Activities to improve the regulatory framework for companion diagnostics step up

Eric Lawson, *Linda Lebon*, *Anne-Virginie Eggimann* and *Anne Dupraz-Poiseau* discuss how the regulatory process for companion diagnostics might be improved to realise the potential of personalised medicine.

Personalised medicine aims to provide the right treatment to the right patient, at the right dose and at the right time.

It is a cutting-edge approach that involves co-ordinating diagnostic and therapeutic tools to tailor medicines to the individual characteristics of each patient, thereby improving the safety and efficacy of the therapy and potentially reducing healthcare and clinical trial costs.

Personalised medicine is a very promising field. But there are challenges involved in having to co-develop, in parallel with a drug, a companion diagnostic that can determine which patients may or may not respond favourably to that drug.

A big hurdle to the co-development of a medicine and diagnostic is that each product type is governed by a different regulatory framework. In many parts of the world, medicines and diagnostics follow different clinical validation and approval paths, which are currently inadequately linked. This situation can pose major difficulties for drugs and diagnostics companies endeavouring to co-ordinate their product development, conduct joint/parallel clinical evaluation, and synchronise and integrate their regulatory submissions.

The need to clear this hurdle is becoming more urgent. Therapeutic products that have recently entered the market – or that are in development – are increasingly demonstrating their need for co-ordination with a companion diagnostic.

Over the past year, diagnostics industry associations in Europe and the US have made great strides in publicising the regulatory issues affecting companion diagnostics development. They have presented their perspectives on the matter, clarified their concerns, informing both their pharmaceutical collaborators and regulatory agencies of their particular experiences. They have also come up with a number of possible solutions and recommendations for improving the regulation of companion diagnostics.

The promise of personalised medicine

Personalised medicine is based on the assumption that every patient has a unique set of molecular parameters – including genotype and expressed phenotype – that make them respond to a therapy in a different way. Companion diagnostics utilise this molecular distinctiveness to identify those individuals in a subset of the stratified patient population who will benefit most from a modern targeted molecular therapy. The traditional approach to drug development, on the other hand, involves finding a therapy that will treat the majority of patients for a particular indication, an approach that often leads to significant disparity in patient response to the therapy.

Companion diagnostics may benefit patients by:

- identifying patients with the disease requiring treatment and determining the particular therapy best suited for a stratified patient population;
- determining the most effective dosage form for patient genetic/metabolic make-up;
- reducing adverse events and providing greater assurance of patient safety;
- increasing efficacy of treatment modalities; and
- increasing the benefit:risk ratio of therapies.

Such products can also bring benefits during clinical trial development by improving controls prior to and during clinical trials and allowing better clinical trial endpoints with biomarker determination (although a biomarker alone should not be the primary endpoint, it may be used as a surrogate endpoint). They can also provide risk mitigation factors for clinical trial subjects; allow strict definition of inclusion/exclusion criteria; and permit analysis of data to refine a therapy for more specific indication for use.

Companion diagnostics include:

- pharmacogenomic tests (which includes determining the genome of the patient and of the infectious agent);
- molecular diagnostics (proteomics and all the other "-omics");
- traditional diagnostics with modern resolution linked to a specific therapy; and
- imaging and high resolution molecular imaging technology.

Although the scientific community and the public tend to perceive that pharmacogenomic testing is the only technology that characterises the companion diagnostic environment, there remains great importance in the analysis of the phenotypic responses for a more direct and often more cost-effective application of companion diagnostics.

The hurdles

The challenges to co-developing a companion diagnostic with its targeted therapeutic are that the two types of products follow widely different development and regulatory timelines, different submission pathways, and are governed by different regulatory review agencies.

Medicinal product development follows a lengthy process that lasts on average between nine and twelve years. It involves classical exploratory and confirmatory steps for clinical development, which includes Phase I to III trials performed under an investigational new drug application in the US or a clinical trial authorisation in the EU. It also involves interactions between biopharmaceutical companies and regulatory agencies (eg end of Phase II meetings in the US and scientific advice meetings either at the European Medicines Agency or at the national level in the EU).

Manufacturers must then submit a new drug application or biologic licence application to the US Food and Drug Administration, while in the EU, manufacturers submit a marketing authorisation application either to national authorities (for approval via the mutual recognition or decentralised procedure), or to the EMA (for approval via the centralised procedure).

In vitro diagnostic product development, on the other hand, is much shorter – around three to five years. It follows a development and a clinical evaluation that focus on validating diagnostic sensitivity and specificity as well as analytical performance and clinical feasibility and clinical utility studies to demonstrate safety and efficacy or, in certain cases for the US, substantial equivalence to a predicate device reference standard. In the US, the review process requires an investigational device exemption during the clinical phase, and submission of an application for 510(k) clearance or pre-market approval.

