

Companion Diagnostics in the pharmaceutical industry

part II: business models

There is an emerging consensus that the development of Companion Diagnostics appears to offer a set of tools as well as the portent of relevant biological and clinical information that addresses many of the current problems that pharmaceutical companies must overcome. This in concert with the advent of personalised medicine and the demise of the therapeutic drug 'Blockbuster Model' has necessitated a re-evaluation of the pharmaceutical business model. The outcome of such considerations will be determined, in part, by the changing landscape, and influence of the various stakeholders associated with the pharmaceutical sector, including patients/consumers, physicians and healthcare providers, payors and Companion Diagnostic companies. In this paper we describe the difference in perceived value that each key stakeholder holds in regards to the pharmaceutical drug versus the Companion Diagnostic test. We also discuss the perspectives of both the pharmaceutical and Companion Diagnostic companies as they struggle to find appropriate business models. Such models must serve their individual company needs in terms of product value as well as support the very necessary collaborative efforts required to co-develop a therapeutic drug in conjunction with a Companion Diagnostic.

The litany of problems that has beset the pharmaceutical sector in the past decade is well documented¹. Many of these analyses have attempted to identify specific causes leading to such questionable performance metrics, as well as suggest possible solutions¹⁻⁵. In the latter case it has involved consideration of better technology investments; build-out of IT, bioinformatics and

knowledge management tools; creation of efficient decision-making processes; emerging stakeholders; new global markets; changing dynamics of healthcare delivery services; and actual business models of drug discovery, development and delivery¹. While all these issues are important and need to be considered, pharmaceutical companies have been reticent to act across such a broad and diverse

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array of problems. However, the tidal wave of consumer-driven, personalised medicine has forced pharmaceutical companies to reconsider their current business model. There is now a general consensus that the blockbuster model has significant limitations⁶ and that the future must include therapeutic agents that are more closely tailored to specific patient populations. By necessity this must mean that such drugs are safer, more efficacious, more specific and less costly to develop⁷. The demands and constraints imposed by such a new model have had the pharmaceutical companies rushing to embrace and adopt Companion Diagnostics (CD).

In our previous paper in the series, we provided an 'Overview of Companion Diagnostics in the Pharmaceutical Industry'⁸. We discussed the current state of CDs, as well as introduced the plethora of key stakeholders. We noted that the stakeholders appear to have common goals but all speak very different languages and possess different expectations since they are driven by very different goals and needs. This has led to a number of distinct CD definitions, and a struggle to adopt a universal business model for the development of CDs in the pharmaceutical sector. In addition, we noted that the adoption and growth of CDs in the pharmaceutical sector has been significant in the past several years. This is evidenced by the number of major pharmaceutical companies undertaking deals as well as the number of CD companies now professing to offer services and products in existence⁸. In this article we examine the different value propositions held by the major stakeholders as well as discuss the difficulties of constructing CD-pharmaceutical company business deals as well as building and adapting the optimal business model. In a subsequent article we will describe the regulatory and reimbursement issues that are looming on the near horizon in this nascent and complex space.

Companion Diagnostic value

Pharmaceutical companies have developed superb infrastructure capabilities in terms of their drug discovery and development (DDD) efforts. In addition they are adept at creating third party outsourcing and joint venture opportunities to facilitate the creation of new therapeutic drugs. However, many pharmaceutical executives have limited experience and understanding of the diagnostic sector, and thus for them, a unifying business model for discovery and development of a CD has been hard to define and determine. This is compounded by the

changing nature of the stakeholders, and the different expectations and needs of pharmaceutical companies versus CD companies.

