



CRA Insights: Life Sciences

CRA Charles River
Associates

June 2014

Balancing the opportunities and challenges of developing companion diagnostics: Part 2 of 2

The combination of persistent growth in health care spending, reduced productivity of pharmaceutical pipelines, a continued push towards evidence-based medicine as a means to improve outcomes, and the growing influence of patients in health care decisions has contributed to renewed interest in companion diagnostics as a step towards personalized medicine. Provider, payer, and patient interests are aligned with the need for more focused and effective health care solutions.

Although less than one percent of currently marketed therapies are associated with a companion diagnostic, revenues generated by these diagnostics were estimated to be \$1.3 billion in 2010,¹ with some suggesting growth potential of up to \$40 billion by 2020.² Growth in companion diagnostics may be attributed to several opportunities related to the associated clinical therapies that we outlined in a [previous article](#) on this topic:

- Shorter development times;
- Smaller and more cost effective clinical trials;
- Better clinical trial outcomes;
- Superior market penetration; and
- Premium pricing supported by increased effectiveness in narrower populations.

These opportunities, however, will need to overcome some substantial challenges that confront companies attempting to integrate the development and commercialization of companion diagnostics and therapeutics, including:

- Building a co-development business model that facilitates companion diagnostic innovation, including the development and management of new alliance partners with expertise in diagnostics;

¹ Visiongain, Companion Diagnostics: World Market Outlook 2011-2021, August 22, 2011.

² Michael Harris, "Recent Companion Dx Nods a Win for Personalized Medicine," *BioWorld*, February 15, 2012.

- Dealing with an uncertain regulatory environment;
- Managing the risk of narrowing the patient population;
- Developing a distribution and marketing channel for the companion diagnostic that is synchronized with the therapeutic;
- Educating physicians regarding appropriate use of companion diagnostics; and
- Securing sufficient and predictable reimbursement.

In this article, we discuss these challenges and related considerations for manufacturers of therapeutics and diagnostics as they pursue the potential of companion diagnostics.

Building a co-development business model that facilitates innovation

Manufacturers have pursued at least three distinct business models to capitalize on growth opportunities associated with companion diagnostics:

- Develop an independent diagnostic group or operating company that can serve pipeline needs (internally and externally) while also pursuing external diagnostic technologies (e.g., Roche and Abbott);
- Develop a diagnostic unit solely dedicated to the needs of the internal pipeline (e.g. Novartis); and
- Rely on business development teams to identify and partner with different diagnostic companies to serve the needs of the internal pipeline (e.g. GlaxoSmithKline, AstraZeneca, and Pfizer).

It is likely that there won't be one right model. Pharmaceutical manufacturers will need to identify the best model and the best partner for the specific diagnostic-therapeutic combination, taking into consideration their existing organizational infrastructure, culture and heritage of diagnostics, and product pipeline. Whichever business model is pursued, a greater degree of integration, including sharing financial risk and upside, will be required to encourage appropriate investment and ensure that the regulatory and commercialization strategies for the diagnostic and therapeutic are complementary.

Dealing with an uncertain regulatory environment

The approval pathways for companion diagnostics are evolving in the US and EU, making development a moving target for manufacturers. It has been nearly three years since the US Food and Drug Administration (FDA) released draft guidance for co-development of companion diagnostics and therapeutics, which requested that the therapeutic and diagnostic be clinically developed and submitted for market approval "contemporaneously."³ This request poses a number of problems for manufacturers. First, biomarkers are often identified later in clinical development or even post-approval. Requiring simultaneous development of the diagnostic and therapeutic could cause significant delays in approval for the therapeutic. Second, the FDA indicated that a therapeutic's label should identify a type of companion diagnostic rather than a

³ FDA, et al., "Draft Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices," July 14, 2011, <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm>

specific manufacturer's diagnostic. This would limit the incentive for companion diagnostic manufacturers that lack exclusivity protections. Between the lack of a reasonable approval pathway and the questionable protection of intellectual property, innovators will need to carefully structure development plans for companion diagnostics as compared to the traditional therapeutic-only approval pathway.