In Europe, it requires a clinical trial application and CE marking to allow market access (either with preliminary review by a notified body for diagnostics listed in Annex II of the EU In Vitro Diagnostic Medical Devices Directive (98/79/EC) or following a manufacturer self-assessment of the compliance to essential requirements of the directive for all other diagnostics (self-certification).

Drug/diagnostic co-development is further complicated by the fact that medicinal products and IVDs follow widely different regulatory processes, particularly in Europe. Medicinal products and their companion

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diagnostics are reviewed by separate regulatory divisions of an agency or indeed by completely different authorities.

The FDA oversees drugs and biologics and IVDs, but does so through separate divisions: drugs and biologics are regulated by the agency's Center for Drug Evaluation and Research or Center for Biologics Evaluation & Research, while IVDs are regulated by its Center for Devices and Radiological Health/ Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD).

In Europe, medicinal products fall under the remit of the EMA or national competent authorities. Diagnostics are the responsibility of competent authorities and notified bodies, who are responsible for evaluating their clinical performance and CE marking in accordance with the IVD Directive. Collaboration between the regulators of drugs and diagnostics are limited in the EU and this lack of co-ordination in evaluation processes and the difference in the information that the regulators review (eg marketing authorisation application versus CE marking conformity assessment) was recently described by a regulatory official as not just an information gap, but a "vacuum".

From the regulatory perspective, key hurdles to product co-development include the following:

- pharmaceutical companies do not grasp the subtleties of diagnostics development requirements or clinical processes and vice-versa;
- there is a lack of specific guidelines/guidance for co-development;
- there are difficulties in synchronising/ co-ordinating the timing between both developments and submissions;
- there are no consistent definitions regarding requirements in terms of co-labelling of the medicinal product with the companion diagnostic (labelling is neither specific nor standardised, there are no defined requirements in terms of labelling when medicinal products and companion diagnostics are introduced at different times and there is no guideline/guidance on when to label the co-use of a companion diagnostic as "required", "recommended" or "informational"); and
- there is a lack of clarity on how to deal with life-cycle management of both products, how to evaluate the impact on, or control of, the other product registration while updating registration of therapeutic versus companion diagnostic.

Laboratory developed tests

An additional stumbling block to regulatory consistency is that certain IVDs fall outside traditional clinical review by regulators.

Such tests, referred to as laboratory developed tests or "home-brew assays", are those that are developed and utilised within a single lab, and thereby are not technically "placed on the market" per se. While the laboratory and the testing service may be certified to a regulatory standard, the diagnostic test itself is not reviewed nor necessarily validated for clinical efficacy and safety by a regulatory authority or notified body. The details and claims of these assays are not transparent to the regulatory authorities that would review a medicinal product utilising a companion diagnostic. All this makes collaboration and communication all the more difficult.

Moves by industry

Over the past year or so, EU and US industry organisations have stepped up the pace in a bid to clear these regulatory and development hurdles. IVD manufacturers convened industry focus groups to consolidate their experiences, determine best practices and bring their concerns regarding companion diagnostics rules to the attention of regulators and their biopharmaceutical industry partners.

In the US, the Association of Medical Diagnostics Manufacturers founded a Companion Diagnostics Working Group in September 2009[1].

The working group has since met with OIVD during FDA-industry roundtables to consolidate the industry's perspective on the matter and to present its proposals for improvements[2]. It is currently assembling these presentations into a white paper that will provide the FDA with specific recommend-ations for revising its upcoming draft guidance document on the development of companion diagnostics, which is expected to be issued by the end of this year.

Another important organisation in the US is the Personalized Medicine Coalition. Its membership includes the AMDM and the Companion Diagnostics Working Group as well as US medical device industry association AdvaMed. The Personalized Medicine Coalition has collaborated with a wide range of policy makers, healthcare providers, payers and other stakeholders. In December 2009, it made a formal request to the FDA for a new guidance on personalised medicine.

In the EU, associations from both the drugs and devices sectors have set up working groups to debate and "cross-fertilise" ideas on how to improve the regulatory landscape for the co-development of products for personalised medicine.

For example, bioindustries organisation EuropaBio has created a Personalised Medicine Task Force. In March 2010, EuropaBio organised a collaborative workshop that included members of the biopharmaceutical and diagnostics industries and European Commission representatives.

This workshop focused on "a better medicine to patients" and considered subjects such as expanding scientific knowledge, molecular basis of diseases, patients and integration of technologies, prevention/treatment and diagnostics including biomarkers, and applying science to personalised medicine to demonstrate safety and efficacy.

