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The Regulation of Companion Diagnostics: A Global Perspective

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Abstract

The emerging trend of validated biomarkers, otherwise known as companion diagnostics (CDx), is playing a key role in helping pharmaceutical companies acquire rapid regulatory approval of their targeted therapeutics while saving on development time and costs. In today's challenging regulatory arena, diagnostics-led treatment can improve the reimbursement and market access for drugs. All of this has prompted research in the use of such biomarkers with targeted therapeutics for predicting response to therapy, hence beginning the revolution of personalized medicine. With the current target area being oncology, other therapeutic areas are also now being explored. As an increasing number of pharmaceutical firms are penetrating the CDx arena and looking to partner with diagnostics developers, this does not come without its challenges. The codevelopment process is complex, and many hurdles may need to be crossed before a perfect model can be achieved. To add further to the complexity, the global regulatory landscape for CDx is in a state of flux, making it extremely challenging for industry to keep up with the increasing demands of the regulators. This article provides an overview of the changing regulatory landscape for CDx in some of these key markets and an insight to deal with the challenges associated with developing a successful global regulatory strategy for a CDx product. The views presented in this article are mainly from a diagnostics perspective.

Keywords

companion diagnostics, personalized medicine, drug diagnostic codevelopment, global, reimbursement, regulation

The health care industry has played a very powerful role in improving people's quality of life. A few centuries ago, an average person had a life span of 30 years; today, most people are exceeding 80, thanks to the advancements in modern medicine. Despite how well medicine has fared in the past few decades, however, some challenges still remain. Since the introduction of modern medicines, scientists and clinicians have wondered why the same drug can be effective in one person but not in another or why some people suffer side effects from certain medication but others do not.

Furthermore, different types of drugs have different efficacy rates. Figure 1 depicts the efficacy rates of drugs in some key therapeutic areas. It can be seen that analgesics can have an efficacy rate as high as 80%, whereas cancer or Alzheimer drugs can be as low as 20% to 30%.[1] As a result, millions of dollars are wasted when valuable drugs do not work on patients and also result in many unpleasant side effects.

To date, most physicians have been practicing "intuitive" medicine whereby they use their clinical judgment to select treatment based on a patient's symptoms. Conventional medicine simply does not take into account a person's genetic characteristics and personal disposition. Over the past couple of decades, advancements in genetics, pharmacodynamics, and other related disciplines have brought about the realization that genetic variations are the probable cause of such a phenomenon. With this realization came the recognition that if patients with a specific genotype can be identified, it may be possible to treat them with medication that would work on them and avoid treating them with drugs that would unnecessarily cause side effects, without resulting in any particular benefit. This has defined the new model for modern medicine, causing doctors to transition to "precision" medicine in which the biological and genetic elements unique to each person and their disease will dictate the most accurate diagnosis. The right diagnosis will lead to the right treatment.[2] This has the potential to improve patient care, while at the same time reducing costs to the health care system.

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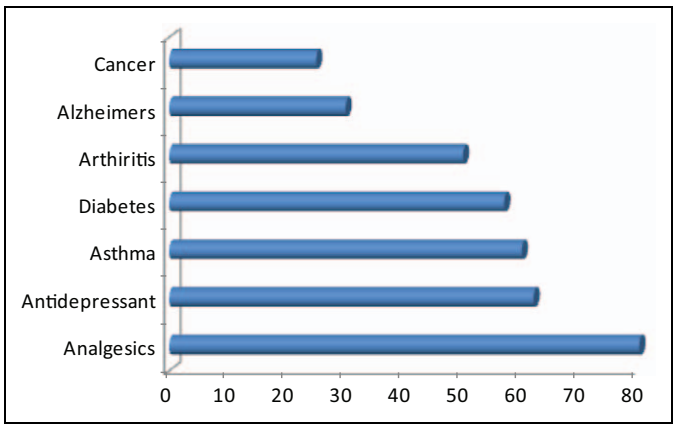

Figure 1. Drug effectiveness in percentages versus various therapeutic areas.[1]

Thus has begun the era of personalized medicine. Recognized by various other names ranging from "personalized health care" and "personalized group treatment" to "stratified medicine" and "precision medicine," some believe that perhaps the term "stratified medicine" better reflects this practice of stratifying groups of patients in terms of their likely response to drug therapy. Regardless of what it is called, this new model of treating patients is now becoming a popular practice in modern medicine. It may be worth noting that in the past 5 years, there has been a 75% increase in investment in personalized medicine.[3] Companion diagnostics (CDx), in vitro diagnostic tests that are intended to predict which patients are most likely to benefit from a particular drug therapy and to assist in the clinical decision on what constitutes the "right drug" for each patient, today stand at the heart of personalized medicine. As per the name, CDx are typically codeveloped and approved alongside the corresponding drug therapy in partnership with a pharmaceutical company, although this practice may vary based on the different regulatory frameworks across the world. Nonetheless, it is indeed when drug and diagnostics companies align that personalized medicine becomes a reality.