Stakeholders

Historically, pharmaceutical companies have tightly controlled the discovery, development, marketing and post-marketing surveillance process of their therapeutic drug products. However, as we described in our first paper, with the creation of an informed patient/consumer base, the advent of personalised medicine and a changing healthcare delivery system, numerous other influential stakeholders now exist. Hence pharmaceutical companies must recognise that these stakeholders hold very different perspectives on the value of the CD versus the therapeutic drug, and this is highlighted below:

i Pharmaceutical companies are in the business of selling therapeutic drugs, thus they place a premium on the safety and efficacy of the drug and look to maximise a return on their DDD investment through effective pricing. In the case of the CD, its usefulness is solely connected to the quality and hence the value of the therapeutic product.

ii Companion Diagnostic companies are responsible for discovering, validating and commercialising the CD product. They also provide CDs to a pharmaceutical company(s) partner. They look to develop a CD with optimised specificity and sensitivity, at minimum cost to themselves and maximum price to their client/payor. Obviously such deals can be constructed in a variety of different way that includes front-loaded premiums for CD development, to back-end loaded deals with a generous royalty payment per CD test. They have limited business interest in the therapeutic agent.

iii CRO companies are primarily responsible for offering a wide range of services to the pharmaceutical industry. Based on their business model both the therapeutic agent and CD themselves have limited value to the CRO.

iv CD testing laboratory: the cost, reliability and reimbursement of the CD test accrue considerable value, whereas there is obviously no value in the therapeutic agent to the testing laboratory.

v Physician/healthcare provider: the safety and efficacy of the therapeutic drug and the specificity/sensitivity of the CD are of critical value to the physician as they look to optimise treatment and disease management of their patients. The cost/pricing of both the drug and the CD are of limited interest to the physician.

vi Patient/consumer: the value of both the drug

Table 1: Assessment of the relative importance and value to the stakeholders of the therapeutic drug compared with the Companion Diagnostic
 a +++ = Very Important, ++ = Important, + = Modest, ---- = No importance

STAKE-HOLDERS	THERAPEUTIC DRUG			COMPANION DIAGNOSTIC		
	COST/PRICE	SAFETY/EFFICACY	VALUE	COST/PRICE	SENSITIVITY/SPECIFICITY	VALUE
Pharma Company	+++ ^a	+++	+++	+	+++	+
CD Company	----	----	----	+++	+++	+++
CRO (Drug)	----	----	+	----	----	----
Testing Lab (CD)	----	----	----	+++	+++	+++
Physician/HCP	+	+++	+++	+	+++	+++
Patient/Consumer	++	+++	+++	+	+++	++
Payor	+++	++	++	+++	++	++
Regulatory	----	+++	+++	----	+++	+++

and its CD are of value only in terms of disease management and decision-making. In addition the cost/price is important only in the context of the reimbursement process.

vii Payor: cost/price of both the drug and CD are of primary importance to the Payor. In addition they are looking for the most cost-effective treatment and increasingly are using comparative effectiveness analyses to make determinations.

viii Regulatory authorities: the performance characteristics of both the drug and CD are the main focus of the regulatory agencies

All the different stakeholders perceive different value propositions of the therapeutic agent versus the CD. In some cases those interests may be radically divergent, as in the case of the cost/price of the CD test. The CD manufacturer as well as the laboratory testing facility would prefer to realise a high margin on the price charged to the end user/payor, whereas the patient would obviously prefer to pay no charge for such information content. Clearly, the value to the patient who needs a cheap or free marker is in the clinical information to help him/her better manage disease. This is in stark contrast to the CD company who has expended considerable financial assets to produce a clinically relevant biomarker and is looking to recoup those sunken costs and build a successful business. To further compound matters, the pharmaceutical companies have no experience in mark-

er/diagnostic discovery and development, and are unsure as to the process and cost of validation and commercialisation, thus they are uncertain as to the monetary value of a CD. All of this is captured and summarised in **Table 1**.

Pharmaceutical company perspective

Andrea Lauber (Head, Technology Transactions-Clinical Biomarkers & Pharmacodiagnosics, Bristol Myers Squibb) and Steven Averbuch (Vice-President, Global Clinical Research, Bristol Myers Squibb) have described the use of CDs in facilitating the “right therapy to the right patients”^{9,10}. They, and others, have argued that this approach when adopted by pharmaceutical companies can bring significant additional value to patient/consumer, physician and payor stakeholders. This is manifested via:

- i Enhanced efficacy:** differentiating patients who will benefit from those patients who may not respond to a specific drug or drug class.
- ii Improved safety:** identify patients at greater risk from therapeutic treatment either due to increased chance of toxicity
- iii Patient stratification in clinical trials:** identify patients and patient sub-populations who respond to treatment.

