

Fulfilling the Promise of Targeted Therapeutics in Oncology via Companion Diagnostics: a perspective on pipeline trends and co-development strategies

by

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Submitted to the Harvard-MIT Division of Health Sciences and Technology on September 6, 2011 in partial fulfillment for the Degree of Masters of Science in Health Sciences and Technology at the Massachusetts Institute of Technology

Abstract

Herceptin was the poster child of personalized medicine that brought forward the notion that contemporaneously developed companion diagnostics (CDx) could lead to more efficacious use of a cancer therapeutic in a selected population. Despite a gap of 12 years, the recent approvals of Zelboraf and Xalkori in quick succession by the FDA are a testament to the fact that the age of cancer therapeutics co-developed with a companion diagnostic is finally upon us.

The purpose of this thesis was to test the hypotheses, that the trend for CDx based therapy launches in oncology is NOT headed towards a dramatic upturn in the next 5 years and in the view of biopharmaceutical executives – increasing price and market share of launched drugs are the dominant drivers for investing in companion diagnostics, and that the other features of CDx, such as improving the productivity of oncology drug development and reducing development costs are essentially dispensable.

These hypotheses were tested using a study design that involved conducting a pilot study comprising of 18 interviews of stakeholders directly involved with the decision making of oncology drug development – to synthesize the extent of contemporaneously developed CDx to be launched with a cancer therapeutic in the coming 5 years.

An analysis of the results obtained from the survey indicate, that a significant number of oncology drug launches within this decade would feature a co-developed companion diagnostic, and that despite challenges and initial trepidations over this business model – the higher probability of success, lower development costs, shorter time to market and pricing power associated with this approach, are incentives that are increasingly attracting more oncology firms to adopt this strategy for developing targeted therapeutics. Based on these findings, the original hypotheses were rejected.

Thesis Supervisor: Richard J. Cohen, MD, PhD

Thesis Supervisor: Keith Flaherty, MD

Thesis Supervisor: Mara Aspinall, MBA

To

Preeti - my soul mate, friend, philosopher and guide

Mouli & Riya - my inspiration & the source of my energy

And, to

Ravi & Shashi - Hardesh & Nili

For their countless blessings!

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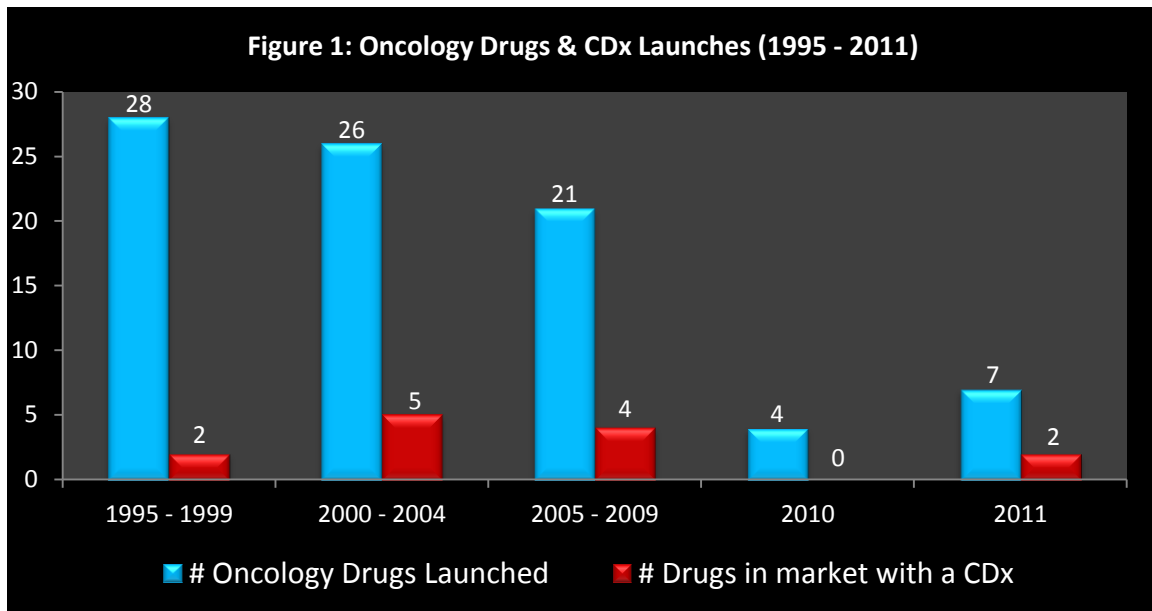
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1. Background

Herceptin was the first successful anticancer therapeutic approved by the Food and Drug Administration in 1998 for the treatment of HER2-positive metastatic breast cancer¹. More importantly, Herceptin was also the first clinically adopted step towards personalized medicine in oncology², whose approval – it was predicted, would usher in a new era of cancer drug development, where biomarker (BM) based drug discovery and development programs, as well as co-development of companion diagnostics (CDx), would become the norm³.

However in the last 12 years⁴ since Herceptin’s launch, there have been only a handful of examples (Appendix A) where **oncology drugs** have been **launched with a contemporaneously developed companion diagnostic**⁵. Why?



¹ US Food and Drug Administration, Table of valid genomic biomarkers in the context of approved drug labels, Available at: <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> Accessed Aug 13, 2011

² Piccart-Gebhart et al. (2005) and Romond et al. (2005)

³ Ginsburg, G.S. and McCarthy, J.J. (2001) TRENDS in Biotechnology Vol.19 No.12 December 2001, 491-496

⁴ CenterWatch, FDA Approved Drug Therapies in Oncology, available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?ArealD=12> Accessed Aug 13, 2011

⁵ Cohen, J., Tufts CSDD Report, Volume 13, Number 4, Page 2, July/August 2011

2. Literature review

The sequencing of the human genome more than a decade ago was expected to drive rapid advancement in the understanding of cancer biology and herald the age of personalized medicine. While the subsequent years have seen many false starts and false hopes, the age of personalized medicine now appears to be upon us⁶. The advances in genomic and proteomic science have led to the development of “targeted” diagnostics and therapeutics that leverage knowledge of a specific cancer’s genetic makeup to create a more personalized approach to medicine. The overall diagnostic and therapeutic market – comprised primarily of pharmaceutical, medical device and diagnostics companies – estimated at \$24 billion in 2009, and growing by 10% annually, is projected to reach \$42 billion by 2015⁷.

While the development of recombinant DNA technology may have been a prerequisite for the emergence of today’s biopharmaceutical giants such as Amgen and Genentech, others believe that the key enabler was the U.S. Orphan Drug Act of 1983 which gave valuable market protection to the first product reaching the market for indications where the market was small⁸. In contrast, the expectation that **biomarker driven patient selection reduces the target market size** for oncology drugs has kept the largest biopharmaceutical companies, and by extension diagnostics companies at an arm’s length from employing a targeted approach to oncology drug development.

⁶ McDougall, G, and Rosamond, M., Personalized medicine - What it means for patient-centered healthcare and how to address its current challenges, PwC View issue 13, 2010

⁷ McDougall et al (2009), The new science of personalized medicine, PwC Oct 2009

⁸ Probst et al. (2009) Diagnostics 2009: Moving towards personalized medicine, PwC Oct 2009

However, there are several factors today that are accelerating the growth of personalized medicine – on one hand there is the recent passage of U.S. Health Reform, with its focus on reducing redundancy and waste in healthcare, as well as cutting drug costs, and on the other hand there’s the desire of payers to reduce costs in the long term by providing precise diagnostics required to avoid unnecessary or ineffective treatments, prevent adverse events, develop prevention strategies and essentially deliver more effective, targeted therapeutics at an optimal cost. Hence, faced with looming patent expiries of current blockbusters in a changing healthcare environment, the **biopharmaceutical industry is showing a renewed interest in the potential of ‘nichebusters’** – drugs targeted to small populations but commanding a premium price – to replace some of the lost income⁹.

In the last few years, biopharmaceutical companies have become increasingly interested in biomarkers for maximizing the economic potential of their assets, and more recently have been incorporating them into drug development programs for their eventual co-development as a CDx associated with their targeted therapies. For the physicians and patients, the **promise of CDx lies in the ability of the assays to assist in making more informed treatment decisions**¹⁰. Typically, a CDx is used to enhance the efficacy and, or safety of a specific drug by targeting a specific group of patients. For the drug developers, co-development of CDx alters the process of drug development and commercialization of drug candidates, which can yield safer drugs or drugs with enhanced efficacy in a

⁹ McDougall, G., Competing in an Era of Personalized Medicine, Drug Discovery, Delivery & Therapeutics, 2009

¹⁰ Emerging Trends in Drug Development: Companion Diagnostics-9th Forum, http://sabpa.org/photos/SciForum11/S&T_2011_Report.htm Accessed on Aug 7, 2011

faster, more cost-effective manner¹¹. In essence, co-development of a CDx can not only reduce the time it might take for a novel therapeutic to complete its bench to bedside journey, it may save billions of dollars as well as avoid unnecessary treatments and potential side-effects for individuals with life-threatening diseases.

Despite all the espoused benefits of associated biomarkers and companion diagnostics to regulators, payers, physicians, patients and drug developers, when Research & Development executives at 16 of the top 20 biopharmaceutical companies were interviewed in a **survey by McKinsey in mid-2008**, they indicated that while **30–50% of drugs in development had an associated biomarker program, fewer than 10% of these drugs were expected to be launched with a companion diagnostic** over the next 5–10 years¹². The research further suggested that for the pharmaceutical and biotechnology companies, the utility of companion diagnostics was exponentially more in the post launch phase of the drug – for generating greater value after marketing by increasing price and market share, than for improving productivity during the development phases of the drug¹³.

That said, much has changed in the recent years – more than ever drug developers recognize that opportunity exists in lower prevalence tumors where unmet need is high or in higher prevalence tumors within specific sub-populations. Coupled with late-stage failures of high profile candidates (e.g. Iniparib, Zebotentan) and emerging pricing risks in developed markets (e.g. Velcade) the trend in oncology drug development seems to be shifting towards '*smaller bets placed wisely*'.

¹¹ Phillips KA, Bebbler S, Issa A. Diagnostics and biomarker development: priming the pipeline. *Nature Reviews Drug Discovery* (2006) 5,463-469

¹² Ma et al. (2009) The microeconomics of personalized medicine: Today's challenge and tomorrow's promise, *Nature Reviews Drug Discovery* Vol. 8 April 2009, 279 - 286

3. Thesis Objective

In this study I hypothesize that – despite the increased focus on personalized medicine – firstly, **the trend for CDx based therapy launches in oncology is NOT headed towards a dramatic upturn in the next 5 years** and secondly, in the view of pharmaceutical executives increasing price and market share of launched drugs are the dominant drivers¹⁴ for investing in companion diagnostics, and that the other features of CDx, such as improving the productivity of oncology drug development and reducing development costs are essentially dispensable.

¹⁴ Ma et al. (2009) The microeconomics of personalized medicine: Today's challenge and tomorrow's promise, Nature Reviews Drug Discovery Vol. 8 April 2009, 279 - 286

4. Methodology

To gain a perspective on the use of associated biomarkers in the current oncology drug development environment and to gauge the potential of companion diagnostic based therapy launches in the next 5 years, I performed **18 interviews** in the summer of 2011 with executives and key opinion leaders from leading oncology companies, consulting firms and venture capital funds.

The interviews had a **dual approach for testing the hypothesis** – quantitatively, study the pipelines of a diverse range of oncology companies with drug candidates at various stages of development, to approximate if CDx associated drug launches could exceed the current trend by at least 100% i.e. could double in the next 5 years, and – qualitatively, explore the thinking and rationale behind the drug development strategies of these firms, to appreciate if pricing and market share were the top drivers for CDx investments.

4.1 Questionnaire Design

Armed with the knowledge gained from my review of the existing literature, I designed an interview questionnaire to elucidate the following:

- Experience and exposure of interviewees to oncology drug development
- Oncology pipeline of participating companies and their current approach to drug launches in the next 5 years – with or without a companion diagnostic
- Strategic approach to associated biomarkers in current oncology drug discovery and development environment

- Co-development strategy for companion diagnostics within the company's active oncology drug development programs
- Key challenges to the development and acceptance of personalized medicine within oncology firms and actions required to overcome them

4.2 Participant Selection

Aiming to keep the study outcome unbiased, and to appreciate the perspective of oncology drug development firms in various stages of maturity, I selected participating companies across the entire spectrum of drug developers – from newly launched venture funded oncology firms to small companies with drug candidates in phase I, and from medium sized companies with at least one launched oncology drug to organizations with the largest portfolios of oncology drugs in the world. In addition, the participant selection was driven by an ambition to learn from, and synthesize the impressions of executives who were directly responsible for deciding the drug development strategy of an oncology company.