CDx benefit the pharmaceutical industry by reducing drug development from 10 to 12 years to 5 to 7 years and by shrinking overall development costs from around US$1 billion to less than US$500 million, as a select target patient population can be used in testing to provide more accurate clinical trial results. Oncology is particularly an area of concern due to high development costs, extremely low efficacy rates, and unpleasant side effects of cancer therapies. Developments in molecular biology have led to the discovery of new biomarkers for oncology treatment. Each day, we learn more about the biology of cancer and how genetic mutations in cancer cells cause them to grow and spread. Meanwhile, industry is under increasing pressure from regulatory bodies to provide more credible clinical results for expensive cancer drug therapies, and CDx can offer a higher probability of better treatments.[4] The increased understanding of cancer's complexity coupled with the understanding of CDx development, albeit challenging, is driving many companies in the area of personalized medicine within oncology. In fact, statistics show that of a total of 16 CDx approvals by the US Food and Drug Administration (FDA) in recent years, all of them have been for cancer therapy.[5] It has been predicted that if current trends continue, within 10 years, nearly all oncology drugs can have a related diagnostic.[6]

Unfortunately, the drug diagnostic codevelopment process does not come without its challenges, and many hurdles may need to be crossed before a perfect model can be achieved. Pharmaceutical companies that partner with a CDx developer to codevelop and commercialize a diagnostic need to account for the fact that the 2 partners have completely different business models based on different development platforms that employ different technologies. The good news is that with increasing awareness and experience in the area, industry is becoming wary of such problems and is becoming better equipped to deal with these for future products and partnerships. The bad news is that regulators may not be that forgiving. The diagnostics development process is regulatory driven under design control and other aspects of compliance. Yet, the global regulatory climate for CDx is in a constant state of flux, and regulatory bodies are still struggling to understand the technology before a solid regulatory framework can materialize in many markets. With more and more companies seeking to become global leaders in personalized medicine, a deeper understanding and appreciation of the complexity of rapidly changing regulatory frameworks are required. This article will focus on the regulatory framework for CDx in some key markets and the challenges in developing a global regulatory strategy in partnership between a diagnostics and drug company.

United States

The US, in addition to its large geographical area, is one of the world's largest economies. With a gross domestic product (GDP) of US$18.9 trillion, it had been deduced that the US spends more on health care than any other economically developed country.[7] The emergence of personalized medicine is introducing drugs into the health care system that target the patient population they are more likely to work on, thus reducing drug wastage and side effects. This is expected to cut down the health care costs significantly. For instance, it has been predicted that routine use of KRAS mutational testing in colorectal cancer patients should save the health care system more than US$600 million in drug costs alone.[8]

The FDA's Office of In Vitro Diagnostics and Radiological Health maintains that CDx carry the same risk profile as the

drug itself. Because they are intended to ensure that certain therapeutic products are used in accordance with their labeling to achieve approved safety and effectiveness, proper use of the diagnostic is critical to the proper use of the drug. Due to this reason, they are generally classified as class III devices of the highest risk in the US and require premarket approval (PMA). After months of discussions on personalized medicine and the use of CDx with targeted therapeutics, the much-anticipated draft of the FDA guidance document on in vitro CDx was finally released by the agency for comments in July 2011.[9] The 2 most important points made by the guidance are the following:

- The FDA states that any CDx product is an "in vitro diagnostic device." This is significant, as it means that the CDx must be approved or cleared by the agency before commercialization, which requires that diagnostics developers comply with the FDA Code of Federal Regulations (CFR), including 21 CFR 820,[10] which pertains to the quality system regulation for medical devices.
- If the CDx are going to be used in a clinical trial to modify the treatment of a patient, or include or exclude patients from the trial, then the diagnostic device generally will be considered a "significant risk device" under 21 CFR 812.3(m)(3),[10] and the sponsor must submit an "investigational device exemption" (IDE) and obtain approval before the use of an "investigational use only" (IUO) device in the clinical study. The implications of this statement are that the putative CDx product will be expected to have certain analytical performance data available before it can be used to make treatment decisions for patients included in the trial.