The workshop paved the way for a common understanding about the basic scientific aspects to consider regarding companion diagnostics and about the definition of personalised medicine. It was followed by a second workshop in September that looked at the impact of personalised medicine on drug discovery and development and considered the policy and regulatory challenges and the opportunities involved[3]. The next workshop, which is expected to take place in February 2011, will focus on market access and how personalised medicine will impact patient access to treatment. It will also consider pricing and reimbursement.

EPEMED, another European personalised medicine association, hosted on 12 October a congress on the premises of the French Senate to discuss and highlight the latest issues in companion diagnostics affecting Europe[4]. Scientific experts and regulatory agency representatives presented their analysis of the status of personalised medicine and companion diagnostics. They also put forward their perspective on translational research, economic challenges in France, impact on cost savings and personalised medicine experience in the US.

The European Diagnostic Manufacturers Association, which represents the European IVD industry, has facilitated a number of presentations by national competent authorities on how companion diagnostics follow practices conformant with the current regulations and with revisions that are being discussed for Directive 98/79/EC.

EDMA has also been active in reviewing and commenting on the upcoming revision of the IVD Directive, considering the possible adoption of the Global Harmonization Task Force recommendation for risk-based classification of IVD products. In such a system, a companion diagnostic could be classified as "C risk" – on a risk scale of A, B, C and D, with A being the lowest risk – and may involve additional clinical validation.

However, despite increasing discussions between and within the therapeutic and IVD industry organisations, medical product regulatory agencies in both Europe and the US

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are struggling to take actions to meet the new regulatory landscape and ever-evolving science.

Regulatory moves on the US front

As for the US regulator's efforts to address the challenges of drug/diagnostic co-development, the FDA has taken an early lead. In 2005, just months after clearing the first DNA microarray for medical use (the Affymetrix GeneChip/Roche CyP450 Assay), the agency published a draft concept paper on drug/diagnostic co-development[5]. This paper served as a preliminary draft guidance for co-developing a drug along with a companion diagnostic, although the term "companion diagnostic" had not yet been coined. The document introduced concepts on how to co-ordinate clinical studies for a drug and diagnostic and recommended key parameters for the diagnostic's clinical utility as well as its sensitivity and specificity.

The paper focused, however, on pharmacogenomic assays to the exclusion of other types of companion diagnostics. Its scope must now be widened to all types of companion diagnostics and the FDA should facilitate interactions between its different divisions involved in drug and diagnostics evaluation to develop best practices guidance.

In line with this, the FDA this year has revitalised its approach toward personalised medicine. In early 2010, it created a "Personalized Medicine Staff" within OIVD. Under the direction of Dr Elizabeth Mansfield, this group is tasked with evaluating processes for companion diagnostics and with providing a revised draft guidance on the subject, hopefully by the end of the year.

CDRH has appointed Francis Kalush as the diagnostics and personalised medicine network leader. Dr Kalush has mapped communication pathways between CDER, CBER and OIVD within the FDA.

In July, OIVD took an aggressive approach to re-evaluating its "enforcement discretion" of the laboratory developed tests, when it held a public meeting on the oversight of such products[6].

Regulatory moves in the EU

The EMA is also moving forward with the assessment of targeted therapies, in part by formalising the use of biomarkers in drug development.

The agency has established a Pharmacogenomics Working Party under the leadership of Dr Eric Abadie, chair of the EMA's scientific committee, the CHMP. The leader of the EMA Innovation Task Force, Dr Marisa Papaluca Amati, is also heavily involved in the development of personalised medicine.

In July, the EMA published a draft reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development[7].

National competent authorities are working to improve the handling of companion diagnostics within Directive 98/79/EC. For example, Dr Anne Van Nerom of the Belgian competent authority for IVDs, the IPH, has presented a paper suggesting development pathways that would link therapies with diagnostics.

The paper provides examples of appropriate interaction points (such as prior to Phase III) and alternative development scenarios. It identifies specifically where IVD investigational products, research-use-only products, "home-brew" tests, testing services and fully CE marked IVD products would or would not be applicable for use in the development and clinical phases of the drug.

More recently, Cécile Vaubelade of French competent authority Afssaps, speaking at EPEMED's October conference, suggested future updates of the IVD Directive could include a new IVD classification system and other elements that would support companion diagnostics development.

Despite these different initiatives in the EU, there is still much progress to be made in consolidating interactions between medicinal product and diagnostic developments, evaluation practices and market access.

Solutions and recommendations

Over the past few months, many questions have arisen and some concrete recommendations have been made regarding improvements on the regulatory oversight of drug/diagnostic co-development.

Topics that have come under discussion on the matter are summarised as follows:

- recommendation for the publication by regulatory agencies of guidelines to introduce best practices and outline a standardised approach to companion diagnostics and drug co-development and co-submissions. In lieu of changes in regulations, these guidances/guidelines would provide a framework in which to plan and collaborate in a more predictive and optimal manner.