5. Interviews Questions – Rationale, results and discussion

Almost 80% of the interviews were conducted in face-to-face meetings lasting over 45 minutes, the rest were via teleconferences. Given below are the questions – with their rationale and a summary of findings consolidated from the responses of all interviewees. **Please note, the questions were asked chronologically as illustrated in the questionnaire (Appendix B) but are presented here in context of their relevance to the implied sub-topics within the interviews.**

5.1 Experience & Exposure

Question #1:

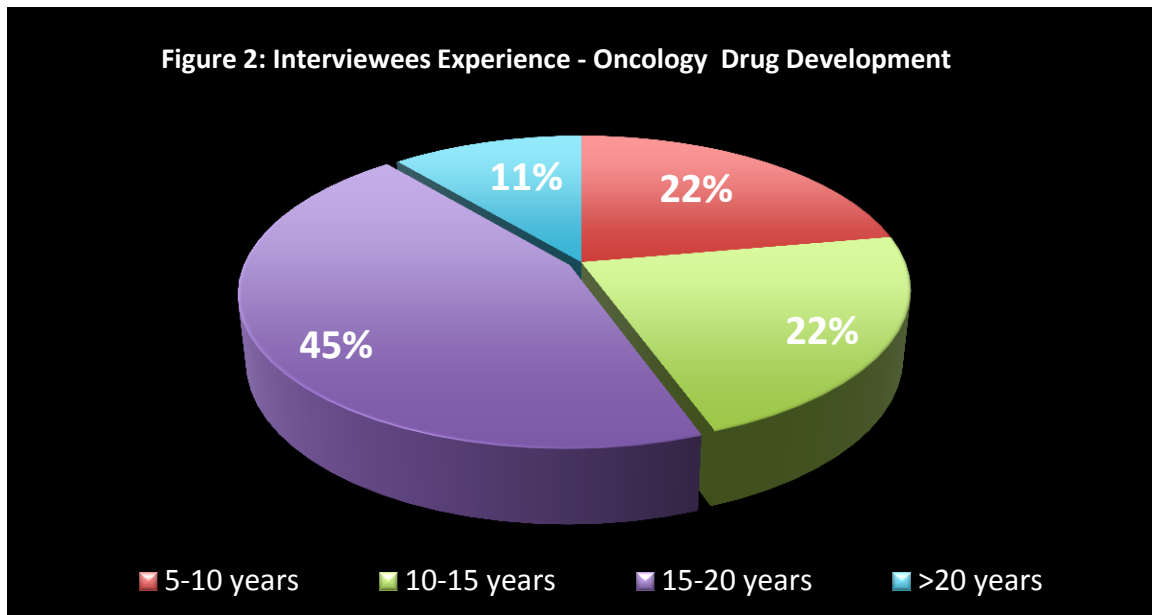
How long have you been associated with commercialization of oncology products, and in what roles?

Rationale

The primary objective was to isolate the oncology drug development experience of the interviewees from their other life sciences careers. The secondary objective was to ascertain if their current roles were directly associated with the decision making of oncology drug development strategy within oncology companies.

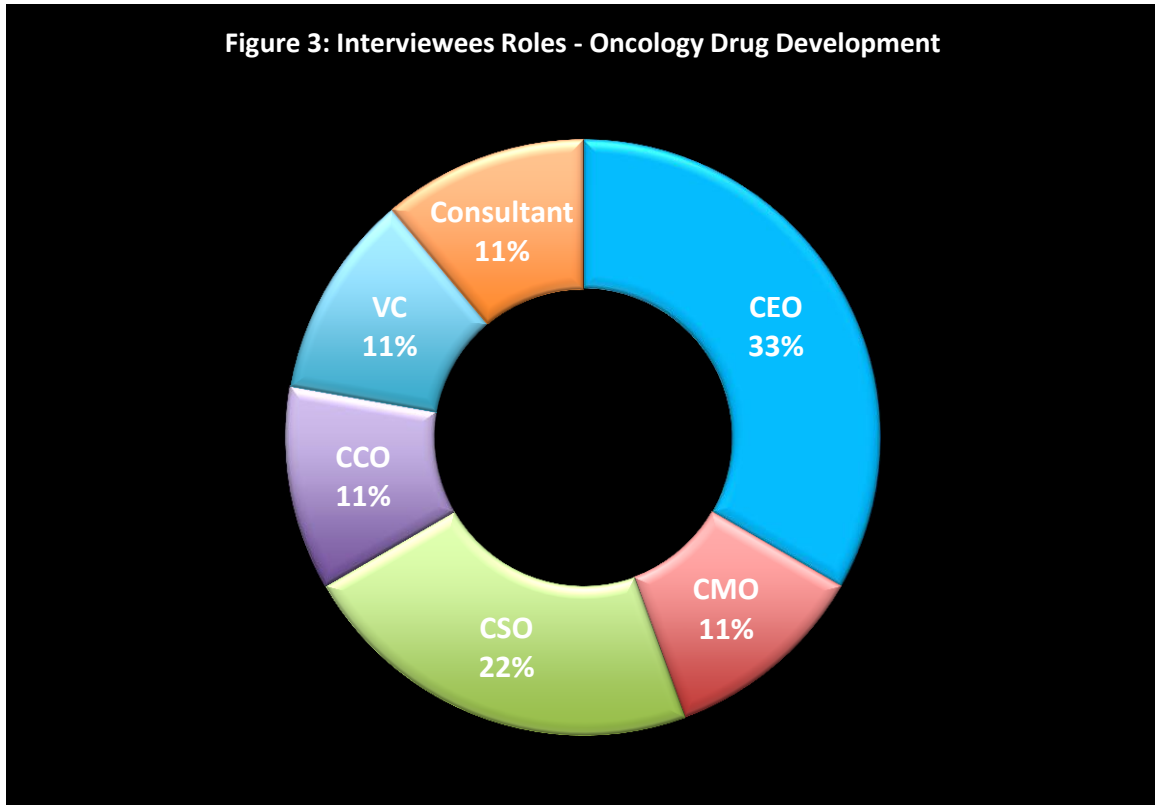
Results

56% of the interviewees had been associated with oncology drug development since Herceptin's approval in 1998, and 78% had witnessed the evolving success story of Gleevec, from its approval in 2001 for BCR-ABL positive Chronic Myelogenous Leukemia patients to 2011 – where it is currently approved for 9 indications¹⁵.



¹⁵ Gleevec: Package Insert http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf Accessed on Sep 3, 2011

Further, resulting from a conscious effort to reach out to the decision makers of drug development strategy within participating companies, 75% percent of the interviewees were senior executives within their organizations.



The venture fund partners were past executives of biopharmaceutical firms and were currently involved with oncology drug development startups in Cambridge, Massachusetts. **A full list of participants and their companies is attached as Appendix C.**

Discussion

In essence, the study participants were well versed with the intricacies and challenges of CDx associated oncology drug development, and the impact of companion diagnostics in the success of a targeted therapeutic.

Question #2:

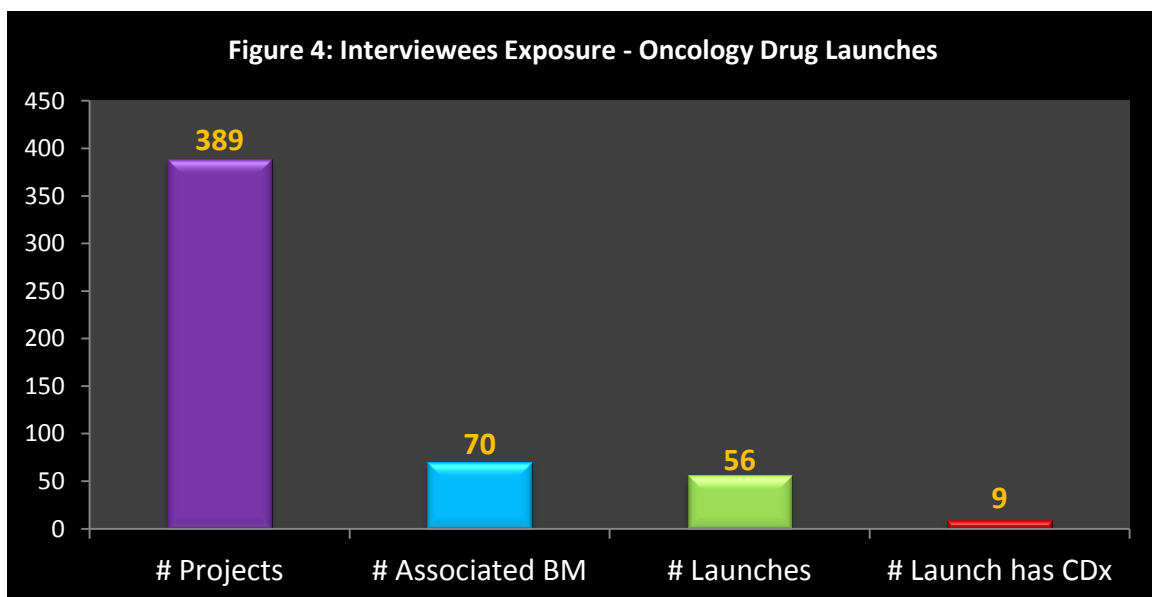
How many oncology drug development projects and launches have you been involved with? Of those, how many had an associated BM during drug development and how many were actually launched with a CDx?

Rationale

The purpose of this question was to establish the actual hands on experience of the participants in developing biomarker driven oncology drugs and, or co-development of companion diagnostics.

Results

Put together, the participants had played a decision making role in the development of 389 New Chemical Entities (NCE) in oncology, of which 70 projects had involved an associated predictive biomarker during any stage of the drug's development. Further, between them the **interviewees had seen through 56 oncology drug launches during the course of their careers, of which 9 drugs have - at least one associated CDx with it, on the market today.**



Discussion

Given, at the time of writing this report, there have been at least 86 oncology drugs¹⁶ launches since 1995, and of them at least 13 drugs have a companion diagnostic¹⁷ available today, the cumulative experience of the interviewees accounted for 65% of all oncology drugs launched and for 69% of all oncology drugs available in the market today together with one or more companion diagnostic. Moreover, a quarter of all the drug development projects that the interviewees had been involved with, had an associated biomarker strategy during the development.

Question #3:

What is your company's approximate annual revenue from oncology products? Also, what's your approximate annual R&D budget within oncology?

Rationale

The goal of this question was to ascertain the revenue range of companies represented by the interviewee pool, and to appreciate the participating companies focus on developing oncology therapeutics, based on the level of resources committed to oncology research and development.

Results

Based on information provided, around half of the participating firms were oncology early stage firms and at present did not have any revenues. The revenues for few of the participating large firms are given below:

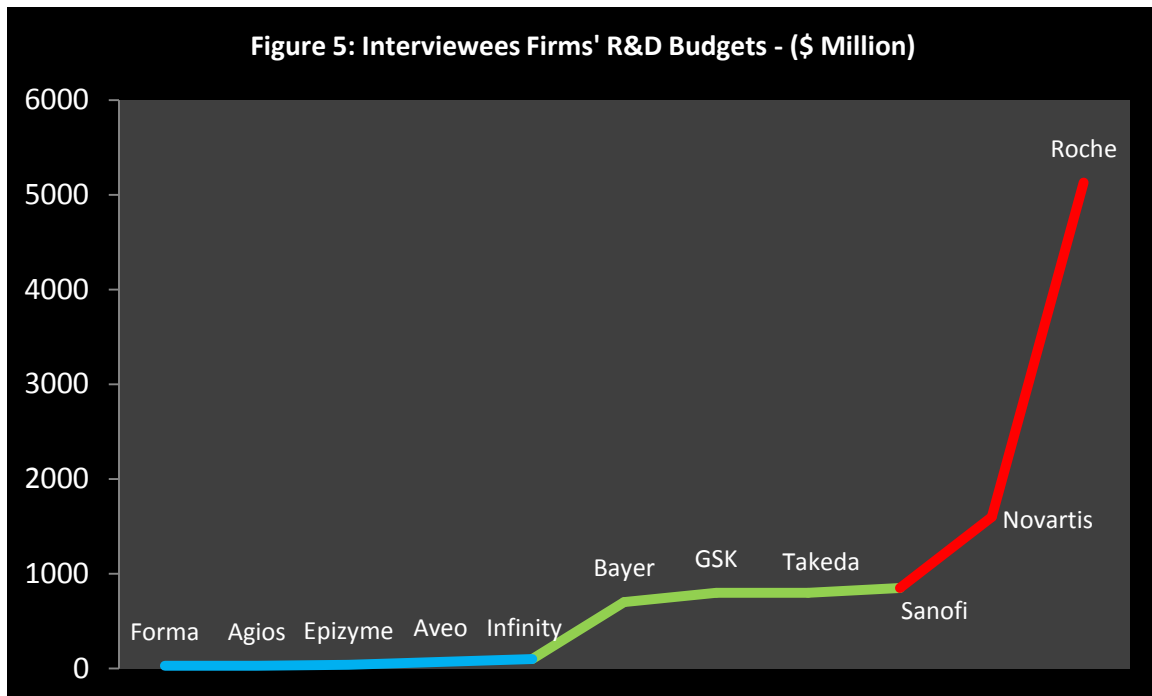
¹⁶ CenterWatch, FDA Approved Drug Therapies in Oncology, available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?AreaID=12> Accessed Aug 13, 2011

¹⁷ Cohen, J., Tufts CSDD Report, Volume 13, Number 4, Page 2, July/August 2011

Table 1 - Annual Revenues of Top Global Oncology Franchises¹⁸ (\$47.2bn)

Companies	Revenue (\$bn)	%MS	Rank
Roche	\$16.52	35%	1
Novartis	\$5.19	11%	2
Sanofi	\$3.78	8%	3
Lilly	\$3.78	8%	4
AstraZeneca	\$3.78	8%	5
Pfizer	\$1.89	4%	6
Takeda	\$1.42	3%	7
MSD	\$0.94	2%	8
BMS	\$0.94	2%	9
J&J	\$0.94	2%	10
All Others	\$8.02	17%	

The oncology revenues and research budgets for Roche and Genentech are combined, so are for Sanofi and Genzyme. While, GlaxoSmithKline and Bayer were represented in the research, their oncology revenues are not mentioned here, although their R&D budgets are illustrated below, with the budgets of other oncology drug development firms.



