁷ High-quality international clinical trials leading to the eventual approval of novel, effective therapies should help to solve these problems in developing and developed countries.

Orphan diseases

At present, the problem of orphan diseases (that is, rare diseases for which industry

sees little financial incentive to develop and market new curative or preventative therapies, such as Alport syndrome) is not necessarily addressed by large pharmaceutical companies.²⁸ Academia should undertake research in this area, conduct the first-in-human studies that are necessary to attract the attention of industry and, therefore, provide a real synergy between academia and pharmaceutical companies. Regulatory systems, such as the FDA Fast Track Process, are now in place to increase the speed of drug development and expedite the availability of drugs to treat serious diseases and fill unmet medical needs (that is, providing a therapy where none exists or providing a therapy that might be potentially better than the available therapy). The aim of such systems is to make new drugs available to patients as rapidly as possible.²⁹

Healthcare in developing countries

As the economic situations and the promotion of science and technology in developing countries improves, the gap between the developed and developing world is narrowing. Governments, regulatory agencies, industry and academia in both developed and developing countries should urgently collaborate to address specific, scientific and clinical problems, including kidney disease and NCDs. Currently, major pharmaceutical companies mainly target markets in developed countries, such as the USA, European countries and Japan.³⁰ However, developing countries are experiencing an increasing demand for advanced healthcare and medicines as a result of high levels of economic growth.³⁰ This demand, coupled with improved medical technology and expanded healthcare systems, has resulted in rapid expansion of pharmaceutical markets in these countries.³¹

Dialysis for patients with ESRD is a good example of an unmet medical need currently faced by developing countries. The strategies implemented to address this need will undoubtedly differ from those used in the developed world, in which haemodialysis is the main form of renal replacement therapy (this modality is used by ~90% of Japanese patients on dialysis and ~70% of patients on dialysis worldwide).³² In contrast to developed countries, in which a gradual increase in the number of patients requiring dialysis has occurred, the number of untreated patients who require dialysis in developing countries is increasing rapidly.³² As the cost of haemodialysis-centered healthcare is prohibitive, the

governments of several developing countries are now exploring alternative options, such as peritoneal dialysis.³³ As this modality is expected to become a standard renal replacement therapy for patients with ESRD in developing countries, the development of new therapies to treat complications associated with long-term peritoneal dialysis, such as ultrafiltration failure as a result of peritoneal sclerosis, will be required.

International academic societies have an important role in promoting drug and clinical development. For example, the ISN has formed an Advisory Committee for Clinical Trials and Studies to support and raise standards in investigator-driven clinical trials in developing countries, and has initiated a number of international clinical research projects to address emerging medical problems in these countries, including altitude polycythaemia in Latin America, Mesoamerican nephropathy in Central America and haemolytic uraemic syndrome caused by *Shigella* infection in India.

Use of surrogate end points

In clinical trials, direct assessment of robust, definitive end points, such as patient survival, mortality and morbidity, is often practically and financially inefficient for both the sponsor industry and for the patients. Use of surrogate end points might provide a solution to this problem. By definition, a surrogate end point predicts and captures the effect of a drug on a true clinical end point.³⁴ Surrogate end points are useful when they are similar to but more efficient to measure than the hard clinical end point of interest. For example, in some diseases, efficacy can be represented by progression-free survival durations rather than overall survival durations. However, surrogate end points might be difficult to validate and, without practical guidelines, the choice of appropriate surrogate end point remains challenging.

The issue of surrogate end points is particularly important in the setting of kidney disease, which requires large trials with substantial human and financial resources. Currently, end points for progression of kidney disease in clinical trials include doubling of serum creatinine levels, a large decline in glomerular filtration rate (GFR), or progression to ESRD, all of which occur late in the course of CKD. Use of these well-accepted end points might, therefore, result in exclusion of patients with earlier stages of kidney disease from clinical trials, although early treatment might prove more efficacious

and cost-effective in this population than in patients with more-severe disease.

Alternatively, use of small changes in estimated (e)GFR as a surrogate end point for progression of kidney disease might increase the number of patients who reach end points in clinical trials and, therefore, enable a reduction in the number of patients or length of follow-up required to demonstrate a statistically significant effect. A *post hoc* analysis of the RENAAL and IDNT trials, which evaluated the efficacy of the angiotensin receptor blockers alosartan and irbesartan in a total of 3,228 adult patients with type 2 diabetes mellitus and nephropathy, demonstrated that use of declines in eGFR that represent increases in serum creatinine levels of <100% (that is, less than doubling) as clinical trial end points might not improve statistical power, particularly if the drugs exert acute effects on GFR (as do angiotensin receptor blockers).³⁵ However, different conclusions might be reached in different populations using different drugs.