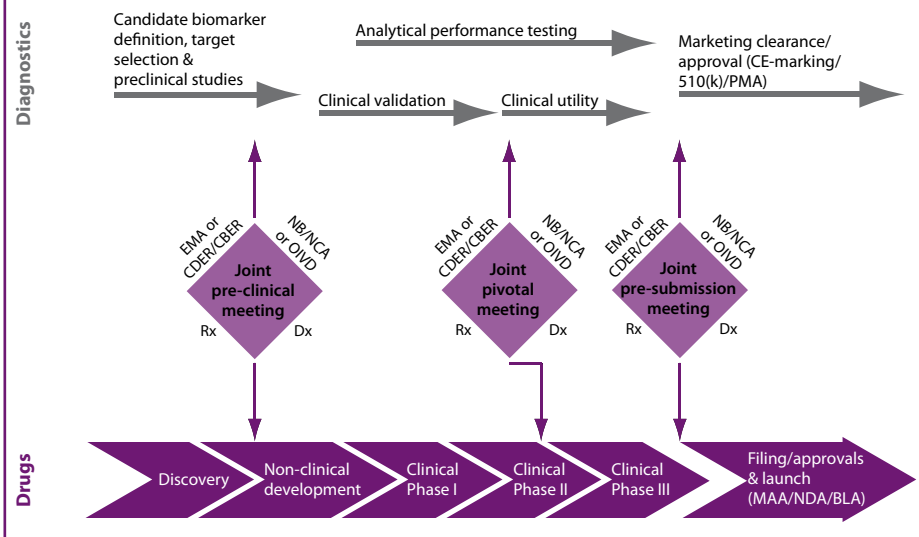
  Such guidances/guidelines would help standardise co-ordination of submission and review of therapeutics and companion diagnostics, such that the timing constraints of review and approval would be transparent and predictable.

  Joint scientific advice meetings including four-party representation should be encouraged, with pharmaceutical and diagnostics industry sponsors and therapeutic and diagnostics regulatory authorities (see Figure 1).

  A standard schedule for such four-party meetings should be encouraged from early-stage up to filing a submission: eg at the initiation of Phase I clinical studies (before finalising the protocol), at the end of Phase II studies and prior to pivotal Phase III trials, and prior to submission of marketing application dossiers to agencies;
- clarification of the definition of companion diagnostics so that it is understood when and how the regulations for companion diagnostics can be applied, distinct from that of a standard IVD.

  A risk-based assignment should be made for companion diagnostics within the classification structure and agency review

Figure 1: Proposal for standardised interactions with agencies for co-development of drugs and diagnostics



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process. In the US, revision of the PMA/510(k) process could include a more standardised definition of the de novo 510(k) procedure where a companion diagnostic may be classified as, for example, a Class 2b risk level within a range of 1, 2a, 2b, and 3 risk levels. In the EU, revision of Directive 98/79/EC could introduce elements of the risk-based approach for classification of a companion diagnostic as a Class C product, on a scale of A, B, C and D, with Class A being the lowest risk level;

- clarification of the definition of the types of IVDs that will be regulated by medical authorities, such that the marketed laboratory developed test services can apply the same level of proven safety and efficacy as any IVD kit placed on the market;
- definition (in the EU) of the portion of companion diagnostics data to be reviewed by the EMA within a marketing authorisation submission versus elements for CE marking (specificity and sensitivity data, for example) and clarification on the situations and timelines for when the EMA could interact with notified bodies (as is currently proposed for combined advanced therapy medicinal products)[8];
- definition of labelling requirements for pharmaceuticals and companion diagnostics (for example, linkage between the drug and diagnostic test that indicates companion medical products, standardising the language and location in label information, and use of specific language to identify required/recommended/informational linkage);
- introduction of guidance on life-cycle management and when to update labelling or registration for a drug/companion diagnostic; and
- retention and use of clinical trial samples to be applicable to clinical validation of the diagnostic and to support the drug trials.

The next step

It is imperative that agencies actively consult with industry organisation representatives (pharma and diagnostics) and with experts from academia to evaluate these issues and recommendations and determine the most realistic and least burdensome approach to improving regulations for companion diagnostics. Diagnostics and therapeutics are no longer independent with regard to their development, evaluation, impact on market access or use in treating patients. Their development is becoming increasingly integrated and intimately linked, ideally starting at the early stage of a programme's development.

By addressing challenges of drug/diagnostic co-development openly – and by actively considering effective corrective actions – regulators will be able to introduce valuable, transparent and practical guidelines that will support innovation, reassure investors and encourage strategic partnerships between drug and IVD developers, ultimately leading to the best results for patient healthcare.

Through such efforts, the goals of personalised medicine can be realised. Bringing the right treatment to the right patient, at the right dose and at the right time, must become a reality in the interest of patients.

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