¹⁸ IMS Health MIDAS MAT December 2010. Oncology defined as L1&L2

Discussion

The annual R&D budgets of the mid to large sized oncology companies varied significantly, and for many companies did not exactly coincide with their relative size of oncology revenues, which points towards the optimism and commitment of the participating firms towards oncology as a lucrative therapy area in the future. The inclusion of several oncology startups in the study was deliberate, owing to the recent strategies of large biopharmaceuticals companies to look for external drug candidates for building their future pipeline¹⁹, and the corroborating growth of in-licensing and partnerships deals²⁰ within in the recent years, which suggest that the **pipeline strategy for large firms is shifting from 'research' to 'search' - where, a dollar invested in in-licensed compounds is expected to deliver 3 times as much value as compared to a dollar invested in in-house research²¹.**

¹⁹ Donnelly, J.M., *Sanofi Chief details innovation strategy*, Boston Business Journal Available at: <http://www.bizjournals.com/boston/news/2011/04/12/sanofi-chief-details-innovation-strategy.html> Accessed Sep 3, 2011

²⁰ CurrentPartnering, *Partnering Agreements in Pharma and Biotech Yearbook 2010*, January 2011

²¹ Morgan Stanley Pharmaceuticals Report, January, 2010

5.2 Current Strategy – Oncology Pipeline

Question #4:

Please complete the following about your current oncology pipeline products:

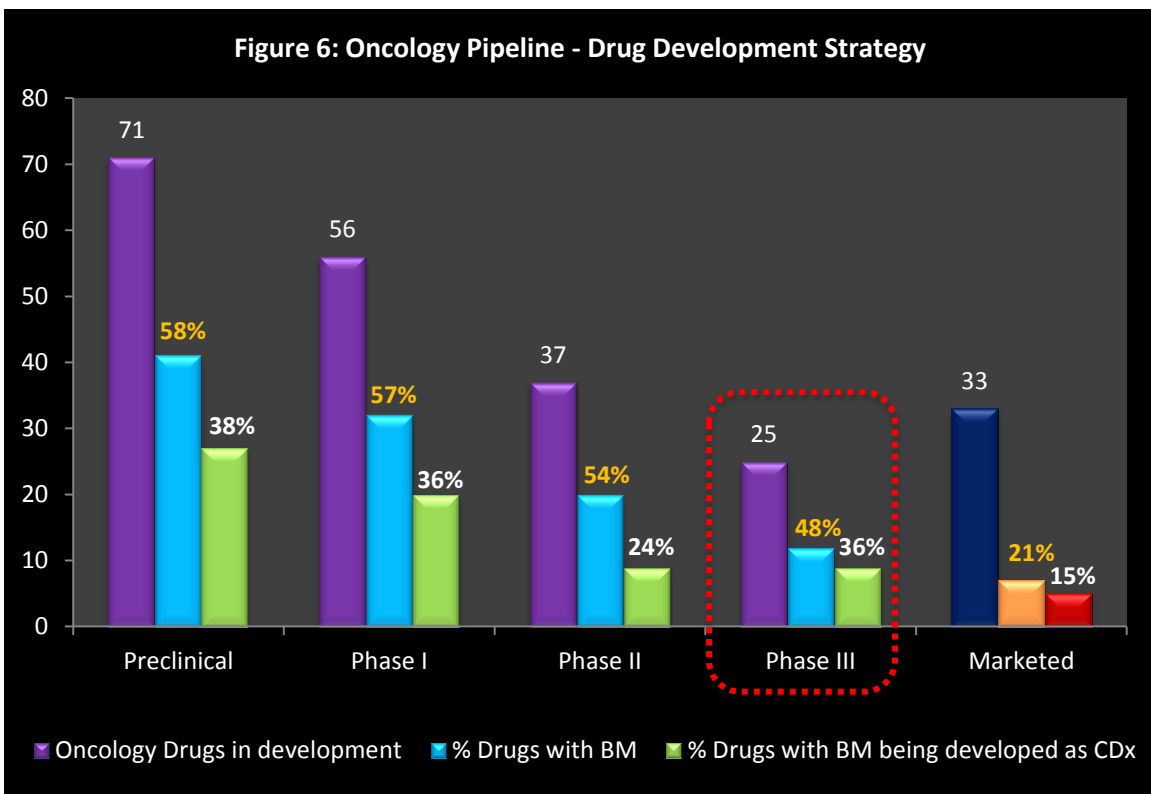
- The number of drugs currently in development, across various phases?
- Of those, the number of drugs that have an associated BM?
- Of those, the numbers that currently have a CDx co-development program?

Rationale

The intention was to gain an understanding of the current strategic approach of oncology companies related to biomarker use in drug discovery and development.

Results

Whereas the number of oncology drugs in development across all participating firms, from 71 NCEs in preclinical stage gets reduced to 25 in phase III, the



proportion of drugs in development that currently have a biomarker associated with it remains fairly stable, from 58% in preclinical to 48% in phase III. Moreover, the number of associated biomarkers being developed with the intent of launching them as a contemporaneously developed CDx remains fairly constant as well, from 38% in preclinical stages to 36% in phase III, except for a phase II dip to 24%.

Discussion

A significant percentage of oncology drug development programs today, are utilizing biomarkers right from the stages of initial discovery and target selection. However, it is also clear that the predominant use of biomarkers in discovery does not translate into an equal number of predictive biomarker programs throughout development. It's interesting to note that although drugs in the initial phases (I & II) have nearly a similar proportion of biomarkers featured in the development programs, in phase III the number of programs featuring biomarkers drops.

This first key observation can be understood in light of the growing uses of biomarkers from markers of drug efficacy, to monitors of treatment effectiveness, drug toxicity and development of resistance – all of which allows a drug developer to utilize biomarkers at different stages of development. Given, an associated biomarker is not considered a requirement for a compound to move into clinical development²², **unless a biomarker has the potential to either assist with positive or negative selection of patients, or act as a surrogate endpoint in clinical trials, its ongoing use in phase III studies may be limited.** A number of interviewees in the study acknowledged that although inclusion of an associated

²² Tufts CSDD Impact Report Volume 12, Number 6 • November/December 2010

biomarker from the preclinical stages is ideal, in some cases biomarkers may enter the development program as late as Phase III.

The second key observation from this question pertains to the proportionate rise in the number of companion diagnostic programs being co-developed in phase III compared to phase II, which indicates that selection of the right patient population prior to approval and launch is becoming intrinsic to oncology drug development strategy, and that **there is some level of positive selection for taking drugs with a potential CDx into phase III.**

In totality, the proportionate number of biomarker programs and CDx in late stage development, when compared to currently marketed drugs, refutes the hypothesis and instead suggest that a significant number of drug launches in the next five years may actually have a contemporaneously developed companion diagnostic associated with it.

Question 7:

Of the drugs in your pipeline with an associated BM, in your view, how many:

- Are likely to be launched in the next 5 years?
- What would be the expected position-in-class at launch?
- Also, of those how many would be launched with an associated CDx?

Rationale

Central to testing my hypothesis, the question's aim was to appreciate the likely number of CDx associated oncology drug launches from the participating companies

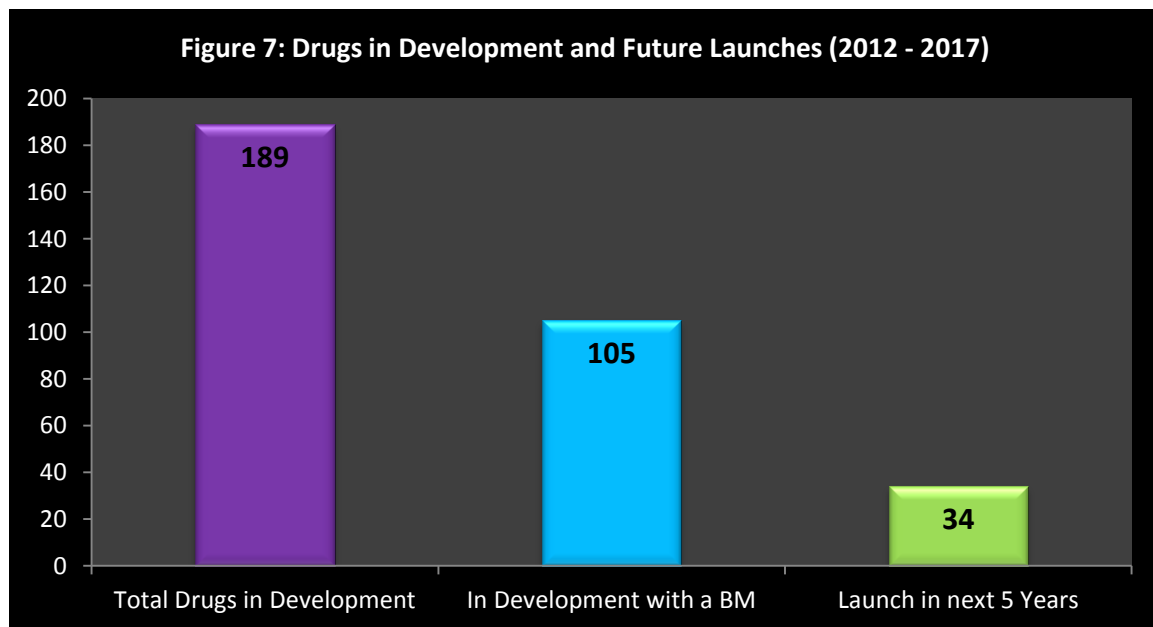
in the next 5 years, and also to understand if the launch position influenced the decision to launch with or without a companion diagnostic.

Results

In the next 5 years, the participants expect their companies to launch 34 oncology drugs put together, of which 20 drugs are likely to be launched with a contemporaneously developed CDx, with most launches being either first or second in class.

Discussion

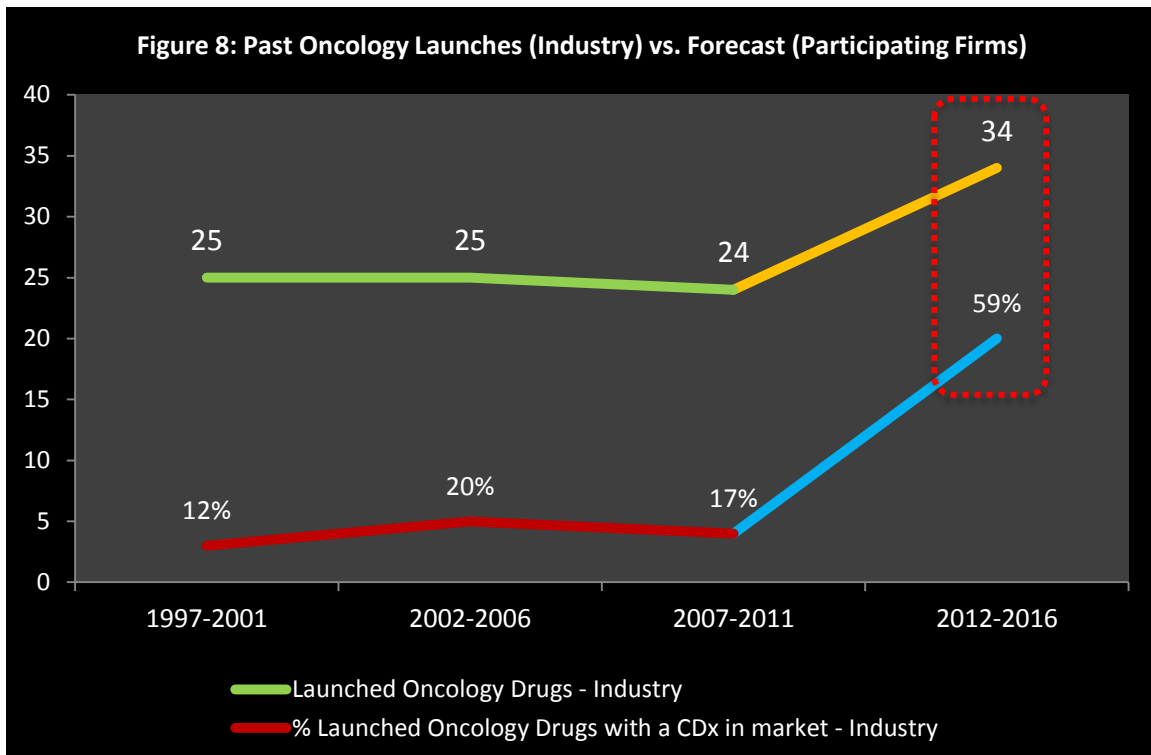
Right from the inception of the analysis the focus was on drawing conclusions based on a developer's strategic intent and preparation to launch, and not on referencing it with FDA's oncology drug approval rate to arrive at an accurate number of launches.



In all, the study participants' companies had 189 drugs in development, of which 56% had an associated biomarker, and based on their strategic approach to clinical trials and the current data emanating from their drugs, the developers were

confident that 34 of those could become approved therapies in the next 5 years. More importantly, the fact that 59% of those potential launches are expected to be with a CDx – indicates that a significant number of CDx associated drug launches in oncology are to be witnessed in the coming years, which does not agree with my hypothesis.