Based on the use of CDs in such a manner, it has been suggested that a significant number of cost

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saving measures will accrue to pharmaceutical companies during their DDD process and include¹¹:

- i Timeframe:** would be cut from current 10-12 years down to 5-7 years.
- ii Clinical trial patients per NDA:** would be reduced from 5,175 to <2,500.
- iii Cost:** would be reduced from ~\$1 billion now to <\$500 million.
- iv Drug launch:** would increase from current 5-10% up to 25-50%.

Clearly the financial gains for the pharmaceutical industry are potentially enormous and thus individual companies have a self interest in ensuring that they set up a combined DDD-CD process that is both efficient, cost-effective as well as a sustainable business model. The question that continues to trouble the pharmaceutical companies is how to adequately value the CD from a monetary perspective as well as adequately control the process of CD development, and validation as it pertains to the drug product.

Companion Diagnostic company perspective

Patrik Dahlen (CEO of Dako) has argued that a CD helps to provide “the right treatment for the right patient at the right time”¹². This is a very similar sentiment expressed by Lauber and Averbush from Bristol Myers Squibb (BMS)^{9,10}. While BMS and Dako have a signed partnership agreement in place, it is reflective of the broader fact that pharmaceutical companies and CD companies both agree in terms of what a CD might provide to the DDD process and ultimately the patient/consumer. Dahlen¹² and other CD companies¹³ have argued that their products provide significant value in the form of:

- i** Enabling targeted therapy by identifying potential responders to a specific drug.
- ii** Facilitates differential diagnosis or identification of patient sub-sets.
- iii** Identifies patients at risk for adverse events.
- iv** Serves as an adjunct tool for monitoring response to therapy.
- v** May aid in clinical trial design and reduce clinical trial costs.
- vi** Permits data mining and re-evaluation of previously studied drugs.

The perceived advantages defined by the CD companies and the pharmaceutical companies are striking in their similarity. However, there is less clarity and agreement on the monetary value of the

CD when applied to the DDD process and patient/consumer outcomes.

In part this is due to the considerable difficulties of developing and commercialising diagnostics which are poorly understood¹⁴⁻¹⁶. This process is fraught with complexity at a number of different levels. Initially, you must plan for the clinical indication and ensure that the specificity and sensitivity requirements are in accord with whether you are developing a screening, staging, diagnostic, prognostic or predictive marker. The stability of the marker and facile/complex nature of the analytical technology platform used to perform the analyses must also be considered and planned. More recently, there has been much debate about the value of a single marker or a multi-analyte approach¹⁶. Other issues to be considered include market size based on the end-user profile and the clinical indication, as well as the regulatory approach to be taken. Once the initial discovery phase is completed a time-consuming and costly validation process has to occur. You must consider ‘levels of evidence’ including patient accessibility as well as sample collection, storage and analysis. In addition, validation must occur in two independent patient populations of sufficient size and you must demonstrate clinical validity and utility in terms of specificity, sensitivity as well as positive and negative predictive value. Assuming that the validation study was positive, it is then necessary to navigate the turbid waters of the regulatory and commercialisation processes. Unlike the therapeutic drug process, regulation and commercialisation in the diagnostic sector are still maturing. For example a diagnostic can be CLIA compliant (often referred to as ‘home brew’), or an FDA compliant product. In the latter case this is achieved via either a 510k or PMA route. Finally, the diagnostic must satisfy certain criteria for clinical adoption. This includes, peer-reviewed publications demonstrating clinical utility, advocacy by key opinion leaders, inclusion in treatment guidelines by oversight groups, and inclusion by payors into acceptable technologies so that reimbursement can occur. All of this has recently been reviewed, detailed and summarised by Bender¹⁶.