Once the IDE has been submitted, 4 essential requirements must be addressed to permit FDA approval of the CDx in parallel with the drug:

1. Analytical validation data for the final device.
2. A robust manufacturing process for the final device.
3. Data to support the clinical utility of the final device: If any changes are made between the IUO device and the final CDx device, a bridging study must be performed using samples retained from the original study to ensure concordance between the IUO and the final version of the device.
4. A successful preapproval inspection of the manufacturing site regardless of where the site is located.

While the draft guidance has been a good starting point, there are issues that still remain unaddressed, and it is hoped that the final guidance will cover these. Some of these issues that would benefit from more details are as follows:

- Drug diagnostic codevelopment process: While the guidance reinforces that collaborating with the FDA is critical throughout development and encourages the pre-IDE process (now known as the Pre-Sub program as explained below) for which clear guidelines are available by the FDA,[11] the unique nature of a CDx product and drug codevelopment calls for more guidance in this specific area. For instance, the CDx guidance document does not go into much detail regarding the interaction of the Center of Biologics Evaluation and Research (CBER)/Center of Drug Evaluation and Research (CDER) and the Center of Devices and Radiological Health (CDRH) with one another as well as with the diagnostics and pharma partner. All CDx approvals in the US, to date, have occurred on a case-by-case basis, and industry is requesting further guidance from the FDA that describes the process and the timelines for this codevelopment interaction in more detail.
- Analytical validation.
- Clinical validation requirements, especially any nuances between retrospective and prospective studies.
- When a CDx product can be a PMA versus a 510(k). Note: To date, all CDx products have required PMAs.

The good news is that the FDA recently released a draft guidance on the presubmission or Pre-Sub program for medical/in vitro diagnostic (IVD) devices, which replaces the pre-IDE concept while making the scope broader than before. The draft guidance encourages sponsors to obtain early feedback on specific questions during the submission preparation stage and to familiarize the FDA review team with the technology in advance of the submission. The guidance reinforces that this would be especially useful for IVD devices that contain new technology, a new intended use, a new analyte, new clinical questions, complex data/statistical questions, and/or where the predicate or the reference method is unclear or uncertain.[11] All these initiatives are very helpful, but industry continues to hold its breath for the final CDx codevelopment guidance to be released by the agency.

In 2010, at the Sixth Annual Keynote Luncheon Address on the State of Personalized Medicine for the Personalized Medicine Coalition, the FDA's commissioner, Dr Margaret Hamburg, explained the FDA's plans for personalized medicine by stating that the FDA will "hone its regulatory approach to adapt to the emerging science of personalized medicine," "form critical interagency collaborations," and "make its processes more transparent."[12]

Regardless of the current challenges, FDA premarket work is being performed in a highly transparent manner, and with the FDA's top staff such as Dr Margaret Hamburg and Dr Stephen Spielberg having a personal interest in personalized medicine, CDx have a bright future in the US.

Japan

With the second largest economy in the world, the country of Japan has a land mass slightly smaller than that of California.[13] Japan has become one of the most medically advanced nations in the world. The total health expenditure (% of GDP) in Japan was last reported at 9.49 in 2010, according to a World Bank report published in 2012.[14] Japan, with the second largest medical device market in the world, is also considered to have the most complex and restrictive regulatory system. At the heart of this system is the Ministry of Health, Labor and Welfare (MHLW),[15] a Japanese government organization responsible for ensuring good living standards among the residents of Japan and for promoting the development of new health programs and innovation to improve current living standards. The Pharmaceutical and Food Safety Bureau is integrated within the organizational structure of the MHLW and is responsible for pharmaceutical and medical device regulatory policy making. The system regulating pharmaceutical products and medical devices in Japan was originally established in 1950. The new Pharmaceutical Affairs Law (PAL)[16] went into effect on April 1, 2005, and the Pharmaceuticals and Medical Device Agency (PMDA)[16] was formed in April 2004 to exercise the PAL for the regulation of medical devices and pharmaceutical products in Japan. The changes take the new PAL towards global harmonization with the introduction of the Summary Technical Documentation (STED) and further details for registering medical devices in Japan.

Personalized health care has become the second largest market in Japan after the US, and the PMDA, like the FDA, has a personal interest in this area and in introducing new CDx into the Japanese health care system. CDx are regulated as high-risk class III devices by the PMDA and require a *shonin*, a term for the approval granted per product based on evidence of testing and clinical trials that prove the product's quality, safety, and efficacy. For any foreign CDx developer looking to register its product(s) in Japan, a marketing authorization holder (MAH)[17] must be appointed in Japan. The appointment of the MAH means that the foreign manufacturer will only be responsible for the manufacture of the medical device, while the MAH will be responsible for the release of the products into the Japanese market place and communication with the MHLW. This may be a distributor or importer or a third-party designate; however, the safest means for a company, if possible, is to establish a local branch, subsidiary, or a representative office. Yet, in any case, it must be ensured that all conditions of a MAH are adhered to.