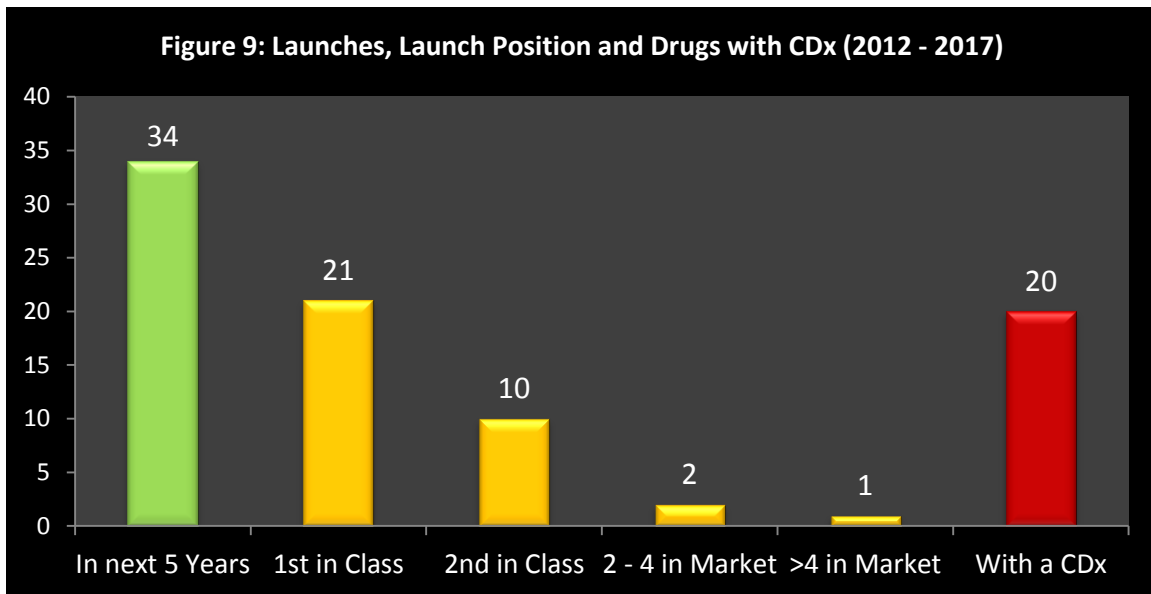
Also, considering that the **participating companies in the study cumulatively represented in excess of 60% of the global oncology revenues²³**, the impact of their pipelines on the future of oncology launches cannot be ignored. Hence, a comparison of the number of expected launches from the participating firms with the past oncology drug launches across the industry, point towards a major shift in CDx associated drug launches in the coming years – which emphatically refutes the hypothesis.



²³ IMS Health MIDAS MAT December 2010. Oncology defined as L1&L2

This finding confirms that in the next 5 years, the trend for the proportion of companion diagnostic based drug launches in oncology – is indeed headed towards a dramatic upturn.

The core assumption for the next part of this question was that the launch position of a drug points towards the intent of the developer in employing a companion diagnostic for their drug, at the time of launch. Based on that assumption, it was interesting to note that **in the next five years a large majority of oncology drug launches with a companion diagnostic are expected to be either 1st or 2nd in class**, which indicates that the strategic intent of the developers today is more focused at launching their drugs within a targeted population right from the start, than maximizing revenues by launching to as broad a population as possible, with little emphasis on the extent of efficacy in different patients.



Hence, only a small percentage of CDx associated drug launches are expected to be utilized in capturing market share from existing players in a class.

Question 13:

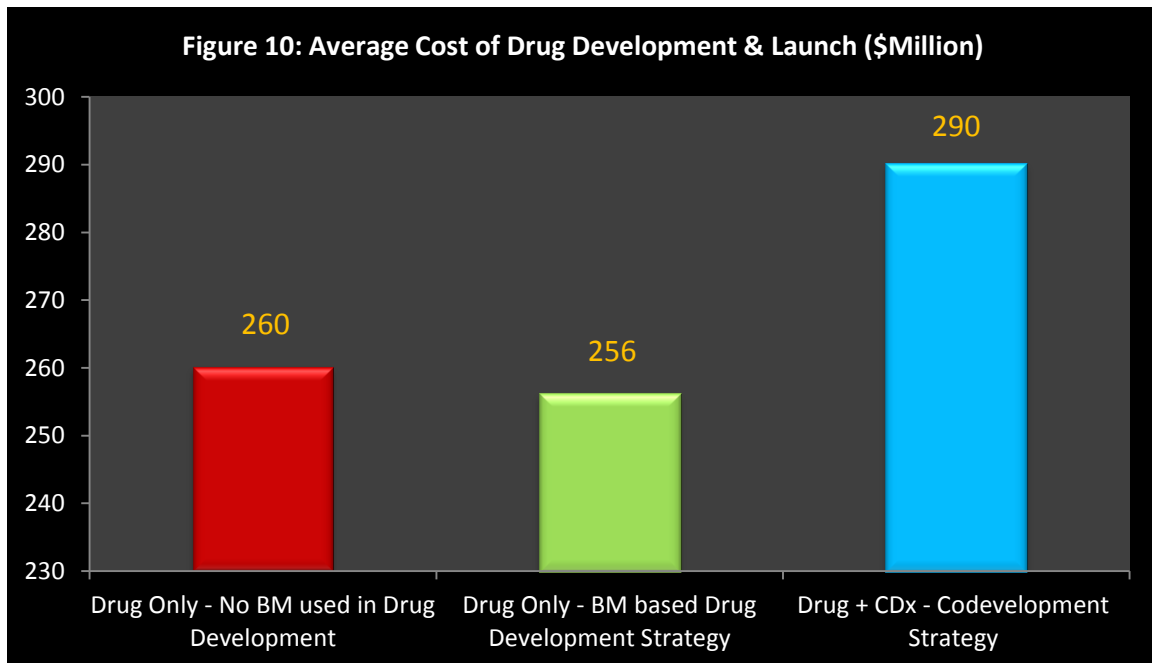
What in your view is the approximate cost of bringing an oncology drug to market? Of that, what percentage is the additional cost of co-developing a BM? In essence, what is the total cost of bringing an oncology drug with a CDx to market?

Rationale

The aim of this question was to ascertain if the cost of co-developing and launching a CDx was a factor in determining, whether a drug gets launched with a CDx or not.

Results

Based on the responses received, the cost of developing and launching an oncology drug ranged from \$120-350million, and averaged at \$260million. The cost of developing the drug with an associated biomarker ranged from \$132-380million, albeit the average was only \$256million, and added to that the cost of further developing and launching the biomarker as a CDx, increased the overall cost to \$150-400million, with an average of \$290million.



Discussion

Excluding the cost of failures and the time value of money, there was general consensus among the interviewees that the **overall cost of developing and launching an oncology drug hovered around \$260million**. Additionally, most interviewees were of the view that the use of biomarkers during the development phases had the potential to reduce this overall cost, even though just marginally.

Moreover, considering the dismal outlook of the current reimbursement environment for companion diagnostics, in the perspective of the interviewees the cost of launching a drug with a CDx was certainly higher. Although it was not considered as significant in the grand scheme of a successful oncology drug launch, where an optimally priced drug for a selected patient population usually has the potential to recoup the additional cost of co-developing and launching of its companion diagnostic.

5.3 Biomarker Strategy – Oncology Drug Development

Question 5:

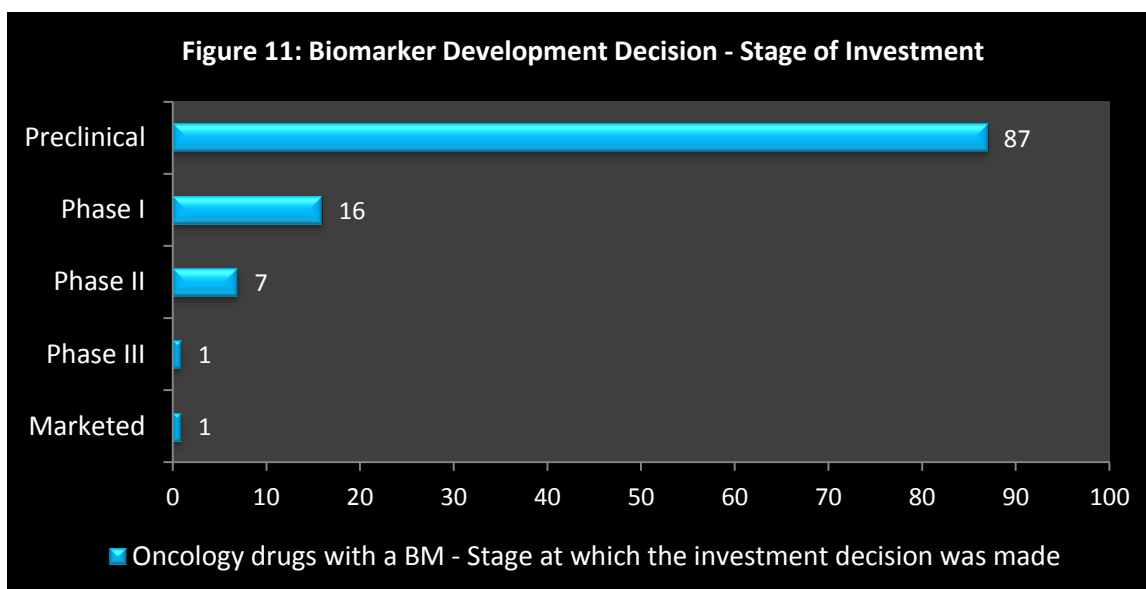
Of the drugs in your pipeline with an associated BM, at what stage of their drug development was the decision to invest in their BM development implemented?

Rationale

Considering that commencement of an associated biomarker program later than Phase I, makes it harder for the biomarker to be included in trials that may allow for its co-labeling on the therapeutic²⁴ - this question was meant to unearth the extent to which biomarkers today are being used for improving development productivity.

Results

The data collected shows that for all oncology drugs with an associated predictive biomarker in various stages of development, the decision to invest in their biomarker programs was predominantly initiated in the early stages of drug discovery and development: 78% in preclinical, 14% in phase I and 6% in phase II.



²⁴ Blair E (2004), Surrogates & diagnostics in today's pharmaceutical development. Caxton, UK: Integrated Medicines Ltd.

Discussion

More importantly though, the data also indicate that for oncology drugs with an associated biomarker program in Phase II and III of development (Figure 6), the decision to invest in their biomarkers was made early on, therefore the **strategic intent of the developers for using biomarkers was to improve development productivity and to positively impact the performance of their drugs in the later stages of clinical trials**. Thus, the finding appears to falsify my hypothesis.

Question 6:

What drove the investment timing in these BM development decisions?

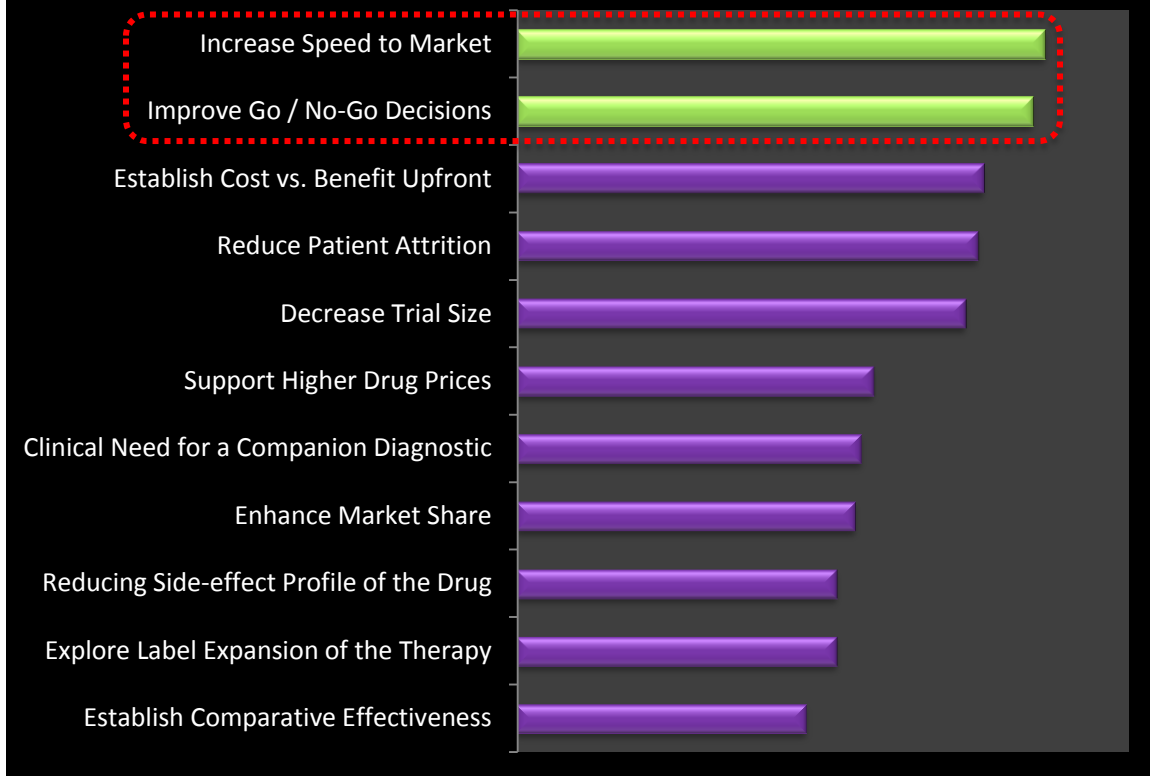
Rationale

Understanding the reasoning behind biomarker investments in oncology drug development was the second part of my hypothesis. Hence, this question was meant to appreciate how important was increasing price and market share of drugs to the drug developers, and if improvement of discovery and development productivity had a significant role. The interviewees were asked to **rank the reasons** that drove their investment decisions for co-developing a predictive biomarker.