This complex, time-consuming process is fraught with shifting regulatory oversight and ill-defined validation and commercial acceptance criteria. As might be predicted, the economic cost of such development and commercialisation is significant. In the specific case of a CD, Stephen Little (recently the VP of Personalised Healthcare at Qiagen) has pointed out that “demonstrating clinical utility requires a clinical trial of both the drug

and the diagnostic¹⁷. In the case of a Phase III clinical trial for a cancer compound, it is widely known that such costs can exceed \$100 million. However, a stand-alone clinical trial for the CD can exceed \$20 million¹⁷. In addition, using typical reimbursement prices such a cancer CD could command \$20-50 million per annum. This creates a dilemma for CD companies. On the one hand many cannot do their own CD development because of the prohibitive cost of the clinical trial. However, the most likely partner, a pharmaceutical company, has an under-appreciation of the real value of the CD. Thus a number of different business models are now being developed and used to address this conundrum for the CD companies, as well as taking into account the myriad concerns of the pharmaceutical companies.

Business models

There is convergence of agreement by the pharmaceutical and CD companies on the potential usefulness of a CD in the development and launch of a therapeutic drug. However, as noted above, there is a divergence of opinion on the actual value of the CD in the process. As a consequence of this disparity the evolving business models of CD companies must consider factors that are significantly different from pharmaceutical companies and the two different approaches are discussed below.

CD company business model

Many CD companies are either early stage or small market-cap entities. As such they are resource-restricted and must be particularly sensitised to the needs of other stakeholders in their business model development. As a consequence, "the need to demonstrate clinical utility linked to a specific drug means that diagnostic companies cannot normally develop their own companion diagnostics"¹⁷. They must of necessity be reliant on the very customer they are trying to sell their products, and must be attuned to the specific needs of the pharmaceutical company. This means that custom designed CDs must be produced that can meet regulatory approval, and result in global sales of the therapeutic agent.

In order to ensure that a successful CD is produced and provided to the pharmaceutical client a number of criteria must be met¹⁷:

- i Clinical:** validation and utility must be demonstrated.
- ii Technical:** assay must be reliable, robust, meet the specificity and sensitivity criteria and be compatible with diagnostic testing laboratory operations.

- iii Regulatory:** approval needed for the drug, CD and in some countries (USA) the analytical instrument on which the test is performed.
- iv Availability:** the CD must match the distribution of the drug in the global marketplace.
- v Reimbursement:** who actually will pay for the CD test and how much?
- vi Legal:** are all technology and reagent licenses in place?
- vii Commercial:** different models needed depending on pharmaceutical company involvement.

One of the most formidable barriers to convincing the pharmaceutical client that the CD has value is to demonstrate clinical utility. CD companies have taken different approaches to this problem and hence have developed different business models to accommodate such an important factor in building key relationships with pharmaceutical clients. Little¹⁷ has described the most common business models and they are influenced by numerous factors including development timeframes and access to capital. One approach is for the CD company to license IP on an assay and create a sufficient revenue stream in order for them to pay for the discovery and development of the CD, and is referred to as the stand-alone option. The less costly approach is to partner with the pharmaceutical company(s) and share the costs. A one-stop shop approach is for the CD company to integrate the drug and CD delivery. Finally, a more risk-laden, short-cut approach is to introduce a test based on preliminary data prior to a more rigorous demonstration of the clinical utility of the CD. The stand-alone, partnership, one-stop-shop and short-cut approaches¹⁷, have been adopted by CD companies in one form or another as executable business models. The attributes and consequences of each of the models for the CD companies are captured and summarised in **Table 2**.

Current CD company business models are for the most part driven by the needs of the pharmaceutical company client. Hence the partnership model is emerging as a favoured model since it helps mitigate risk and reduce upfront CD costs. However, it is important for CD companies to recognise that certain criteria need to be considered when selecting a pharmaceutical company as a partner of choice and they include⁹:

- i** What are the current and future aspirations of the CD company, as well as assess synergies and needs since the pharmaceutical company will own the drug product?