The 3 conditions of the MAH require it to be based in Japan, formally licensed by the MHLW, and employ at least 3 staff members. These staff members are a general controller, quality controller, and safety controller. The general controller is responsible for the shipment of products in the market, the quality controller is responsible for quality assurance control, and the safety controller is responsible for safety and vigilance activities. An MAH has far more legal, logistical, and regulatory responsibilities than an EU-authorized representative or US agent for the FDA and therefore must be selected very carefully.

Japan's Quality Management System Ministerial Ordinance 169[18] is similar to International Organization for Standardization (ISO) 13485 and FDA's Quality System 21 CFR 820; however, there are some minor differences that must not be discounted. Some of these are specific time periods for the retention of documentation, requirement for the engineering manager to be the management representative (whereas in ISO 13485, it can be anyone), and some additional requirements for facilities and infrastructure. An on-site inspection of an MAH, which includes a paper audit of the foreign manufacturer, is conducted. If the PMDA is not satisfied—a condition that depends on the capability of the MAHs, their quality system, how well they understand the product, and how good the dossier is—it may conduct an on-site inspection of the foreign manufacturer as well, at a cost of about US$12,000.

The PMDA has specific requirements for analytical validation, which include sensitivity, accuracy, and reproducibility, but it also requires a correlation study with a Japanese standard, which may not always be Sanger sequencing. Stability requires real-time and transport simulation, with a minimum expiration of 6 months. Developers of CDx may qualify for a priority review, and a specific strategy can only be decided after meeting with the PDMA; therefore, early consultations are encouraged.

The PMDA is looking to develop and align its CDx regulation to make it similar to the FDA's drug diagnostic codevelopment model and is currently in the process of developing a guidance document. Yet, there are opinions within the Japanese pharmaceutical industry that in comparison with FDA's draft guidance, which encourages prospective trials for contemporaneous codevelopment, the European Medicines Agency (EMA) guidance draft, which supports retrospective studies according to need, is more "practical and realistic." Regardless of how this is going to be developed, it will be interesting to see how the new regulatory framework for CDx in Japan pans out over the next few years.

China

China has become one of the most attractive markets for Western businesses in recent years. With its huge health care market and strong economic growth, China presents an attractive prospect for diagnostics firms. In 2011, investment in China's medical and health care industry reached a record US$3.5 billion, 2.7 times more than the total amount over the whole of 2010. China's

medical device market has grown to US$6 billion, making it the second largest in Asia after Japan. An aging population and rising individual incomes have increased the demand for medical and health care products and services.[19] The Chinese government has backed the concept of personalized medicine; however, there is an obvious but nonetheless important point: a CDx developer must understand China's medical device registration requirements to sell in China. This is no easy task, as China's regulatory framework is complex and cumbersome.

The regulatory arena for medical devices in China has been subject to a great deal of change in the past few years. This change started in 2002 with the revision of regulations[20] and the restructuring of the China Food and Drug Administration (CFDA), formerly known as the State Food and Drug Administration.[21] The CFDA is responsible for the regulation of pharmaceuticals, food, nutritionals, and medical devices in China. An important part of this change has been to raise the quality of the regulatory framework in China, introducing new procedures such as stricter monitoring of medical device factories, curtailing corruption, and improving the CFDA's overall efficiency. Medical devices in China follow the risk-based classification system, with class III being the highest risk.

The CFDA regulates CDx as class III IVD devices.[22] Being devices with the highest risk, these are subject to strict premarket scrutiny. A condition for foreign manufacturers looking to register in China is the appointment of a local agent, who must have a valid license and a letter of commission from the manufacturer. The local agent also serves as a liaison for the foreign manufacturer in regards to dealings with the CFDA. A class III dossier is required to be submitted to the Beijing office of the CFDA, which reviews the applications for all class III devices (local and foreign) and all classes of foreign devices. This office is known to be much stricter than other provincial offices of the CFDA, such as the Shanghai office, and is responsible for reviewing CDx submissions. The dossier requires data on foreign and local clinical trials. The local requirements are very strict and require a category III trial to be conducted at 3 CFDA-accredited clinical trial sites within mainland China. The sample size needs to be negotiated with the CFDA, and a correlation with the gold standard, normally bidirectional sequencing, is a must. A very critical component of a Chinese registration is type testing. This is when an engineer from a CFDA-accredited laboratory repeats some of the analytical validation studies conducted by the manufacturer to confirm that claims being made on the performance characteristics of the CDx test kit are accurate. While this process can take from 2 to 6 months, failure rates can be high so it is important that the manufacturer accounts for such unprecedented delays in the launch timelines.