In Europe, there is even less clarity regarding the regulatory process for companion diagnostics and the European Medicines Agency (EMA) has yet to release guidance regarding the development of clinical guidelines. Currently, companion diagnostics are regulated through a self-certification process under the IVD Directive 98/79/CE, which provides for mandatory CE markings to facilitate the delivery of diagnostic tests in a harmonized fashion across the EU. In September 2012, however, the European Commission (EC) proposed revisions to the directive, which would classify companion diagnostics as "Class C" (High Individual Risk and/or Moderate Public Health Risk) devices. The proposal lays out mandatory steps for submissions to regulatory bodies, but does not define a clinical pathway for approval.⁴

Managing the risk of narrowing the patient population

Historically, some companies may have been unwilling to place bets that a diagnostic could drive sufficient higher value utilization in a narrower patient segment to overcome a substantial shrinking of the potential target population. For example, most companion diagnostics have been or are being developed for oncology therapeutics; from 2009 to 2010, 34 of the 44 companion diagnostic-therapeutic deals were for cancer indications.⁵ While this metric is driven by cancer biology, there are also commercial realities that make limiting the patient population less financially risky in oncology. First, due to the seriousness of the disease and payers' historically "hands off" approach, manufacturers of oncology products have greater flexibility to charge higher prices when their products address a narrower population in a more effective manner. Second, oncologists have shown willingness to use oncology products in situations that are not specifically supported by the label, and payers have been willing to pay for these applications as long as they are supported by appropriate studies. Thus the benefits of getting to market, even with a narrow patient population, are substantial and the opportunity to expand into other patient sub-groups often remains intact. The potential to significantly expand the companion diagnostics' model beyond oncology (and perhaps rare genetic diseases which feature some of the same commercial opportunities described above) will require a scientific basis that may be less likely in other diseases and customers who recognize and are willing to pay for the value of the therapeutic in a narrowed population. To capture greater profits than they would have realized with a broad-spectrum approach, manufacturers will need carefully constructed clinical development plans, evidence-based value propositions, and financial assessments from a variety of perspectives to appropriately target their therapies.

⁴ European Commission, "Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices," September 26, 2012, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0541:FIN:EN:PDF>

⁵ PricewaterhouseCoopers, "Diagnostics 2011: M&A surges, companion diagnostics accelerate, and early detection offers new prospects," December 2011, https://www.pwc.com/en_GX/gx/pharma-life-sciences/pharmaceutical-industry-thought-leadership/assets/diagnostics-2011-executive-summary.pdf.

Synchronizing therapeutics and diagnostics in marketing and distribution channels

To maximize product acceptance, it is important to ensure that the linkage between the diagnostic and therapeutic remains strong when considering the coordination of marketing activities and distribution channel development. Peak market acceptance of diagnostics is usually four to five years after market approval which is far longer than that of a typical therapeutic which may peak only one to two years after FDA approval.⁶ There are already several marketed examples where a therapeutic and companion diagnostic launched together and had a slow adoption period due to poor diagnostic acceptance. A prime example of this is the diagnostic test that launched concomitantly with Genentech's Herceptin (trastuzumab) in 1998, an immunohistochemistry (IHC) test called HercepTest. The diagnostic was developed by Dako Corporation under an exclusive license granted by Genentech and received FDA approval for identification of populations that would best respond to Herceptin, which treats HER2-overexpressing metastatic breast cancer. While Genentech and Dako worked closely to ensure national coverage under Medicare before receiving FDA approval, some patients still had difficulty accessing HercepTest in the period immediately following the Herceptin launch. Insurance companies denied coverage because the laboratories contracted by the payers either did not have access to HercepTest or simply did not use the same IHC methods for HER2 tests. In turn, this affected Herceptin since the initial Herceptin label specified HER2 testing using HercepTest.⁷ Hindsight suggests that the HercepTest was doomed from the outset. Studies conducted after its launch identified serious flaws regarding its accuracy and variability, but such a narrative ignores the laboratory adoption problems early on. Fortunately for Genentech, alternative screening tests were developed for HER2 and its label was expanded accordingly, helping foster its rapid ascent to blockbuster status.⁸

In this example, the initial distribution channel for the diagnostic was not meeting marketing expectations promised by the therapeutic, and, as such, the therapeutic and diagnostic suffered in acceptance and sales. The marketing activities of a therapeutic need to be tailored to the experience delivered by the therapeutic and diagnostic combination. It is important to set appropriate expectations for the speed of distribution channel development. Stakeholders need to be prepared for the diagnostic launch in order to keep up with the typical market acceptance of a therapeutic.