Results

Consolidation of all rankings indicate that increasing speed to market and improving go/no-go decisions were the two highest ranked reasons for investing in an associated biomarker program. The next tier of key drivers were establishing the cost vs. benefit of drug candidates early on, reduce patient attrition during trials and decreasing the size of clinical trials.

Figure 12: Ranking of Decision Drivers - Biomarker Investment Strategy



Discussion

Quite unanimously, the interviewees pointed out that the **single most important use of an associated biomarker program was to enhance the probability of success for their drug in development, approval and launch.** They reasoned that in the background of high Phase III failures rates for oncology therapies, coupled with a more conservative FDA approval process, the most important consideration for drug developers today was improving the chances of their drug’s launch, translated which meant having a more productive discovery and development program. A few interviewees also spoke about the upcoming challenges in the reimbursement environment, where **the idea of “pay-for-performance” in oncology was beginning to take hold.** Payers, they said, are no longer willing to

pay for drugs that just work 10% of the time, and regulators were challenging improved progression free survival rates as clinical benefit, and instead were seeking to see significant improvements in overall survival rates. **Premium pricing in oncology drugs, they thought was still possible, as long as the therapy provoked a remarkable improvement in the condition of a well-defined patient population.** To sum it up, the interviewees were more interested in using biomarkers for increasing the efficiency and the overall number of successful launches, than adding value to their franchises by price increases and market share capturing strategies.

Question 11:

Would you take a candidate forward, in absence of an associated biomarker, and under what circumstances? Please explain briefly.

Rationale

The purpose of this question was to understand the extent to which the use of biomarkers is assumed as critical to oncology drug development.

Results

The breadth of responses to this question can be best observed by reviewing some of the actual replies – a selection is given below:

Large biopharmaceutical executives:

- “Yes of course! This is cancer we are talking about – as long as our drug can increase the overall survival rate, we will launch it”

- “If the efficacy and safety profile of the drug is interesting, we will proceed – BM or not”
- “You can’t always find a biomarker, as long as the NPV is positive we continue moving forward”
- “Absolutely, you need to be opportunistic – as long as the drug can target a well-defined population, you don’t always need a biomarker to personalize a therapeutic”

Small biotechnology executives:

- “No, not in oncology at least – today CDx are a must”
- “Not really, without the knowledge of MOA it’s very hard to assure a thumping success in phase III trials”
- “Yes, if the response rate is at least >30%, however if a biomarker increases it to >70%, then we will prefer to wait and co-develop”
- “Yes, if my drug targets a genuine unmet need. In some cases, any response is better than none – of course, awareness of pharmacological properties and MOA always helps. Our focus is to continuously model our drug’s success, right until launch, and launch only if makes business sense”

Discussion

Despite the fact that currently a majority of oncology drugs are launched in absence of an associated biomarker as a CDx, many interviewees felt that **today we are at an inflection point in terms of biomarker use in late stage clinical trials and their ultimate launch as co-developed diagnostics**. Most also felt strongly about oncology as a therapy area where using a biomarker based development strategy

was crucial to success. The overall impression was that although efficacy, safety and commercial potential of a therapy, with or without a biomarker, were the primary considerations in a launch strategy – the knowledge of the drug’s mechanism of action, its pharmacological properties and the identity of the group of patients it benefited most, greatly enhanced its chances of approval and launch success. According to interviewees, **even in the absence of a biomarker, the core principle of selecting and catering to the patient population that best responds to a drug, stands.** Therefore, in a situation where in absence of a biomarker a drug’s response rate was 30% in a relatively undefined population, and was 70% in a stratified population with a biomarker, developers preferred to launch in the smaller but more responsive patient group, albeit with premium pricing.

5.4 Companion Diagnostic Strategy

Question 8:

Of the drugs in your pipeline that have an established associated CDx program, at what stage of their BM development was the decision to invest in a CDx made?

Rationale

Considering that not all associated biomarkers are co-developed as CDx (Figure 6), the aim here was to identify the extent to which the decision to co-develop a biomarker into a CDx were being taken in the later stages of drug development – where the decisions are more often driven by pricing and market share concerns, than for enhancing the clinical performance of a therapeutic.

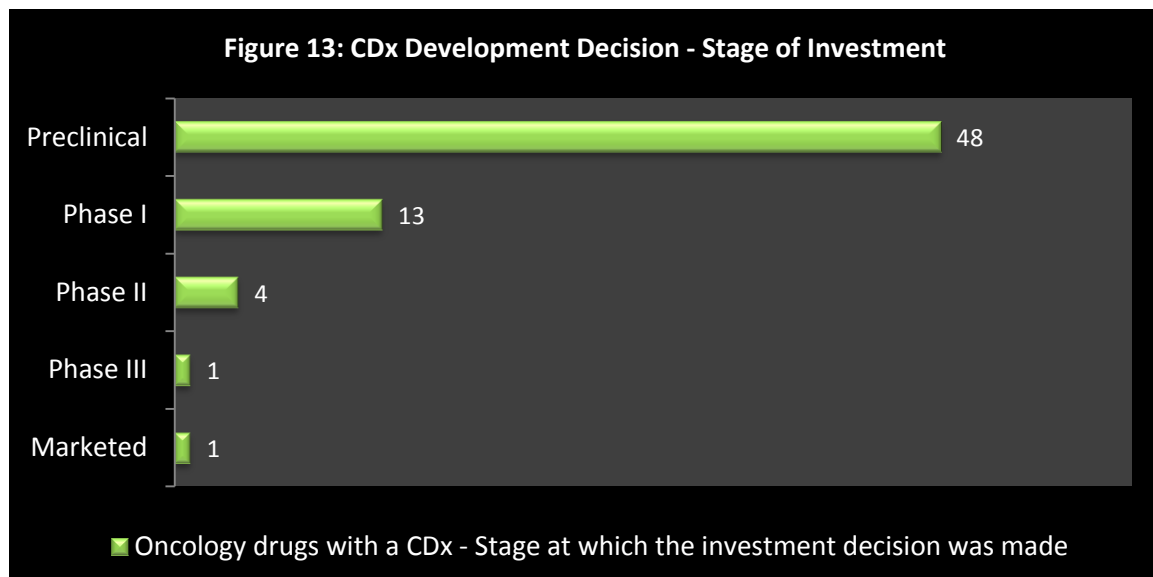
Results

Inferring from the participating firms data, for 72% of the oncology drugs with a contemporaneous CDx currently in development, the decision to invest in a CDx program was made in the preclinical stages. Another 19% of the drugs got their CDx investment in phase I of their development. There were a handful of decisions made in phase II (6%) and minimal investment decisions made in phase III or post launch.

Discussion

Until recently, the CDx strategy for most drug developers was to wait until receiving FDA approval for their drug, and only then, if it made commercial sense, make that extra investment into developing a CDx. In few cases, a Phase III failure could also motivate the drug developer to investigate the possibility of investing into a CDx, to give their drug another shot at approval.

However, in the last 5 years the trend has been shifting towards exploring the possibility of co-developing a companion diagnostic right from the discovery stages, when core decisions about target selection and associated biomarkers are being made. This can be demonstrated by the data collected for this question – of all drugs being co-developed with CDx today, 91% of the programs were initiated in the preclinical and phase I of development.



Translated which means, that **most oncology firms today are embracing the idea of developing personalized therapies for a stratified population**, which could lead to superior clinical outcomes and better therapy compliance²⁵, which in turn could establish their drug’s comparative effectiveness²⁶, thus allowing them to achieve premium pricing for their launches. Moreover, launching their drug as a first or best in class therapeutic, with a proprietary CDx could potentially raise the barrier to entry for future competitors – hence prolong their drug’s lifecycle.

²⁵ Silver et al (2009), The Case for Personalized medicines, Ernst & Young Global Biotechnology Center, Personalized Medicine Coalition, page 3

²⁶ Weinstein MC, Skinner JA. Comparative effectiveness and health care spending—implications for reform. *N Engl J Med* 2010;362:460–465.

Question 10:

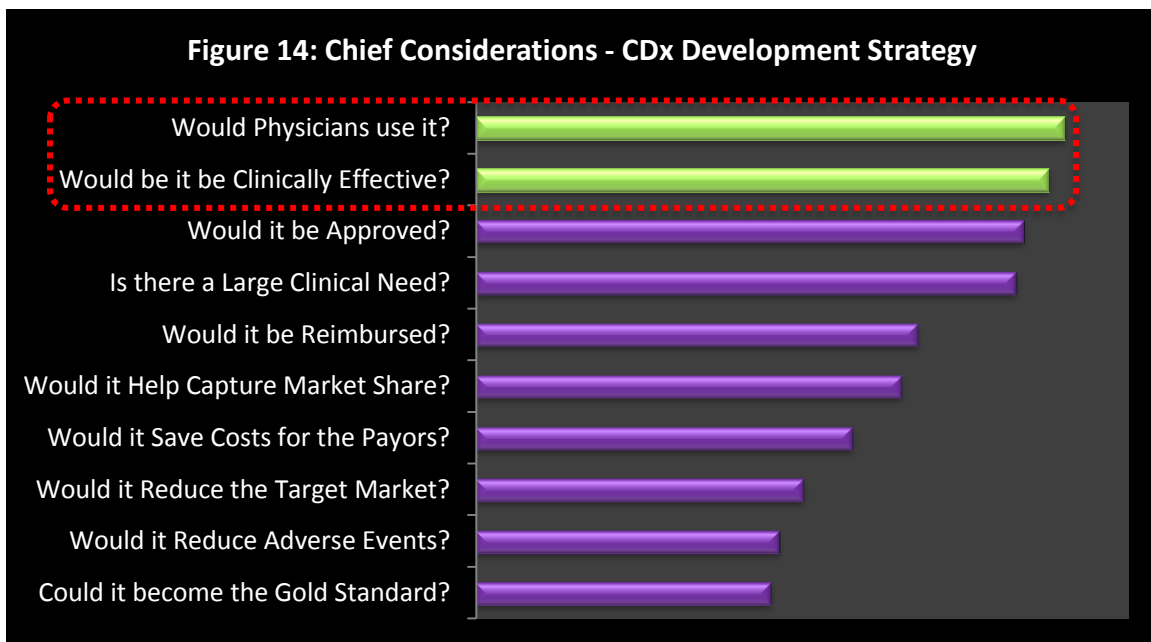
What are the chief considerations that may influence the investment decision for a CDx development program?

Rationale

Only a handful of oncology companies today have a fully integrated diagnostic division; the majority of CDx co-development depends on collaborations with external partners²⁷, as evidenced by the rise of oncology biomarker and diagnostic deals in the past few years – from just 15 in 2006, to over 200 deals in 2011²⁸. Consequently, to appreciate the motivations of drug developers while inking these deals became crucial to testing my hypothesis.

Results

Among all motivations for developing a CDx, the drug developers ranked adoption of



²⁷ Dawkes, A., (2007), The Strategic Importance of Biomarkers to the Pharmaceutical Industry, available at http://files.pharmaventures.com/biomarkers_pharmaventures.pdf, Accessed Aug 21, 2011

²⁸ Poile, S., (2011), Recent trends in personalized medicine oncology deal making, available at <http://www.londonbiotechnology.co.uk/Events-and-publications/Publications/Recent-trends-in-personalized-medicine-oncology-de.aspx>, Accessed Aug 21, 2011

the CDx by the physicians and the assays' effectiveness in making clear clinical decisions, as being most important.

Discussion

The feedback from the interviewees clearly indicated that the **ability of a CDx in assisting physicians make treatment choices in the clinic was the prime motivator** for developing it. It was less important for the drug developers to enter into a CDx co-development agreement merely to improve their ability to capture market share, which demarcates a clear departure from the earlier stand of biopharmaceutical companies (McKinsey, 2009)²⁹ to employ a CDx strategy only in the later stages to maximize the revenue potential of their therapeutic.

Question 9:

What is your preferred approach towards a CDx development program? Please briefly mention your rationale.

Rationale

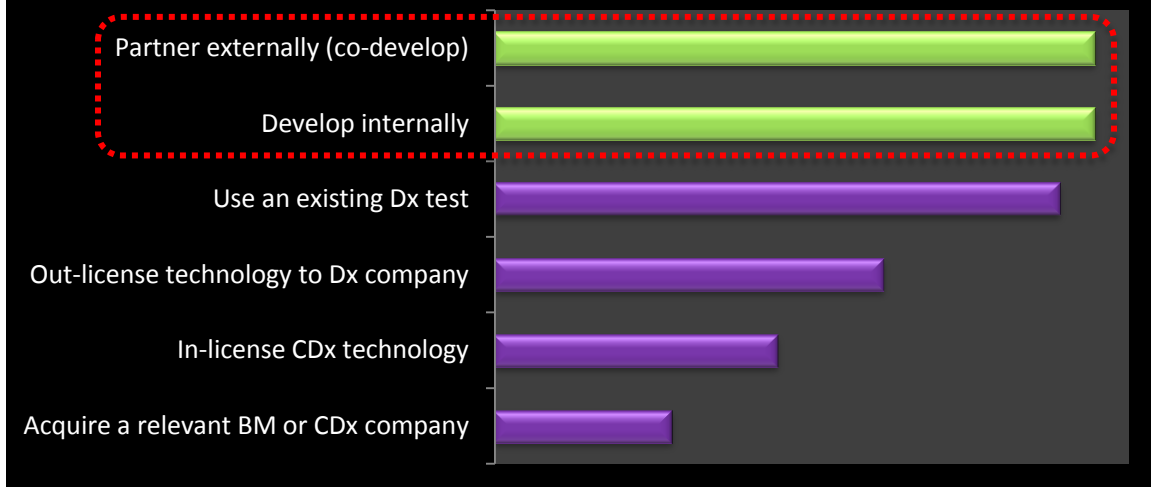
The goal was to unearth if a particular CDx development approach was attractive to small and large oncology firms alike, and additionally understand that besides external partnerships, what other strategies were being employed by firms to enhance the co-development nexus between their drug and diagnostic.