The identification of specific patient populations in which use of surrogate end points rather than hard end points might be appropriate, remains important for drug development. The validity of appropriate surrogate end points should, therefore, be established scientifically and statistically, hopefully as a result of adequate collaboration between regulatory agencies, academia and industry.

Assessment of benefits and risks

The risks and benefits of new treatments should be assessed in patients. For example, the prognosis of patients diagnosed with pancreatic cancer remains poor. As the survival of patients with this disease is low, a large sample size with survival as the clinical end point is required to demonstrate a drug benefit. Such an evaluation of efficacy ignores a possible improvement in patient quality of life. An industry sponsor, therefore, proposed use of a clinically relevant end point of quality of life assessed using weight, pain killer usage, maintenance of disease status and pain. A clinical trial of gemcitabine in 126 patients with advanced pancreatic cancer that used this end point showed that treatment resulted in a better quality of life and longer survival.³⁶ The sensitivity of the study might have depended on any component of the chosen end point but statistical reviewers at the FDA, conducting sensitivity analyses, confirmed that each component provided

benefit and the data based on the newly defined clinical benefit variable were robust.

Despite their limitations, use of surrogate end points might be necessary to expedite drug approval with an attendant increase in patient benefits. Rigorous application of a definitive end point might sometimes result in depriving a subgroup population (for example patients with early stages of kidney disease) of a useful treatment. The example of gemcitabine illustrates that the sponsor might not have developed the drug if only a robust end point had been considered. Surrogate markers should, therefore, occasionally be taken into consideration for drug approval in view of the potential benefits for patients.

The respective roles of academia and industry sponsors in the assessment of the risks and benefits of new drugs should be clearly delineated. Collaboration between academia, industry and regulatory agencies is necessary to efficiently and effectively maximize the benefits and minimize the risks of new agents.

The Japanese framework

To stimulate closer collaboration between academia, regulatory authorities and experts, the Japanese government and regulatory authority introduced initiatives to accelerate registration of innovative drugs, medical devices and cellular and tissue-based products. Although these initiatives have not yet yielded reliable results, they are expected to boost collaborations between academia and regulatory agencies in Japan.

Consultation

The wealth of basic research conducted by academia in Japan is recognized worldwide. However, the country lags behind other developed nations, including the USA and countries in the European Union, in the translation of basic research into practical products such as new drugs or medical devices. Many obstacles, particularly budget shortfalls, insufficient knowledge of regulatory systems, and poor development strategies result in attrition of potential therapies. Researchers involved in the approval of innovative drugs and medical devices should, therefore, be fully aware of the regulatory requirements stipulated in the Japanese Pharmaceutical Affairs Law.³⁷

In July 2011, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan launched a consultation system called Pharmaceutical Affairs Consultation on Research and Development Strategy

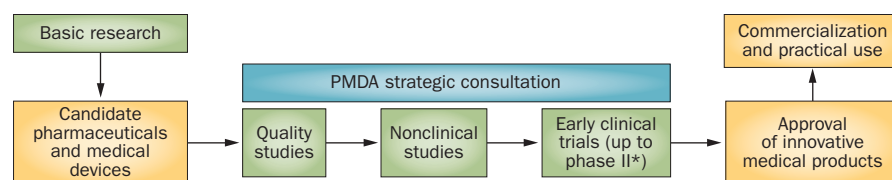


Figure 2 | The PMDA Pharmaceutical Affairs Consultation on Research and Development Strategy. This Japanese system was launched by the PMDA to foster the creation of innovative medical products by academia and venture businesses by providing guidance on the tests needed in the early development stages (that is, quality and toxicity studies of biologics, cell-based and tissue-based products) and the design of the clinical trials (that is, end points and sample sizes) required to enable commercialization of these products. *Further studies are handled by the conventional PMDA consultation system. Abbreviation: PMDA, Pharmaceuticals and Medical Devices Agency. Permission obtained from PMDA.

(Figure 2).³⁸ This system offers guidance and advice to academic researchers on the design of nonclinical and early-stage clinical studies, which conform to pharmaceutical regulations, and ultimately determine the approval of submissions. Applicants are strongly recommended to take part in a free introductory consultation, which explains the procedures of the consultation system and the Japanese pharmaceutical system. Those researchers who are already familiar with these procedures can omit the introductory consultation and address relevant issues identified in a free pre-consultation. Finally, scientific discussions are conducted in a face-to-face consultation session. As of the end of December 2013, PMDA had conducted 600 introductory consultations, 669 pre-consultations, and 158 face-to-face consultations.³⁹ This assistance is expected to provide new, safe and effective strategies for drug development, eventually leading to the approval of innovative products.