Educating physicians regarding appropriate use

According to a survey of 800 physicians (oncologists, cardiologists, and primary care), 80% agreed that companion diagnostics will influence their practice. However, only 50% were confident in their ability to identify the right patient for testing, choose the right test, and interpret and explain the results to patients. Additionally, most physicians expressed uncertainty regarding

⁶ Carol Preisig, "Companion Diagnostics from a Business Perspective," *MDDI Medical Device and Diagnostic Industry News*, March 8, 2013, <http://www.mddionline.com/article/companion-diagnostics-business-perspective>.

⁷ Bill Dupere, "Companion Biomarkers and Cancer Treatment: Lessons Learned for Oncology New Product Planning," *Oncology Business Review*, September 2008, pp. 24–29, https://obroncology.com/documents/OBR_sept08_CB&CT.pdf.

⁸ Aruna Rajan, et al., "An overview of the technology and key success factors of companion diagnostics, including case studies highlighting the challenges of developing viable products," *European Medical Device Technology*, September 27, 2011, <http://www.emdt.co.uk/article/developing-and-commercialising-companion-diagnostics>.

where to send lab tests and lacked understanding of insurance coverage, including appropriate coding and reimbursement practices.⁹

Poor physician acceptance of a companion diagnostic had a significant impact on Pfizer's Selzentry, indicated to treat a sub-strain of HIV. Selzentry's companion diagnostic had a high price and a slow turnaround time. Complexities around testing logistics contributed to the product achieving only \$55 million of its forecasted sales of \$500 million in 2010.¹⁰ Physician education and acceptance of companion diagnostics is required to achieve associated success with the therapeutic. Promotional initiatives by manufacturers need to extend beyond product detailing and include education and training initiatives supporting all stakeholders that are part of an integrated companion diagnostics platform.

Securing sufficient and predictable reimbursement for companion diagnostics

The uncertainty and variability of reimbursement to providers and clinical labs is a hurdle to ensuring adoption of innovative diagnostics in the US and EU. Historically in the US, many companion diagnostics are reimbursed through code stacking, where US payers aggregate the technical components of a test to determine reimbursement rather than reimbursing the test itself. This makes it difficult for US payers to track utilization and appropriateness of individual tests and hampers the development of an effective payer policy for the reimbursement of companion diagnostics, and by extension, their attached therapeutics.¹¹ To address these concerns, the Current Procedural Terminology (CPT) editorial panel of the American Medical Association (AMA), helped rewrite how molecular tests are coded for reimbursement. These new codes, introduced in January 2012, include many specific codes for specific tests.¹² Going forward, it is expected that payers will be able to more effectively distinguish between types of tests and track utilization by test. As a result, providers and patients may become more certain of reimbursement. Unfortunately, the Centers for Medicare & Medicaid Services (CMS) decided to temporarily adopt a "gap fill" payment methodology where each Medicare carrier individually determines reimbursement for new diagnostics. This is likely to perpetuate the reimbursement uncertainty and risk for diagnostic and pharmaceutical manufacturers.

In Europe, companion diagnostic reimbursement is even less defined. Currently, drugs are reviewed for reimbursement at the national level while tests are reviewed at the local or regional level, creating heterogeneity across and within European countries. Pharmaceutical manufacturers have developed work-arounds, including subsidization or sponsorship of diagnostic test reimbursement. This has happened with HER2, KRAS, EGFR, and BCR-ABL testing (sponsors include Roche, Novartis, Merck, Amgen, and AstraZeneca),¹³ but it is likely not a sustainable model for companion diagnostic market penetration in Europe. Until the major

⁹ Jerry Coamey, "Engage the Physician!" *Pharmaceutical Executive*, March 1, 2011, <http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=711572>.

¹⁰ David Phillips, "FDA Offers Pfizer's HIV Drug Selzentry New Life—For All the Good It Will Do," *CBS Interactive, Inc.*, November 30, 2009, http://www.cbsnews.com/8301-505123_162-33745550/fda-offers-pfizers-hiv-drug-selzentry-new-life----for-all-the-good-it-will-do/.

¹¹ Bill Malone, "Big Changes Coming to Molecular Dx Reimbursement," *Clinical Laboratory News*, vol. 37, no. 9, September, 2011, <http://www.aacc.org/publications/clin/archive/2011/September/Pages/MolecularDxReimbursement.aspx>.