Results

80% of drug developers favored external partnerships, and only a couple of large biopharmaceuticals chose internal development strategy as their first preference.

²⁹ Ma et al. (2009) The microeconomics of personalized medicine: Today's challenge and tomorrow's promise, Nature Reviews Drug Discovery Vol. 8 April 2009, 279 - 286

Figure 15: Ranking of CDx Development Strategies - Participant Firms



Discussion

Considering that only Roche and Novartis in the study group had an internal diagnostic division, their preference to develop CDx internally is well understood. For the rest of the study participants, **external partnerships made most sense**, especially considering the amount of resources needed to build a new non-core business with low margins. However, few of the large biopharmaceuticals also noted that with a more favorable regulatory and payer environment, they would consider internal development of their CDx or even prefer it.

Question 12:

Would you launch a 2nd or 3rd in class drug to market without a CDx, if the first therapy to market did not launch with one? Please explain briefly.

Rationale

The aim here was to understand the role of CDx in capturing market share in an undifferentiated market.

Results

The question provoked interesting responses from the interviewees, few chosen ones are presented here:

Large biopharmaceutical executives:

- “It depends. Our aim is to differentiate our drug right from the launch and show superior value via better efficacy and safety data, so if a CDx helps our cause, we will invest for developing one”
- “Yes, if the NPV is positive”
- “If we could isolate a patient population that closely matched our drug’s profile based on science and data, and allowed us to corner a market – the non-CDx path is better, it’s less complex and saves resources”

Small biotechnology executives:

- “Generally speaking we’ll shy away from ‘me-too’ approaches, unless we could show efficacy where others have failed – which may well require a CDx approach”
- “Yes, there is a strong business case for launching more efficacious drugs in several crowded markets – a CDx is not always necessary to cross the bar”
- “Yes, if the efficacy and benefit/risk profile of the drug in a defined niche population is superior to competitors”

Discussions

In the view of the interviewees, within oncology, it increasingly making less sense to launch a “me-too” drug – **any new launch must significantly improve the efficacy and safety outcomes for patients compared to existing therapies.**

5.5 Personalized Medicine – Challenges

Question 14:

In addition to what has been covered above – what else in your view encourages or discourages the inclusion of a CDx program during the course of drug development?

Rationale

With an open ended question like this, the objective here was to explore – what, if anything still hindered the oncology drug developers from increasing the proportion of companion diagnostic driven personalized medicine launches in years to come.

Results

This was one of the most profusely discussed portions of the interview and evoked passionate responses from the interviewees, few of which are accounted below:

- “Co-development is not easy; the approaches differ significantly for the drug and diagnostic development, so bringing them together on the same page in quite challenging. Historically the industry has not been structured for this kind of work, although things are changing”
- “Finding the right development partner is crucial – if the incentives are not aligned - it’s almost impossible to make progress”
- “The fact that you need to file for a NDA and a PMA simultaneously in two different sections of the FDA doesn’t help”
- “A single stable technology platform during development is critical, any loss of data can set you back by years, and standardization of hardware, software and test reagents through the life of a project still poses a major challenge”

Discussion

Consolidating the findings from this section of the interview, gives an impression that the presence of a distinct biomarker, and its co-development as a CDx, at least in theory, has the potential to bestow on its associated drug in development, the benefits of an orphan drug – fast track approval, premium pricing and possibly a monopolistic market position, reasons that should adequately encourage drug developers to think about co-development of a CDx. However, the dearth of CDx associated launches, indicate towards developmental or launch hurdles – potentially due to the misaligned perspectives and incentives of the stakeholders involved³⁰. Despite known benefits, there are several challenges to biomarker driven drug discovery and co-development of CDx within the current environment, which could discourage an oncology drug developer in taking on the personalized medicine approach to R&D. Some of these challenges are illustrated below:

Scientific Challenges

- Our ability to truly appreciate the complex molecular mechanisms of a heterogeneous disease like cancer is still limited, and by extension so is our understanding of the mechanism of action of drugs used for treating it
- Target identification and validation is largely hypothesis driven, and less often data driven, which adds to the complexity of accurately isolating a clear biomarker early in the drug discovery process
- Lack of relevant animal models to identify and develop candidates, make biomarker discovery inefficient and cumbersome

³⁰ Dunn et al, Advocacy in personalized medicine: a developing strength in a complex space, *Personalized Medicine* (2010) 7(2), 179-186

- Most conduct the work in humans, due to a lack of models but also due to the limited availability of diverse tissue types in tissue banks, which restrict the extent to which prospective studies can be conducted

Economic Challenges

- Until recently, the economic incentives for drug developers to co-develop a CDx has remained largely unclear
- CDx by themselves are not widely reimbursed, hence its appeal as a standalone business model is limited

Regulatory Challenges

- Despite the proposed guidance on July 14th, 2011 (Appendix D), the obscurity of FDA policies for development and approval of CDx, keep co-development a daunting undertaking for majority of oncology drug developers

Industry Legacy Challenges

- Historically, the pharmaceutical industry has been organized for producing mass used products, therefore to many the concept of stratification of patient population still sounds like the death knell of a potential blockbuster. Consequently, even until 2009, several corporations confirmed that CDx was not a priority and they were taking a 'cautious' approach to investments³¹
- The realization that the **payer attitude towards reimbursement of oncology therapies is shifting from 'pay to play' to 'pay to perform'**, is gradual across the industry, leading to a continued wait-and-watch approach towards the success of CDx co-development programs

³¹ Ma et al. (2009) The microeconomics of personalized medicine: Today's challenge and tomorrow's promise, Nature Reviews Drug Discovery Vol. 8 April 2009, 279 - 286

Notwithstanding the challenges noted above, several interviewees observed that in the last 5 years the biopharmaceutical industry's mindset has been shifting slowly, and since it takes time to develop drugs, it will be sometime before this shift can be witnessed in CDx associated drug launches.

Given that perspective, and also considering that today the biopharmaceutical industry has a lot more targeted therapeutics in the pipeline than ever before and some of them, like Zelboraf and Xalkori, are on the market, most interviewees concurred that it is safe to assume that the value proposition of co-developing a CDx is beginning to be appreciated across the industry, and that this strategic approach to drug development has probably achieved critical mass.

6. Conclusion

The aim of the study was to test my hypothesis that in the next 5 years, CDx associated drug launches could exceed the current trend by at least 100% i.e. could double, and also to ascertain if increasing prices and market share of launched drugs were the top drivers for CDx investments.

Based on data collected from the interviews, whereas only 15% of the drugs marketed by the participants firms have a CDx, their current oncology pipelines has on average 54% drugs associated with a predictive biomarker across all phases of development, of which 62% are being developed as a companion diagnostic. Thus, across all oncology drugs in development, within the firms represented, close to 34% of drugs have a CDx in development (Figure 6), which means that in this decade a much larger proportion of oncology drugs would be launched with a CDx. More specifically, the participants expect their firms to launch close to 34 oncology drugs in the next 5 years, of which 20 are expected to be launched with a contemporaneously developed CDx (Figure 8). Considering that in the previous three 5-year periods the share of CDx associated oncology drug launches has been 12%, 20% and 17% (Figure 8) – the expectation that the share in the next 5 years would be 59%, indicates a jump of more than 350% - which refutes my hypothesis.

Further, the data indicated that of all expected oncology launches from the participating firms, nearly 90% were expected to be launched either as 1st or 2nd in class (Figure 9), which are launch positions where conventionally drugs do not need

to focus on capturing market share from an existing competitor, which suggests that investments in predictive biomarkers were not being driven by pricing or market share concerns. Additional data confirmed that the investment for discovering 92% of the predictive biomarkers were made either in preclinical or phase I stages of drug development (Figure 11) - similar results were observed for CDx investment decisions as well (Figure 13), these findings support the assertion that the developers' decision to invest in predictive biomarkers and develop them as CDx, were NOT driven by an objective to increase prices or market share of their associated drugs' post launch. Furthermore, results obtained from the drug developers ranking of reasons for investing in discovering a predictive biomarker (Figure 12) and developing a CDx (Figure 14) confirmed that shortening the drug development time and improving the quality of decisions during development was more important, than raising prices and enhancing market share - both of which were ranked lower than the top 5 reasons. Taken together, these observations falsify my hypothesis that increasing prices and market share of launched drugs are the top drivers for making predictive biomarker discovery and CDx development investments.

6.1 Limitations

Bearing in mind that today there are in excess of 2,500 oncology drugs in various stages of development³², this study just scratches the surface in terms of isolating drugs in development that may be utilizing a biomarker strategy or co-developing a CDx – but then, the study was never designed to reach statistically significant conclusions.

The selection of companies and participants was driven by a conscious effort to learn from the perspectives of a broad genre of oncology drug developers, in various stages of maturity. Nonetheless, the possibility that a selection bias might have crept in and partially skewed the study's outcome - is real, some of which are presented below:

Participant Selection Bias

Although 90% of all participants selected for the study responded, the selection was based on personal contacts and networks, where few of the interviewees knew each other, which may have induced some degree of collective bias in their perspective.

Company Selection Bias

While the inclusion of 4 top oncology companies³³, with a market share in excess of 60%, ensured that the study had a solid foundation, the perspectives gathered from some of the most promising oncology startups guaranteed that the study benefitted from the cutting edge thinking around early stages of oncology drug development. However, addition of few midsize firms could have furthered enhanced the study's integrity.

³² Pharma R&D Annual Review 2010, Pharma Projects, available at: http://www.pharmaprojects.com/therapy_analysis/annual-review-2010-therapies.htm Accessed at Aug 28, 2011

³³ IMS Health MIDAS MAT December 2010

Geography Selection Bias

Considering that most interviews were conducted with firms based in US or EU, and none from emerging markets, the study's results cannot be extrapolated globally.

7. Discussion

Although, the concept of personalized medicine pervades several therapy areas, it is more frequently explored within oncology, and considering that majority of the CDx associated drug launches have been within oncology – it was chosen to be the focus of this study.

Designed as a pilot study to examine the prevailing trends in oncology drug development, in particular pertaining to the use of biomarkers in drug discovery and co-development of companion diagnostics, the aim was to get an impression of the extent of expected CDx associated drug launches in the next 5 years, and to develop an understanding of the oncology drug developers' motivations when embarking on a CDx co-development program.

Drawing on the interviewees' responses, it was apparent that the **core business question** for oncology firms, like any other business, remains unchanged – **how to secure a market quickly and efficiently, and how to keep it secure for the longest possible duration**. In other words, the more closely aligned the market definition is to the drug's profile, the harder it is for the competition to break in. Isolating a clear biomarker during discovery and co-developing it as a CDx are yet another set of tools that can be used to identify a market, and emphatically win the battle of efficacy and safety between oncology brands within a defined market.

While there is consensus that biomarker driven discovery and development improves the probability of success of a drug program, the wisdom of co-developing the biomarker as a CDx is still questioned – drug developers do not want to target smaller populations. However in the wake of recent successes of CDx associated drug launches like Zelboraf and Xalkori, it is becoming clearer that the benefits of co-developing a CDx outweigh the risks and costs.

That a BM narrows the patient population is true, but that gives the potential for greater efficacy in selected patients, as the underlying mechanism is better defined. Considering that clinical trials are the single-largest expense item associated with drug development, both in terms of cost of recruitment and the time taken to recruit the relevant patients – it pays to have a selected population, which is more likely to respond well. Smarter, shorter clinical trials not just increase the probability of a drug's success but allow for a premium pricing option for the drug on approval. **Taken together, the higher probability of success, lower development costs, shorter time to market, pricing power and potential to corner a market or secure an increased market share – are serious economic benefits, which can more than offset the risks and cost of co-developing a CDx.**

Essentially, the study refutes the initial hypothesis, and instead indicates that in the next 5-10 years the number and proportion of CDx associated drug launches would significantly increase, which is evidenced by the trends observed in the current pipeline of participating oncology companies.

Moreover, recent data obtained from Roche – the largest oncology company in the world, point towards the rise in collaborations between Roche’s biopharmaceutical and diagnostic arms, from just 1 CDx project in 2006, to 22 in 2010 – of which most were in oncology³⁴ - further endorses the study’s finding that CDx associated drug launches in oncology would become more common within this decade.

Additionally, an analysis of drug developers’ motivations for adopting a biomarker driven CDx co-development strategy, failed to confirm the hypothesis that increasing price and market share of launched drugs was more important to drug developers, on the contrary **most drug developers wanted to use biomarkers to increase their drug’s probability to launch**, by making more informed go/no-go decisions along the developmental pathway and, to reduce the time it takes to launch their drug.

Bottom line, in oncology, launching more efficacious drugs, more efficiently, will be the key to future commercial success – it no longer matters if the launch is a blockbuster or a nichebuster.