The Science Board

In May 2012, the Science Board was launched by the PMDA with the aim of strengthening its scientific foundation. The Board is connected to PMDA through the Office of Review Innovation (Figure 3). Through discussions with PMDA review officers, the Board intends to establish evaluation methods for state-of-the-art technologies at all stages, from basic technology to developmental support, application review, and post-marketing authorization.⁴⁰ The Science Board includes experts from academia, most of whom are leaders in their field who are involved in the development of medical products. To foster transparency, no individual products are discussed by the Board and statements on possible conflicts of interest of Board members are open to the public. Meetings of the Board are closed to the public because agenda items and data might be confidential but, with the exception of

confidential information, all materials and meeting minutes are released on the PMDA website.⁴¹

The Science Board is made up of four subcommittees: the Pharmaceuticals & Bio-Products subcommittees discuss issues related to biomarkers, the Medical Devices subcommittee is concerned with the scope of generic medical devices and the development of combination products, and the Cellular & Tissue-Based Products subcommittee discusses how to ensure the quality and safety of cell-based and tissue-based products, particularly with regard to tumourigenicity. Each subcommittee also addresses subjects in its area of expertise, put forward by the PMDA and experts on the Science Board. PMDA reviewers and experts, fully informed on the new technologies, discuss opinions from relevant PMDA offices on evaluation methods and provide appropriate consultation, advice and reviews during the application process. If needed, the subcommittees also invite outside experts to discuss the issue at hand. Eventually, a list of discussion topics is reported to PMDA by the Science Board.

Exchange of human resources

MHLW launched 21 new collaborative projects in the 2012 fiscal year and a further three projects in the 2013 fiscal year.⁴² These projects involve PMDA, the National Institute of Health Sciences and academia. PMDA implements exchanges of human resources with universities and research institutions under the Initiative for Accelerating Regulatory Science Concerning Innovative Drugs, Medical Devices, and Regenerative Medicine, which was launched by MHLW on 1 October 2012.⁴³ This initiative should satisfy regulatory requirements to facilitate the research and development of innovative drugs, medical devices and biologics. Synergies between those activities are expected to make a global contribution by bringing innovative products to market.

Conclusions

The tedious and expensive path to the approval of new drugs and medical devices curbs innovation in developed and developing countries. Fortunately, new technologies for drug discovery and clinical development are now available (including *in silico* approaches and molecular imaging techniques) and drug efficacy can be documented in investigator-driven clinical trials. Evaluation of the efficacy of a new drug currently relies on difficult to reach hard end

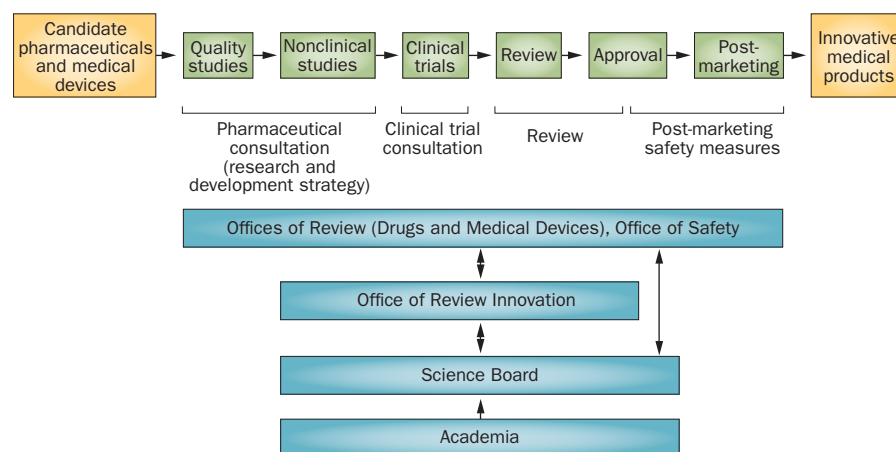


Figure 3 | The role of the Science Board in the regulation of drug discovery in Japan. Through discussions with the Office of Review Innovation of the PMDA, the Science Board aims to establish evaluation methods for state-of-the-art technologies at all stages, from basic technology to post-marketing authorization safety guidelines. Board members are external experts from academia. Abbreviation: PMDA, Pharmaceuticals and Medical Devices Agency. Permission obtained from PMDA.

points, such as overall survival, mortality and or morbidity. Use of surrogate end points might enable a quicker evaluation of efficacy but these have not been validated in kidney diseases. Regulatory agencies are keenly aware of the current problems in drug development and have shown readiness to adapt their requirements. For example, the Japanese regulatory authorities provide a novel, thoroughly delineated framework which promotes collaboration with academia. In the future, regulatory agencies, industry and academia must collaborate closely to enable new drug development to extend globally beyond its current reach.

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Author contributions

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