¹² *Ibid.*

¹³ Miller, et al., "Market access challenges in the EU for high medical value diagnostic tests," *Personalized Medicine*, vol. 8, no. 2, pp. 137–148, March 2011, <http://www.futuremedicine.com/doi/abs/10.2217/pme.11.2?journalCode=pme>.

markets in the EU and US establish a reliable model for reimbursement that can be successfully applied to innovative diagnostics, providers and clinical labs will be slow to adopt new diagnostics.

Considerations for companion diagnostic investment

In conclusion, we offer some potential solutions and considerations for diagnostic and therapeutic manufacturers as they continue to develop and implement strategies for companion diagnostics.

Challenge	Solutions/Considerations
Business model innovation	<ul style="list-style-type: none"> Review each step of the companion diagnostic value chain and decide whether to invest in in-house capability, pursue deep and durable partnerships, or partner <i>à la carte</i> with diagnostics experts Redefine profitability/risk benchmarks so that diagnostics with lower potential margins are not dismissed simply because they do not meet traditional pharmaceutical margins
Uncertainty in regulatory guidance	<ul style="list-style-type: none"> Solicit regulatory guidance earlier in clinical development Develop advocacy efforts to influence regulatory policies in favor of innovation, IP protection, and consistency across therapeutic categories and geographies
Reluctance to limit a drug's potential market	<ul style="list-style-type: none"> Adopt new "go"/ "no go" decision rules that anticipate a broader portfolio of products, with shorter development timelines and smaller patient populations Recognize later-to-market products as potential leaders in niche patient populations Identify innovative pricing models to capture the combined value of the therapeutic and diagnostic
Synchronizing marketing and distribution of therapeutic and CDx	<ul style="list-style-type: none"> Integrate marketing and develop plans Ensure messaging between diagnostic and the therapeutic is aligned Communicate the nuances of utilization and coverage to involved stakeholders
Physician acceptance	<ul style="list-style-type: none"> Build diagnostics education (clinical, logistics, reimbursement, etc.) initiatives into the commercialization plan for products coming to market Understand decision drivers for all stakeholders that will be involved in the patient care paradigm (pathologists, lab directors, health care IT)
Reimbursement for companion diagnostics	<ul style="list-style-type: none"> Advocate for favorable reimbursement, particularly when diagnostics provide clear treatment guidance Understand the reimbursement hurdles and educate stakeholders on the challenges and the best practices to overcome them Monitor reimbursement policies of evolving diagnostics and incorporate those policies into pricing and access strategies Consider innovative pricing, packaging, and distribution strategies to mitigate reimbursement deficiencies

The relevance of these solutions may vary according to scientific and market factors associated with each development project. Nonetheless, a careful identification and analysis of the strategic options, early in and throughout the development process, will help unlock the growth potential promised by companion diagnostics, providing payers with more cost-effective solutions, physicians with a targeted approach for individual patients, and patients with the reassurance that they will receive the best opportunity for a positive outcome.

Contact

Matthew Majewski

Principal

New York

+1-212-520-7260

mmajewski@crai.com

About CRA's Life Sciences Practice

CRA is a leading global consulting firm that offers strategy, financial, and economic consulting services to industry, government, and financial clients. Maximizing product value and corporate performance, CRA consultants combine knowledge and experience with state-of-the-art analytical tools and methodologies tailored to client-specific needs. Founded in 1965, CRA has offices throughout the world.

The Life Sciences Practice works with leading biotech, medical device, and pharmaceutical companies; law firms; regulatory agencies; and national and international industry associations. We provide the analytical expertise and industry experience needed to address the industry's toughest issues. We have a reputation for rigorous and innovative analysis, careful attention to detail, and the ability to work effectively as part of a wider team of advisers. To learn more, visit www.crai.com/lifesciences.



The conclusions set forth herein are based on independent research and publicly available material. The views expressed herein do not purport to reflect or represent the views of Charles River Associates or any of the organizations with which the authors are affiliated. The authors and Charles River Associates accept no duty of care or liability of any kind whatsoever to any party, and no responsibility for damages, if any, suffered by any party as a result of decisions made, or not made, or actions taken, or not taken, based on this paper. If you have questions or require further information regarding this issue of *CRA Insights: Life Sciences*, please contact the contributor or editor at Charles River Associates. This material may be considered advertising. Detailed information about Charles River Associates, a registered trade name of CRA International, Inc., is available at www.crai.com.

Copyright 2014 Charles River Associates