The registration is valid for 4 years; 6 months before the expiration period, a new dossier needs to be submitted to the CFDA with any changes that may have occurred over the course of the device registration period.[23] The good news is that new clinical trial data are not required, but the bad news is that type testing must be repeated. Chinese registration can be costly and time consuming, and the entire process, which covers clinical trials, type testing, preparation, and review of the submission from inception to approval, can take up to 2.5 years and cost over US$2 million. In addition, with copyright issues in China, companies really must think twice about company proprietary information that they are sharing with their local agent (if not the company's local branch) and the CFDA, and decide whether the risks and costs entailed are worth the benefits in long-term investment in the country.

Canada

Canada is the world's second largest country, with an area of 9,984,670 km^2 and a population of only 34.5 million people. There are 1500 Canadian medical device firms with 35,000 employees. While there is not much focus on the development of CDx in Canada from the private sector at present, the Government of Quebec and various private companies are planning to invest $21.1 million in a public-private partnership to focus on clinical biomarkers and other personalized health care solutions within oncology over a 4-year period.[24] There is also an increased interest from foreign manufacturers in selling their CDx in Canada. Health Canada,[25] Canada's federal body that enforces the food and drug regulations, also controls the importation and production of food, drugs, cosmetics, medical devices, and natural health products in Canada.[26] As per Rule 4 of Health Canada's risk-based classification system,[27] IVD devices intended to be used for genetic testing are classified as class III: moderate public health risk or high individual risk. Therefore, CDx are regulated as class III IVD devices by Health Canada. At present, a license application for a class III medical device is required to be submitted to Health Canada, but this is expected to change in the near future as Health Canada will soon mandate applications in the STED format. Although this requirement was already mandated for medical devices in November 2011, for IVD devices, the draft guidance for the "Preparation of Summary Technical Document (STED)–based Class III and IV Premarket In Vitro Diagnostic Device Licence Applications and Amendments"[28] recently opened for public comment. Once final, this is meant to replace the 1998 "Guidance for Manufacturers in Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications V.2."[29]

It is difficult to predict at this point to what extent Health Canada will change this guidance when it is made final, but it appears that this is going to be a very structured submission in a modular format. There will be 2 modules to this submission. Module 1 will contain administrative and other Health Canada–required specific information. Module 2 will follow the Global

Harmonization Task Force (GHTF) IVD STED Guidance[30] format, and references are made to the GHTF IVD STED Guidance for many sections. Similar to the 1998 guidance, there is no requirement to provide any detailed information on the manufacturing process, but a list of manufacturing sites should be provided. However, while there was no mandatory clinical requirement in the past (even though experience has showed a clinical study certainly worked in favor of the applicant), now Health Canada will require a clinical (correlation) study against a Canadian-approved reference standard conducted with samples representative of the specific population.[28] Health Canada also has very specific requirements for labeling, and a copy of the draft labeling must be submitted for review in the application package. Manufacturers of CDx are required to implement quality systems compliant with ISO 13485. This requires an audit by a registrar accredited under the Canadian Medical Devices Conformity Assessment Scheme (CMDCAS)[31] by Health Canada.

Health Canada has established a Health Portfolio Working Group on personalized medicine, mandated to conduct a comprehensive policy analysis on personalized medicine. Activities that Health Canada has been involved in so far include the Pharmacogenomics Guidance document,[32] participation in CHE-15 and E-16 initiatives, and regulatory modernization. Health Canada recognizes that there is a need to ensure that there is a coordinated approach that protects and promotes the health of Canadians, while maximizing the advantages offered by personalized medicine.[33]

European Union

The European in vitro diagnostics landscape is presently in a state of turmoil. With the current in vitro diagnostics Directive 98/72/EC[34] under revision, it is anticipated that it would be sometime after 2014 before the new directive can be enforced. Under the current directive, the regulatory requirements for Conformité Européenne (CE) marking of CDx are minimal. They are not addressed in the list of devices in Annex A and B and are therefore only required to be self-certified. That basically means that conformity assessment procedures are required by the manufacturer in the form of in-house technical documentation and a declaration of conformity but without any notified body intervention. It is, however, mandatory for manufacturers to implement an ISO 13485 quality system. Because the bar for the regulation of CDx is very low in the EU compared to other key markets, competent authorities and other stakeholders have been raising their concerns.