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Table 2: Properties and characteristics of different Companion Diagnostic business models. Adapted from Stephen Little¹⁷

	STAND-ALONE	PARTNERSHIP	ONE-STOP SHOP	SHORT CUT
Costs – CD company	High	Revenue generation	High	Medium
Revenues	High	Medium	Very low	Low
Marketing	Independent	Pharma support	Partnership	Independent
Exclusivity	IP driven	Clinical Trial or IP	Clinical Trial or IP	None or IP
Risk	High	Low	High	Medium
Regulatory	LDT or 510K	IVD-PMA	IVD-PMA	LDT
Geography	Company dependent	Global	Global	USA
Examples	Genomic health	Qiagen & Dako	Roche	Caris

ii What is the potential for follow-on products with partner?

iii Expertise in development and commercialisation of drug and CD products are essential.

iv How will decisions be made regarding test format, scoring, methods, validation, complete control of clinical results and commercialisation strategy including co-ordination of activities?

v Will the CD company business model/risk sharing strategies fit with potential partner?

In addition, Ferrara¹⁸ has noted that CD companies are very cognisant of the importance of pharmaceutical companies and are deploying two different, time-dependent business approaches that impact clinical development and market risk. The long-term opportunity is in the co-development of the CD and the therapeutic drug with a subsequent co-launch of the two products. This approach affords the opportunity of an optimal outcome since the clinical trials for drug and CD can be co-designed in tandem at the outset, and this is the ‘partnership’ model delineated in **Table 2**. The problem with this model for the CD companies is that the drug may not ultimately clear clinical trials and thus the CD would not make it to market. A more near-term, less risky approach is the development of a CD linked to a currently used drug therapy. Such a CD would identify for example, optimal responders to the drug, and could be reimbursed by the payor. However, such an approach would necessitate adequate clinical data in the form of validation and an efficient commercialisation plan. In either model there is still significant risk and cost associated with the development and

use of the CD even when considering the needs of the pharmaceutical company.

Pharmaceutical company CD business models

There are numerous factors that individual pharmaceutical companies must make when considering the incorporation of a CD into the development and launch of a therapeutic drug. A primary factor is defining the role of the CD in the drug development and post launch surveillance, for such matters as patient stratification, identify responder/non-responder and develop new indications for therapeutic agents. In addition the CD must not add a prohibitive cost to the payor such that it becomes a barrier to the actual therapeutic drug use. Also, the CD test needs to be readily available, analytically and clinically validated and approved in all global drug markets. Such stringent requirements by pharmaceutical companies must also be weighed against the risks, benefits, priorities, development costs, business terms, regulatory and market considerations of the CD itself⁹.

In the ideal situation for the pharmaceutical company, the CD is tied to the development of the drug indication. In such a case Lauber has laid out the generic considerations that each pharmaceutical company must ponder in the development of an appropriate business model⁹, and these include:

i Internal CD development or partner: this necessitates consideration of CD discovery and assay development; CD analytical and clinical validation; manufacturing scale-up; registration strategy and plan; reimbursement strategy; legal/IP due diligence and marketing strategy and plan.

ii Alignment of partners with different business models: this requires consideration of the fact that the CD and drug have different value considerations.

Assuming that a partner in the form of a CD company is preferred, then Lauber⁹ points out that the pharmaceutical company must also:

i Assess needs and priorities before seeking a best-fit partner. Since the CD company may own the CD product then alignment is critical and communication essential.

ii Determine preferred formats/platforms for current and future CD type(s) as well as regulatory considerations, availability, and costs.

iii Consider how decisions will be made regarding test format, scoring, methods, validation, control of clinical results, commercialisation strategy including co-ordination of activities – joint or sole.

iv Consider what are potential partners' business models/risk sharing strategies; and competing products.