³⁴ Roche Presentation - ASCO 2011, 47th Annual ASCO Meeting, Roche Analyst Event, Sunday June 5, 2011 - Chicago

7.1 Further Research

It was in the midst of this study, on July 14th that FDA proposed guidelines for the development and approval of CDx. Although the proposed development pathway is still complicated, the policies do bring clarity to the processes involved, and is likely to encourage drug developers interested in pursuing a co-development strategy. More importantly though, with two fast approvals of Zelboraf and Xalkori, all within the timeframe of writing this thesis, FDA has in-effect reinstated its stance (Appendix D) on CDx associated drug launches, which in effect will encourage more drug developers to consider this strategy.

In light of these events, this study should serve as a roadmap for follow-up research with larger, more balanced samples of drug developers, to gain a broader perspective on co-development of CDx as a strategic approach, for launching safer, more efficacious and premium priced oncology drugs, within record approval times.

Future studies should also include other key stakeholders, such as providers and payers, so that their impact on the strategic choices made by oncology drug developers can also be appreciated.

7.2 Implications

Oncology companies today, have to continue being opportunistic and data driven while making strategic development decisions – a dogmatic approach to biomarkers, or making a companion diagnostic strategy mandatory for every drug candidate is not conducive to the high risk, and fast evolving environment of cancer drug development.

That being said, **the transition of companion diagnostics from a ‘nice to have’ to a ‘must have’ is inevitable** - as crowding in oncology therapies become rampant with more drugs targeting the same pathway and molecular target.

In essence, contemporaneously developed companion diagnostics are a potent strategy for truly differentiating novel oncology therapeutics and showing superior value to stakeholders involved.

Appendix A: List of Oncology Therapeutics approvals¹ (1995 - 2011)

Cancer NDA Approvals - USA FDA -1995 - 2011																
1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Ethylol	Aredia	Femara	Herceptin	Aromasin	Mylotarg	Gleevec	Eloxatin	Iressa	Alimta	Arranon	Dacogen	Ixempra	Treanda	Afinitor	Halaven	Sylatron
Intron A	Arimidex	Gliadel	Neupogen	Busulfex	Trisenox	Zometa	Faslodex	Velcade	Clolar	Nexavar	Sprycel	Tasigna	Mozobil	Folotyn	Jevtana	Caprelsa
Leukine	Camposar	Rituxan	Nolvadex	Doxil	Trelstar	Femara	Eligard	Plenaxis	Tarceva	Revlimid	Sutent	Torisel	Degarelix	Istodax	Provenge	Yervoy
	Eulexin	Taxol	Photofrin	Ellence	Viadur	Campath	Neulasta	UroXatral	Vidaza		Zolinza	Tykerb		Votrient	Xgeva	Zytiga
	Gemzar		Proleukin	Temodar	PACIS		Zevalin	Bexxar	Sensipar		Vectibix	Hycamtin		Arzerra		Zelboraf
	Hycamtin		Valstar						Avastin							Adcetris
	Lupron		Xeloda					Eribitux								Xalkori
	Taxotere															
	Zoladex															
3	9	4	7	5	5	4	5	5	7	3	5	5	3	5	4	7
0	1	0	1	0	1	1	0	1	2	0	2	2	0	0	0	2

Drugs with Companion Diagnostic

Oncology Drugs with a companion diagnostic on the market²

¹ CenterWatch, FDA Approved Drug Therapies in Oncology, available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?AreaID=12> Accessed Aug 13, 2011

² Cohen, J., Tufts CSDD Report, Volume 13, Number 4, Page 2, July/August 2011

Industry Survey for Student Research

Name	
Position	
Company	
Phone	

Despite the widely accepted promise of biomarker (BM) and companion diagnostics (CDx) in improving outcomes for cancer patients, payors and regulators – there are but a few examples of successful prospective diagnostic and therapeutic co-development. Why??

Please answer the following questions based on your own experiences, perceptions, and opinions. **Your responses will be kept strictly confidential and anonymous**, and will be used solely in connection with my research as a graduate student in the Biomedical Enterprise Program of the Harvard-MIT Division of Health Sciences and Technology and MIT Sloan School of Management.

Question 1:

How long have you been associated with commercialization of **oncology products**, and in what roles?

Experience (Tick one)		Roles (Please mention all that apply)	
5-10 years	<input type="checkbox"/>	1.	<input type="checkbox"/>
10-15 years	<input type="checkbox"/>	2.	<input type="checkbox"/>
15-20 years	<input type="checkbox"/>	3.	<input type="checkbox"/>
> 20 years	<input type="checkbox"/>	4.	<input type="checkbox"/>

Question 2:

How many **oncology drug development projects and launches** have you been involved with? Of those, how many had an associated BM during drug development and how many were actually launched with a CDx?

# Projects	# Launches	# Associated BM	# Launched with a CDx
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Question 3:

What is your company's **approximate annual revenue** from oncology products? Also, what's your **approximate annual R&D budget** within oncology?

< \$100 M	\$100 – \$500M	\$500M – \$1B	> \$1 B
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Annual R&D budget - Oncology	\$
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Question 4:

Please complete the following about your **current oncology pipeline** products:

- The number of drugs currently in development, across various phases?
- Of those, the number of drugs that have an associated BM?
- Of those, the number those currently have a CDx co-development program?

Drug stage	# Drugs in pipeline	# Associated BM	# Associated CDx
Preclinical			
Phase I			
Phase II			
Phase III			
Marketed			

Question 5:

Of the drugs in your pipeline with an associated BM, at what stage of their drug development was the **decision to invest in their BM development** implemented?

# Preclinical	# Phase I	# Phase II-a	# Phase II-b	# Phase III	# Marketed

Question 6:

What drove the **investment timing in these BM development** decisions? Please rank the following reasons in their order of importance (1 = most & 11 = least). If your rationale differed across your pipeline, please rank for your **top 3 candidates**.

Reasons for Investment	Drug 1	Drug 2	Drug 3
Decrease trial size			
Reduce patient attrition			
Enhance market share			
Increase speed to market			
Support higher drug prices			
Improve Go / No-Go decisions			
Establish cost vs. benefit upfront			
Establish comparative effectiveness			
Explore label expansion of the therapy			
Clinical need for a companion diagnostic			
Reducing side-effect profile of the drug			

Question 7:

Of the drugs in your pipeline with an associated BM, in your view, how many:

- Are likely to be **launched in the next 5 years**?
- What would be the expected position-in-class at launch?
- Also, of those how many would be launched with an associated CDx?

# Drug Launches	1 st in class	2 nd to launch	2 - 4 in market	>4 competitors
With a CDx				

Question 8:

Of the drugs in your pipeline that have an established associated CDx program, at what stage of their BM development was the **decision to invest in a CDx** made?

# Preclinical	# Phase I	# Phase II-a	# Phase II-b	# Phase III	# Marketed

Question 9:

What is your preferred **approach towards a CDx development program**? Please select one, or more if multiple approaches are being employed.

Develop internally	
Use an existing Dx test	
In-license CDx technology	
Partner externally (co-develop)	
Out-license technology to Dx company	
Acquire a relevant BM or CDx company	

Why? Please briefly mention your rationale.

Question 10:

What are the chief considerations that may influence the **investment decision for a CDx development program**? Please rank the following in their order of importance (1 = most & 10 = least).

If the investment rationale differs for each CDx, please rank the considerations below for the top 3 CDx development programs that you were involved with.

Consideration for a CDx	CDx 1	CDx 2	CDx 3
Would it be approved?			
Would physicians use it?			
Would it be reimbursed?			
Is there a large clinical need?			
Would be it clinically effective?			
Would it reduce adverse events?			
Would it help capture mkt. share?			
Would it save costs for the payors?			
Would it reduce the target market?			
Could it become the gold standard?			

Question 11:

Would you take a candidate forward, in absence of an associated biomarker, and under what circumstances? Please explain briefly.

Question 12:

Would you **launch** a 2nd or 3rd – in – class drug to market **without a CDx**, if the first therapy to market did not launch with one? Please explain briefly.

Question 13:

What **in your view** is the approximate cost of bringing an oncology drug to market? Of that, what percentage is the additional cost of co-developing a BM? In essence, what is the **total cost of bringing an oncology drug with a CDx** to market?

Launch Strategy	Cost of Development (\$)
Drug Only	
Drug + Proven Biomarker; but no CDx	
Drug + Effective Companion Diagnostic	

Question 14:

In addition to what has been covered above – what else in your view encourages or discourages the inclusion of a CDx program during the course of drug development?

Thank you indeed for your thoughts and time!! I will send you a copy of my thesis with the consolidated output from this industry wide survey later this fall.

Best regards,

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**To enhance homogeneity, the titles of few participants have been simplified in Figure 3*

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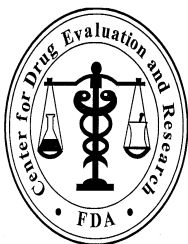
In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
Document issued on: July 14, 2011**

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709, or ocod@fda.hhs.gov; for questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research**

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number (1737) to identify the guidance you are requesting.

Additional copies of this guidance document are also available from:

Center for Biologics Evaluation and Research (CBER),
Office of Communication, Outreach and Development (HFM-40),
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448,
or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This guidance is intended to assist (1) sponsors who are planning to develop a therapeutic product¹ that *depends on* the use of an in vitro companion diagnostic device (or test) for its safe and effective use and (2) sponsors planning to develop an in vitro companion diagnostic device that is intended to be used with a corresponding therapeutic product.

Specifically, the guidance intends to accomplish the following:

- Define *in vitro companion diagnostic device* (hereafter referred to as an “IVD companion diagnostic device”)
- Explain the need for FDA oversight of IVD companion diagnostic devices
- Clarify that, in most circumstances, if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling
- Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA’s regulatory enforcement policy

¹ As used in this guidance, *therapeutic product* includes therapeutic, preventive, and prophylactic drugs and biological products. Although this guidance does not expressly address therapeutic devices intended for use with in vitro diagnostics, the principles discussed in this guidance may also be relevant to premarket review of such devices.

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- Describe certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device to ensure safety and effectiveness of the therapeutic product

FDA encourages sponsors considering developing either the therapeutic or IVD companion diagnostic devices discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions to ensure that product development plans will produce sufficient data to establish the safety and effectiveness of the IVD companion diagnostic device/therapeutic product pair.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word “should” in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Diagnostic tests have been employed for many years to enhance the use of therapeutic products. Tests are also used during therapeutic product development to obtain the data FDA uses to make regulatory determinations. After a therapeutic product is commercially available for use, health care professionals may use a relevant diagnostic test, for example, to select the appropriate patient for a particular therapy or to optimize a dosing regimen.

Recently, the development of therapeutic products that *depend on* the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. One reason for increasing interest is the emergence of new technologies that can distinguish subsets of populations that respond differently to treatment. These technologies are making it increasingly possible to individualize, or *personalize*, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect.

When an appropriate scientific rationale supports such an approach, FDA encourages the development of therapeutic products that *depend on* the use of approved or cleared IVD companion diagnostic devices — several such IVD companion diagnostic devices for use with corresponding therapeutic products have already been approved or cleared.²

When results from a diagnostic device are a determining factor in patient treatment, health care professionals must be able to rely on those results. Inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences. Such a device might

² Examples of currently approved IVD companion diagnostic devices that illustrate the importance of established performance parameters for both the therapeutic product and the IVD companion diagnostic device include FDA approved HER-2 testing to determine whether Herceptin (trastuzumab) therapy is indicated for treatment of metastatic breast cancer and gastric cancer. Herceptin lacks effectiveness in the HER-2 marker negative population, and also has the possibility of causing severe adverse effects. Therefore it is important to use an IVD companion diagnostic device to identify only those patients who could benefit from the therapy.

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fail analytically (e.g., by not accurately measuring the expression level of a protein of interest), or clinically (e.g., by not identifying those patients at increased risk for a serious adverse effect). Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy. Therefore, FDA believes that use of an IVD companion diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product. Because an IVD companion diagnostic device with inadequate “performance characteristics”³ or other issues related to safety and effectiveness could expose a patient to preventable treatment risks, FDA will assess the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic when a therapeutic product depends on the IVD companion diagnostic device for its safe and effective use.

To facilitate the development and approval of therapeutic products that are intended for use with IVD companion diagnostic devices, as well as the development of the IVD companion diagnostic devices themselves, FDA is clarifying relevant policies related to these devices and products. FDA is also developing appropriate internal policies and procedures to ensure effective communication among the relevant centers and to promote consistent and efficient product review.⁴

III. Definition and Use of an IVD Companion Diagnostic Device

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.⁵ The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic product.

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from a particular therapeutic product⁶

³ See 21 CFR 809.10 (b)(12).

⁴ In some cases, an IVD companion diagnostic device intended for use with a therapeutic product and that therapeutic product may together constitute a “combination product.” See 21 CFR 3.2(e)(3) and (4). Whether an IVD companion diagnostic device and therapeutic product would together, in fact, constitute a combination product should be determined on a case-by-case basis. Also, combination product status could affect regulatory requirements beyond the scope of this guidance. For additional information, please contact the Office of Combination Products or refer to their webpage on the Agency’s website at <http://www.fda.gov/CombinationProducts/default.htm>

⁵ Generally, this means that the use of the IVD companion diagnostic device with the therapeutic product allows the therapeutic product’s benefits to exceed its risks.

⁶ This may include identifying patients in a specific population for which the therapeutic is indicated because there is insufficient information about the safety and effectiveness of the therapeutic product in any other population. An example is a therapeutic that is indicated only for patients who by virtue of the presence of a marker in tumor cells are believed to be unlikely to respond to other therapies.