In June to September of 2010, the European Commission launched a public consultation on the technical aspects of the revision of Directive 98/79/EC in which a question regarding the regulation of CDx was posed. The proposal[35] for the new regulation of in vitro diagnostics in the EU introduces a new risk-based classification system, built on the GHTF principles.[36] Under the new classification system, IVD devices will be divided into 4 classes of risk: A (lowest risk), B, C, and D (highest risk). Companion diagnostics have been specifically addressed in this proposal, and it is proposed that they will be regulated under Rule 3 as class C IVD devices, which means that they will now require notified body intervention for a quality management system as well as technical documentation. The different conformity assessment procedures will also be tightened and streamlined. This includes additional controls for clinical and postmarket surveillance requirements. For CDx intended to be used to assess patient eligibility to a treatment with a therapeutic product, the notified body will be consulted for issuing a design examination certificate on the basis of a draft summary of safety and performance and draft instructions for use. The opinion of the European Medicines Agency (EMA)[37] or competent authorities is also likely to be considered in this process.

Although the European Commission is raising the bar much higher than it has been, if not equivalent, to the US FDA, the new legislation will also require more interaction between the EMA and the notified body in the review and approval process of a CDx product. It is imperative that CDx manufacturers study these new requirements in detail so that they are prepared well in advance and in good shape when the new regulation is implemented.

See Table 1 for a comparison of key market requirements for CDx.

Rest of the World: Is There Such a Thing as a *Global* Regulation for CDx?

While the regulation of CDx varies greatly from country to country, one thing is a given: the regulations are getting more stringent, complicated, and structured with time. Many countries such as Australia, Singapore, and South Korea that had minimal or no regulations for IVD devices until a few years ago and readily accepted CE-marked or FDA-approved devices without any local preapproval requirements have developed new regulatory frameworks only within the last couple of years. These new regulations require CDx applications to be submitted under the STED format as class C (high individual risk) devices defined by the GHTF. The Australian Therapeutic Goods Authority (TGA) has given a 4-year transition period to companies to re-register any existing IVD devices in the Australian market. South Korea requires all IVD devices to be registered under its new regulations by the end of 2012. Singapore and Saudi Arabia mandated premarket registration at the end of 2011.

Several countries follow the GHTF (now International Medical Device Regulators Forum [IMDRF]) risk classification

Table 1. Comparison for key market requirements.

	US	Japan	EU	Canada	China
Regulatory body	FDA	PMDA	Competent authority based on legal manufacturer's physical location	Health Canada–Therapeutics Products Directorate	CFDA
Local agent for foreign manufacturers	US agent	Marketing authorization holder	Authorized representative	Not required	Appointed agent
Class	III	III	Self-certification, non-Annex A/B	III	III
Application	Premarket approval application	*Shonin*	Technical documentation	Medical device license application	Class III dossier
Compliance	Quality system regulation (21 CFR 820)	MHLW Ministerial Ordinance 169	ISO 13485	ISO 13485, CMDCAS	Certificate issued to the manufacturer by the authority in the country (region) of origin of the medical device
Performance evaluation	✓	✓	✓	✓	✓
Clinical trial	✓	✓	×	✓	✓
Review time	180 days	1-1.5 years	No notified body review presently	6-9 months	1 year

FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Device Agency; CFDA, China Food and Drug Administration; CFR, Code of Federal Regulations; MHLW, Ministry of Health, Labor and Welfare; IVD, in vitro diagnostic; ISO, International Organization for Standardization; CMDCAS, Canadian Medical Devices Conformity Assessment Scheme.

guidelines for CDx that may be translated into their local regulations. Others such as South Africa and New Zealand lack a premarket approval process at this time (although new frameworks are currently under consideration, with South Africa's expected to be implemented later in 2013). Mexico, which has a very cumbersome process that lacks transparency, has developed a new accelerated mechanism that allows manufacturers that have approval in Canada, the US, or Japan to apply. India gives preference to CDx products that have prior US or Japanese approvals. The Australian TGA prefers to review devices that already have the Canadian medical device license (and manufacturers have an ISO 13485 quality management system qualified under the CMDCAS). Therefore, although there is no such thing as one global regulation for CDx, securing approvals in key markets makes it easier to get approvals in other markets.