Lauber has described the complex decision-making process for the pharmaceutical company on whether to partner or undertake in-house CD development efforts⁹. In addition there are several other critical factors to consider. For example the creation of development timeline for co-development of a CD and drug is a difficult and interwoven process. Several initiatives from the US FDA, including the Drug-Diagnostic Co-Development Concept Paper and the Critical Path Initiative¹⁹, seek to promote CD usage in an attempt to speed the development process and create safer compounds. However, as Meltzer and Johnston have noted: "The Co-Development Concept Paper provides a framework for combination product submissions, but lacks a sustainable business model to account for the differences in timing between clinical development studies and diagnostic device trials"²⁰. In addition, another significant issue is the language in the drug label, since this could be a point of conflict between the CD and pharmaceutical company. In the USA, the FDA decides on final language and the CD can be described as either 'required', 'recommended' or 'for information only'. Clearly the CD company would prefer the strongest recommendation for the CD use. However, the pharmaceutical company might see that it violates therapeutic drug ease of use by the patient/consumer. This issue has been discussed in much more detail by Meltzer and Johnston elsewhere²⁰. Finally, the thorny issue of reimbursement continues to bedev-

il the pharmaceutical companies. Unlike the value-based reimbursement of therapeutic drugs, a CD test is usually reimbursed on a cost basis relative to the procedural (CPT) codes employed for that assay. This makes it difficult for the pharmaceutical company to make an estimate on the ROI "based on higher pricing for costs and procedures outside the CPT system such as royalties, patents and extensive clinical trials"²⁰. Meltzer and Johnston have argued that the reimbursement system in effect does not adequately compensate the CD assay, and we have discussed this issue from the CD company perspective above.

At present at least four different pharmaceutical business models have emerged to take into account the complexities and difficulties of co-developing a drug with a CD, and they include:

i Partnership/licensing model: collaborate with a CD company(s) to bring in a defined CD assay. This model is practised by companies such as AstraZeneca and Bristol Myers Squibb (BMS). For example, DxS-BMS agreement in September 2009.

ii Buy-in model: the pharmaceutical company actually acquires a diagnostic/CD company. For example, Solvays acquisition of Innogenetics in 2008.

iii In-house model: develop in-house capability and expertise to develop the CD assay. This necessitates the fact that in-house knowledge and experience of diagnostic discovery and development is available. Companies such as Abbott, Johnson and Johnson and Roche, which already have both therapeutic drug and diagnostic development expertise practise this model. In the latter case it is noteworthy that they are also listed as three of the top five diagnostics companies.

iv Hybrid model: collaborate with tool companies to bring in diagnostic expertise but actually develop an in-house CD development capability. Very recently, Novartis announced that it was taking this approach to CD development²¹.

The pharmaceutical companies continue to grapple with their business models to accommodate the co-development of a CD with their therapeutic drugs. They are cognisant of the usefulness of CDs in the DDD process and post market launch, but they continue to struggle on how to monetise the value of the CD itself. This is a rapidly-evolving situation as the regulatory authorities begin to weigh-in with their thoughts and directives. Ultimately executive management will have to decide on the importance of CDs to their products and invest resources in a timely, proactive manner.

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Conclusions

The growth of the CD sector has been significant in the past several years. This is evidenced by the number of major pharmaceutical companies undertaking deals as well as the number of CD companies. There appears to be widespread acceptance of the potential usefulness of Companion Diagnostics. Based on the current optimism it is possible that CDs afford part of the panacea needed to produce cheaper, safer more efficacious drugs. In part this is fuelled by the common goals of the pharmaceutical and CD companies in recognising the usefulness of CD assays in the DDD process. Numerous business models are evolving for both the CD and pharmaceutical companies as they seek to address the varied issues raised above. Ultimately, the regulatory and reimbursement issues will be delineated by the regulatory authorities and the payors respectively, and this will have a dramatic impact on any future business model development for both the CD and pharmaceutical companies. Meltzer and Johnston²⁰ have suggested that: "It is likely that the successful models will require the co-operation and co-ordination of a diverse array of companies to navigate the evolving regulatory and reimbursement environments. Part of this will also include devising ways of sharing the economic rents of success and the risks and costs associated with development, which in many cases will be a moving target". At present we will continue to watch the fascinating growth of this important new diagnostic application arena.

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