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- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product.⁷

Ideally, a therapeutic product and its corresponding IVD companion diagnostic device would be developed contemporaneously, with the clinical performance and clinical significance of the IVD companion diagnostic device established using data from the clinical development program of the corresponding therapeutic product — although FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD companion diagnostic device that supports the safe and effective use of a particular therapeutic may be a novel IVD device (i.e., a new test for a new analyte), a new version of an existing device developed by a different manufacturer, or an existing device that has already been approved or cleared for another purpose.

The following section outlines FDA’s policy regarding approval of a therapeutic product for use with a corresponding IVD companion diagnostic device.

IV. Review and Approval of IVD Companion Diagnostic Devices and Therapeutic Products

Applications for an IVD companion diagnostic device and its corresponding therapeutic product will be reviewed and approved according to applicable regulatory requirements. The IVD companion diagnostic device application will be reviewed and approved or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (Act) and relevant medical device regulations; the therapeutic product application will be reviewed and approved under section 505 of the Act (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations.⁸ FDA intends to review each IVD companion diagnostic device submission within the context of, or in

⁷ Examples of such tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) used to monitor organ function. Note, however, that circumstances may occur when use of such tests, in the context of the therapeutic product, rises to an IVD companion diagnostic device level and approval or clearance for such use will be necessary. Note also that a novel IVD device providing information that is useful in, but not a determining factor for the safe and effective use of a therapeutic product, would not be considered an IVD companion diagnostic device.

⁸ To the extent an IVD companion diagnostic device and a therapeutic product together meet the definition of a combination product, a single application for the combination product may be submitted in some cases, though where appropriate, and the Agency may require separate applications for the constituent parts of the combination product. See 21 CFR 3.4(c).

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conjunction with, its corresponding therapeutic product, and FDA review of the test/therapeutic product pair will be carried out collaboratively among relevant FDA offices.

A. Novel Therapeutic Products

For a novel therapeutic product, an IVD companion diagnostic device should be developed and approved or cleared contemporaneously to support the therapeutic product's safe and effective use (e.g., co-development). The results of the IVD companion diagnostic device will be *essential* for the safe and effective use of the therapeutic product, and its use will be stipulated in the labeling of the therapeutic product (i.e., the therapeutic product is considered safe and effective *only* if used with the IVD companion diagnostic device). Before approving the therapeutic product, FDA will determine that the IVD companion diagnostic device is properly validated and meets the applicable standard for safety and effectiveness or for substantial equivalence for the use indicated in the therapeutic product's labeling. Because the IVD companion diagnostic device is essential to the safe and effective use of the therapeutic, with some exceptions (see next section), FDA does not believe it may approve a novel therapeutic product or new therapeutic product indication for use with an IVD companion diagnostic device if the IVD companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the IVD companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

B. Approval of a Therapeutic Product without an Approved IVD Companion Diagnostic Device

FDA may decide that it is appropriate to approve a therapeutic product even though the IVD companion diagnostic device for which it is labeled for use is not being approved or cleared contemporaneously. Two such scenarios are discussed below. In general, if a therapeutic product is approved without approval or clearance of its IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic will be subsequently approved or cleared through an appropriate IVD device submission, and the therapeutic product label will be revised to include the IVD companion diagnostic device. In addition, FDA will consider whether additional protections are necessary to address the safety issues presented by the use of the therapeutic product without an approved or cleared IVD companion diagnostic device.⁹

1. New Therapeutic Products to Treat Serious or Life-Threatening Conditions

FDA may decide to approve a therapeutic product even if its IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.

⁹ Safety measures might include a risk evaluation and mitigation strategy (REMS), or a postmarket requirement, if necessary,

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2. *Already Approved Therapeutic Products*

FDA will generally not approve a supplement to an approved therapeutic product application to update the product's labeling to stipulate the use of an IVD companion diagnostic device until the IVD companion diagnostic device is approved or cleared. Nevertheless, FDA recognizes that there may be occasions when the labeling for an already approved therapeutic product must be revised to address a serious safety issue and that the change made to address this issue may stipulate use of a diagnostic test that is not yet approved or cleared. Under these circumstances, if the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared.

C. General Policies

If safe and effective use of a therapeutic product *depends on* the use of an IVD companion diagnostic device, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved. FDA expects that the therapeutic sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan. The sponsor of the therapeutic product can decide to develop its own IVD companion diagnostic device; the sponsor can partner with a diagnostic device sponsor to develop the appropriate IVD companion diagnostic device; or the sponsor can explore modification of an existing IVD diagnostic device (its own or another sponsor's) to accommodate the appropriate intended use. The following general policies apply whether a therapeutic product and its IVD companion diagnostic device are developed and manufactured by the same, or different, entities.

- FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket application (PMA) or, a 510(k),¹⁰ FDA advises sponsors to consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device. Premarket review by FDA will determine whether the IVD companion diagnostic device has adequate performance characteristics for its intended use.
- Except for the situations described in B, above, after completing review of the applications for a therapeutic product and an IVD companion diagnostic device and after determining that both products are ready for approval or clearance, FDA intends to issue approvals or approval and clearance for both products at the same time. FDA strongly

¹⁰ Experience indicates that most IVD companion diagnostic devices will be Class III devices, although there may be cases when a class II classification with premarket notification (510(k)) or other type of submission is appropriate.

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encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent approval.

- If an IVD diagnostic device is already legally marketed and the IVD diagnostic device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would consider the new use of the IVD diagnostic device with the novel therapeutic product a major change in the intended use of the device, raising new or additional questions of safety and effectiveness (see 21 CFR 807.81(a)(3)(ii), 814.39(a)). Accordingly, an appropriate premarket submission (either PMA or 510(k)) for the new use must be approved or cleared for use with the novel therapeutic product.
- New IVD companion diagnostic devices intended to be used in the same manner as an existing approved or cleared IVD companion diagnostic device (e.g., different manufacturer, different technological characteristics) will be reviewed under a PMA or a traditional 510(k), as appropriate.

V. Labeling

A. Therapeutic Product Labeling

The Federal Food, Drug, and Cosmetic Act requires the labeling of prescription therapeutic and device products to include the information health care professionals need to use the products (21 U.S.C. 352(f), 21 CFR 201.100(c)(1), Part 801.109(c), (d)). The labeling often includes information about diagnostic tests that determine how, when, or whether a therapeutic product is used. The regulations for drug and biological product labeling expressly recognize the importance of diagnostic tests to the safe and effective use of these therapeutic products. According to the labeling regulations for drugs and biological products (21 CFR 201.56 and 57), product labeling must include information about (1) specific tests necessary for selection or monitoring of patients who need a drug; (2) dosage modifications in special patient populations (e.g., in groups defined by genetic characteristics); and (3) the identity of any laboratory test(s) helpful in following a patient's response or in identifying possible adverse reactions. The labeling regulations identify labeling sections where such discussion is appropriate (e.g., Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations). For example:

- If a drug or biological product has been shown to be safe and effective in only a certain patient population identified by a diagnostic test, the Indications and Usage section must clearly define the patient population in whom the drug is approved (21 CFR 201.57(c)(2)(i)(B) and (C)).
- If a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test must be identified under Warnings and Precautions (21 CFR 201.57(c)(6)(iii)).

Because it is important that the approved labeling for an IVD companion diagnostic device and its corresponding therapeutic product be complete and consistent, FDA makes the following clarifications.

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- Ordinarily, information about the use of an IVD companion diagnostic device will be included in the labeling of its corresponding therapeutic product when the device meets the definition of an IVD companion diagnostic device (see Section III). As already clarified in Section IV.B, there may be situations when information about an unapproved or uncleared IVD diagnostic device is included in the labeling of a therapeutic product.
- When appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared IVD companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer's IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product.
- In cases, when an IVD companion diagnostic device is approved or cleared and is marketed *after* the therapeutic product is approved, the therapeutic product labeling should be updated to refer to the use of the IVD companion diagnostic device or type of IVD companion diagnostic device (21 CFR 201.56(a)(2)).

B. IVD Companion Diagnostic Device Labeling

The labeling for an in vitro diagnostic is required to specify the intended use of the diagnostic device (21 CFR 809.10(a)(2)). Therefore, an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

When an IVD companion diagnostic device has been approved or cleared for use with a therapeutic product in one disease or setting, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement if new or revised therapeutic product labeling becomes available that stipulates that the use of the IVD companion diagnostic device or type of IVD companion diagnostic device is essential for the safe and effective use of the therapeutic product in another disease or setting.

When an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement (in accordance with Section IV, above) to include the new therapeutic product. Labeling of the therapeutic product should also be amended through submission of a supplement.

VI. Investigational Use

All diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product will be considered investigational devices, unless employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices. In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations.¹¹

If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations and the investigational new drug (IND) regulations (21 CFR Part 312).

Information about the planned use of an IVD companion diagnostic device and its use in clinical trials should be included in an investigational submission. This information will help FDA understand and provide advice on how the IVD device will be used to enroll subjects into the trial(s) and how the test will be validated for use. For therapeutic product INDs, the therapeutic product review center (Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research (CBER)) will engage appropriate expertise from the diagnostic product review center (Center for Devices and Radiological Health or CBER), and joint advice will be provided to the sponsor.

In addition, it will be helpful if both the IVD companion diagnostic device product sponsor and the therapeutic product sponsor submit information about the proposed IVD companion diagnostic device in a *preIDE* (a consultative submission designed to ensure that appropriate validation studies are planned and carried out) to the diagnostic review center. This will enable a more focused and in-depth discussion about the validation of the IVD companion diagnostic device and will aid in planning for a device PMA or 510(k) that is complete and timely. When appropriate, expertise from the relevant therapeutic review center will be included in the diagnostic review center meetings.

FDA strongly encourages sponsors considering developing either of the products discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions as early in development as possible.

¹¹ Alternatively, if the IVD companion diagnostic device and therapeutic product are considered a combination product, FDA will expect the investigational device to be investigated under the IND for the therapeutic product

References

1. US Food and Drug Administration, Table of valid genomic biomarkers in the context of approved drug labels, Available at: <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> Accessed Aug 13, 2011
2. Ginsburg, G.S. and McCarthy, J.J. (2001) TRENDS in Biotechnology Vol.19 No.12 December 2001, 491-496
3. CenterWatch, FDA Approved Drug Therapies in Oncology, available at: <http://www.centerwatch.com/drug-information/fda-approvals/drug-areas.aspx?AreaID=12> Accessed Aug 13, 2011
4. Cohen, J., Tufts CSDD Report, Volume 13, Number 4, Page 2, July/August 2011
5. McDougall, G, and Rosamond, M., Personalized medicine - What it means for patient-centered healthcare and how to address its current challenges, PwC View issue 13, 2010
6. McDougall et al (2009), The new science of personalized medicine, PwC Oct 2009
7. Probst et al. (2009) Diagnostics 2009: Moving towards personalized medicine, PwC Oct 2009
8. McDougall, G., Competing in an Era of Personalized Medicine, Drug Discovery, Delivery & Therapeutics, 2009
9. Emerging Trends in Drug Development: Companion Diagnostics-9th Forum, http://sabpa.org/photos/SciForum11/S&T_2011_Report.htm Accessed on Aug 7, 2011
10. Phillips KA, Bebbler S, Issa A. Diagnostics and biomarker development: priming the pipeline. Nature Reviews Drug Discovery (2006) 5,463-469
11. Ma et al. (2009) The microeconomics of personalized medicine: Today's challenge and tomorrow's promise, Nature Reviews Drug Discovery Vol. 8 April 2009, 279 – 286
12. Gleevec: Package Insert http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf Accessed on Sep 3, 2011
13. IMS Health MIDAS MAT December 2010. Oncology defined as L1&L2
14. Donnelly, J.M., *Sanofi Chief details innovation strategy*, Boston Business Journal Available at: <http://www.bizjournals.com/boston/news/2011/04/12/sanofi-chief-details-innovation-strategy.html> Accessed Sep 3, 2011
15. CurrentPartnering, Partnering Agreements in Pharma and Biotech Yearbook 2010, January 2011

16. Morgan Stanley Pharmaceuticals Report, January, 2010
17. Tufts CSDD Impact Report Volume 12, Number 6 • November/December 2010
18. Blair E (2004), Surrogates & diagnostics in today's pharmaceutical development. Caxton, UK: Integrated Medicines Ltd.
19. Silver et al (2009), The Case for Personalized medicines, Ernst & Young Global Biotechnology Center, Personalized Medicine Coalition, page 3
20. Weinstein MC, Skinner JA. Comparative effectiveness and health care spending—implications for reform. *N Engl J Med* 2010;362:460–465.
21. Dawkes, A., (2007), The Strategic Importance of Biomarkers to the Pharmaceutical Industry, available at http://files.pharmaventures.com/biomarkers_pharmaventures.pdf, Accessed Aug 21, 2011
22. Poile, S., (2011), Recent trends in personalized medicine oncology deal making, available at <http://www.londonbiotechnology.co.uk/Events-and-publications/Publications/Recent-trends-in-personalized-medicine-oncology-de.aspx>, Accessed Aug 21, 2011
23. Dunn et al, Advocacy in personalized medicine: a developing strength in a complex space, *Personalized Medicine* (2010) 7(2), 179-186
24. Pharma R&D Annual Review 2010, Pharma Projects, available at: http://www.pharmaprojects.com/therapy_analysis/annual-review-2010-therapies.htm Accessed at Aug 28, 2011
25. Roche Presentation - ASCO 2011, 47th Annual ASCO Meeting, Roche Analyst Event, Sunday June 5, 2011 - Chicago