Vigilance Issues for CDx

Vigilance in the world of personalized medicine is not a very transparent process at this time. In markets such as Mexico or the EU where CDx have not yet been formally connected with a targeted therapeutic, reporting requirements for regular in vitro diagnostics apply, for example, MEDDEV 2.12-1 in the EU[38] or GHTF SG2-N008R4.[39] For countries such as the US or Japan, which is likely to follow the FDA's footsteps in regulating these with the drug therapy, this can be a more complicated process. An adverse event could be the result of one of the following reasons: (1) an erroneous test result due to device failure may result in delayed treatment; (2) physician negligence in not correctly following the drug labeling and therefore not referring to the test results for treatment decisions; (3) misdiagnosis based on a *false-positive* result whereby a patient has to suffer from side effects but does not benefit from the therapy or whereby a patient is not given the drug when he or she could have benefited from it, *depending on the nature of the biomarker*; or (4) misdiagnosis based on a *false-negative* result whereby a patient has to suffer from side effects but does not benefit from the therapy or whereby a patient is not given the drug when he or she could have benefited from it, *depending on the nature of the biomarker*.

This is where the pharmaceutical company and the diagnostics company need to work very closely together to determine whether the cause of the adverse event is a physician/pathologist error, an issue with the drug's safety and effectiveness, or a failure of the CDx test kit. In the US, in the future, vigilance for CDx may be improved by the use of electronic health records and the new proposed rule to require that all devices have a unique device identifier (UDI).[40] The UDI "will contain 2 types of information: the device identifier, a unique numerical or alphanumerical code specific to the version or model of a

device; and a production identifier, including the specific lot or serial number and expiration date of the device. The UDI will be presented on the label of a device in some form of automatic identification and data capture technology, such as a barcode or radiofrequency identification tag."[41] The IMDRF also recently released a major guidance outlining the UDI framework for medical devices and IVD devices.[42]

However, due to the unique involvement of both the drug and the diagnostic, thorough investigations are required, and appropriate procedures should be in place to ensure these are performed correctly. All relevant staff should be aware and appropriately trained on these procedures. It may be that based on the outcome of the investigation, the diagnostics company as well as the pharma partner may have to report separately to the respective FDA centers, namely, the CDER or CBER and the CDRH, respectively.

Reimbursement Challenges: Alignment of Development and Commercialization

The transition from development to commercialization is another challenge. Obtaining regulatory authority approval does not necessarily clear an assay's path to the market. Unlike in the pharmaceutical industry in which reimbursement is value based, diagnostics testing is usually reimbursed on a cost basis relative to the procedural (Current Procedural Terminology) codes used for that particular assay.[43] Yet, due to the nature of the codevelopment model in personalized medicine, coverage of the targeted therapeutic demands diagnostics coverage, and payers are starting to ask drug developers if they considered a biomarker in their development process. Generally, payers do not cover a test until there is demonstrated clinical utility. Yet, generating evidence of clinical utility, especially in different ethnic populations, is a major challenge for ensuring the clinical adoption of valuable diagnostics.[44] Limited or unclear reimbursement of CDx in key countries has become an important issue for routine testing uptake. In the US, the Centers for Medicare and Medicaid Services and its contractor Palmetto GBA (Augusta, Georgia) are in the process of transitioning stack coding to unique reimbursement or Z-Codes per biomarker within tier 1 or a larger group of biomarkers within tier 2. Palmetto GBA's introduction of Z-Codes is to establish a value-based reimbursement price for each molecular diagnostic based on the impact that it has on health care costs and patient outcome.[45] Yet, the recent communication by Palmetto GBA of preliminary results of average reimbursement levels per payer indicates a decisive reduction of the total reimbursement level of CDx. This causes serious concerns within the drug and diagnostics industry. Another hurdle to overcome is the financial incentive for laboratories to continue using their low-cost laboratory-developed tests, which can lead to a dislink between the approved assay and test technologies used for routine testing after approval. The situation is similar in Japan, as reimbursement for CDx is given, but the first approved tests are hardly used in routine testing for financial reasons. Reimbursement in Europe differs from country to country, for example, stack coding in Germany, limitation of the total number of reimbursed tests per disease in the UK, or no reimbursement for CDx existing in Spain. In emerging countries such as China, India, or Brazil, no reimbursement of CDx is given; in several cases, this financial gap is covered by the pharmaceutical company distributing the drug or by the patients themselves. Other Asian-Pacific nations are also a few steps behind in developing that market structure access for personalized medicine as the reimbursement process in these countries has not yet caught up. While the health economics and outcomes research data prove the value of CDx, the mismatch between regulatory approval and routine diagnostics usage still exists.

How Can My Company Be a Global Leader in Personalized Health Care?

As more and more companies are aspiring to become leaders in personalized health care, there are many other hurdles that need to be overcome. Some of these are discussed here:

1. Early communication between both partners is key. It cannot be emphasized enough that the earlier it is, the better it works in the interest of both companies. One of the greatest challenges in codevelopment partnerships is that they are not adequately aligned. Drug companies often do not approach diagnostics developers until the late clinical phases of drug development or until after the clinical trials are complete. This is a grave error that can cost the company significant amounts of money if they have to repeat the clinical trials because proving the clinical utility of the CDx for use with a therapeutic is necessary if the diagnostic is being used for patient treatment decisions.
2. It is critical to align the CDx registration strategy with the drug registration strategy. This is where drug and diagnostics partners need to work very closely together to develop a global strategy for registrations based on country requirements. The approval timelines for each country should be aligned, and factors such as complexity of the regulatory framework and unplanned delays should not be discounted.
3. Both drug and diagnostics partners should be well prepared in advance to overcome the reimbursement and commercialization challenges discussed in the section "Reimbursement Challenges: Alignment of Development and Commercialization."

4. It should be decided early who will cover the costs of registration. Often, the drug developer pays for the development of the diagnostic, and it works in the interest of the drug company to have the diagnostic registered in countries where it is intending to sell the drug. However, to prevent any misunderstandings later on, it is advised to establish, at the time of the contract, who will pay for international registrations, be it the diagnostics company or the pharma partner, or whether these costs can be split.
5. For success in global approvals, the onus is on the diagnostics company to set up a regulatory department with key personnel who understand design control as well as the changing global regulatory requirements.
6. The diagnostics developer should consider whether it has affiliates or distributors in the countries where it is intending to sell. Many regulatory bodies have frameworks that require the presence of a local business for a foreign company to register its products. Therefore, a local office already in place employing a regulatory contact is very useful in such countries. If there is no local office, but there is a local distributor, the company should carefully decide if it wants to give the local distributor the authority to be the license holder for its products. Factors such as long-term relationship with the distributor and past dealings should be considered, and it should be ensured that adequate contracts are in place. In the absence of a local office or distributor, the company may also consider contracting a local consultant. An example scenario to consider is for a company that is equipped with regulatory staff in China and an administrative office in Taiwan. It then has the option to use this office as the local business to report to the Taiwan Department of Health (DOH), while the regulatory staff based in China can carry out all communication with the Taiwan DOH as there is no language barrier.
7. Companies should be well prepared to deal with cultural challenges and time differences in the registration process. These 2 aspects are a very challenging aspect of international registrations, and the key is to develop a good relationship with the local contacts. The Japanese, for instance, have very different business customs compared to Americans, and these should be respected. In addition, regulatory authorities can be demanding and, during the review and approval process, may demand urgent answers. This is where the time differences can become a challenge. Thus, it is also critical that local affiliates/contacts have a sound understanding of the technology.
8. Last but not least, the diagnostics developer must decide whether it wants one global product or different products that are each customized to the market they are intended for. Each scenario has its own pros and cons and depends on the structure of the company. To have one global product, it is critical that the regulatory strategy for the CDx is established very early on in the game. This must be achieved in collaboration with the regulatory, product development, and marketing/product management staff as well as the pharma partner. A global regulatory strategy must be developed, considering all the markets identified in the marketing plan, and it is recommended that requirements for these markets are incorporated in the first design of the product. Once the product is ready for launch, the registration activities in key markets can be initiated right away. A disadvantage to this method is that the development time may be longer, and regulatory project managers may have to go through the challenge of having to deal with pushback from their marketing colleagues and senior management. For the latter scenario, a company may first develop its product, considering only the key market in mind, which may be the US or Europe, among others. Even though the FDA has the bar set very high for CDx, some requirements for product design may still not be covered for other markets, in which case the development team may have to revisit the design history file. This may be a problem for many companies because often, after the product has been launched, the design team moves on to other projects so it can often be a challenge to get the right people back on board. This is even more of a challenge for CE-marked products for which often compromises can be made in the development process due to the self-declared nature of CDx under the IVD directive at present.

Registrations can be time consuming and costly, so the success of a company depends on the farsightedness and resilience of its staff and unrelenting support from senior management.

Conclusion

Although many countries have their own set of local regulations, securing approvals in key markets makes it easier to get approvals in other markets. The best strategy for a CDx developer is to develop a kit considering the regulatory requirements of the most stringent key markets (discussed in this article). Moreover, companies need to be vigilant of the constantly changing regulatory requirements and must stay current on all these changes to penetrate the global marketplace. The drug diagnostic codevelopment process does not come without its challenges, and early and open communication between the diagnostics and pharma partner as well as the regulatory authorities is key.

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