

Standardizing the Decision Process to Personalize a Therapy with a Theranostic: The Options for Test Index (OFTi)

Mollie Roth

ABSTRACT

While the top pharmaceutical companies have all made investments at an R&D stage in biomarkers and genetics to aid drug selection and clinical trials, only a few have taken targeted therapies all the way through the development pathway and onto the market. A key question for those companies who have not yet acquired this level of experience is, "What exactly are the decision processes essential to guide early commercial commitment, i.e. the commitment to market a therapy alongside a theranostic, in Personalized Medicine?" Although not all "personalized medicines" may require diagnostics, most targeted therapies are likely to depend upon new or existing diagnostic testing methods to determine their appropriateness in terms of prescribing and/or dosing decisions. To address this overall issue, we have used a Case Based Reasoning ("CBR") methodology to help define and build the Options for Testing Index ("OFTi") to learn from and improve upon the 7-8 year experience of the first movers and new entrants into the PM market.

INTRODUCTION

Personalized Medicine is slowly coming of age after years of hype and expectancy. In the past year we have witnessed the launch of several new therapies which have harnessed companion diagnostics, or theranostics, to help guide provider treatment choices outside of oncology, the first disease area to embrace personalized therapies. For example, in September, Pfizer launched Selzentry CCR5 for use in treating HIV and Vanda submitted a new NDA to the FDA in September for Loperidone, an investigational atypical antipsychotic for the treatment of schizophrenia.¹

We have also seen the increased value in diagnostics being recognized both by investors and pharmaceutical companies alike. Two separate acquisition and tender offers for diagnostic companies by much larger players in the space—Roche for Ventana and GE Healthcare for Abbott Diagnostics respectively—were made within the past year. Indicative of the increasing role of the diagnostic industry in the development of targeted therapies, both offers were rebuffed although Roche and Ventana continue to face off against each other.²

In another milestone for the space, the FDA acted publicly on its intent to align test and therapy labels in the interests of improved efficacy and safety of therapy by updating the

label for the blood thinner Warfarin to reflect its differential dosing in specific genotypes, although the update stopped short of referring directly to or requiring testing before dosing. This is set against a backdrop of ongoing policy discussions,³ ancillary debates⁴ and probing publications⁵ exploring the dimensions and possibilities of Personalized Medicine. None of us expect these shifting sands to stop anytime soon since so much of how Personalized Medicine will actually work on the ground, and how the stakeholder industries will converge, remain unresolved. Stated another way, there is as yet no clear business model around which all of the stakeholders—payers, regulators, diagnostic and pharmaceutical companies—can converge.

There is broad agreement, however, on the increasing vision of Personalized Medicine among stakeholders in the space, including regulators, pharmaceutical and diagnostic companies and provider groups. While at present there are approximately only fourteen therapies approved in the USA that would be described as targeted by some type of diagnostic (Table 1), there are almost two dozen targeted therapies in late-stage clinical trials that are expected to reach the market within the next ten years.⁶ The degree of investment by large and small pharmaceutical and biotech companies, as well as by the FDA and the venture capital industry,⁷ suggests that these are only the forerunners of a continued shift away from the predominance of the "one

COPYRIGHT © 2008 BY
THE JOURNAL OF BIOLAW & BUSINESS



WWW.BIOLAWBUSINESS.COM

Mollie Roth BIO

Cite as: Mollie Roth, *Standardizing the Decision Process to Personalize a Therapy with a Theranostic: The Options for Test Index (OFTi)*. J. BIOLAW & BUS., Vol. 11, No. 2, 2008.

size fits all” model of drug development towards more personalized medicine.

WHEN INDUSTRIES CONVERGE

Those studying convergent industries will tell you that to survive in converging industries, you must change your approach to your existing business model:

“the boundaries separating traditional industries are blurring and there is a convergencein a convergent industry, traditional rules of competition are challenged.”⁸

The primary danger in a converging market is that the large incumbent companies are unable to adapt to the changing business environment sufficiently rapidly to readily capitalize on it, whereas new entrants or first movers will more rapidly adapt to the shifting opportunities.

Although pharmaceutical development is embedded in long cycle time frames, and the top pharmaceutical companies have all made investments at an R&D stage in biomarkers and genetics to aid drug selection and clinical trials, only a few have taken products all the way through the development pathway and onto the market. In terms of actual market presence, there is now evidence of both new entrants and first movers in the development and launch of targeted therapies. Roche, for example, by combining its own diagnostics capability with its ownership of the drug maker Genentech, and the vanguard commercialization of Her2 and Herceptin in the treatment of breast cancer, appear well placed to project the image of a first mover in Personalized Medicine. This image is supported by recent comments by Franz Humer, Roche’s chairman.

Humer argued that greater benefits could be reaped from joint research and development on diagnostics and treatment when both functions were controlled by a single company. The alternative approach of alliances between drugs and diagnostic companies that remained independent from each other were less effective because:

both sides protect their IP ...over time companies offering a combination of diagnostics and ever more personalised drugs to doctors would have a competitive edge because you can justify your pricing based on the diagnostic.⁹

Other new entrants into the Personalized Medicine field may be coming from a very different quarter, with Genomic Health and Ventana leading the way as exemplars of a new line of highly significant diagnostic companies which are using high value tests to critically impact treatment decisions. While they may not be pharmaceutical companies per se, their importance as companies shaping therapy markets via personalization for treatment choices is clear.

Paradoxically, the primary advantage of being the first to market for these pioneers is also the greatest risk, namely, that they are learning on the job.¹⁰ Herceptin and the HER2 test oft heralded as “the” poster child for

Table 1
US Personalized Therapies/Procedures.

Therapy	Test	Indication
Herceptin® (trastuzumab)	HER-2/neu receptor	For the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. ²⁶
Anti-retroviral drugs	TruGene® HIV 1 Genotyping Kit	Guides selection of therapy based on genetic variations that make the HIV virus resistant to some anti-retroviral drugs.
Cancer treatment regimens	Oncotype DX 21-gene assay	Detects mutations linked to the likelihood of breast cancer recurrence in women, and benefit from certain types of chemotherapy.
Camptosar® (irinotecan)	UGT1A1	Colon cancer: Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. ²⁷
Coumadin® (warfarin)	PGxHealth test	Label Updated: Individual variations in CYP2C9 and VKORC1 may need lower dosages than people without these genetic variations.
Drugs metabolized by cytochrome P450	Amplichip® CYP2D6/ CYP2C19	FDA classification 21 CFR 862.3360: This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information. ²⁸
Gleevec® (imatinib mesylate)	BCR-abl	Chronic myelogenous leukemia (CML): Gleevec (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. ²⁹
Gleevec® (imatinib mesylate)	C-KIT	Gastrointestinal stromal tumor (GIST): Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). ³⁰
Immuno-suppressive drugs	AlloMap® gene profile	Monitors patient's immune response to heart transplant to guide immunosuppressive therapy.
Selzentry® (maraviroc)	Trofile	Guides use of therapy for patients with CCR5-trophic HIV-1.
Pharmaceutical and surgical prevention options and surveillance	BRCA1/2	Guides surveillance/preventive treatment based on susceptibility risk for breast and ovarian cancer.
Pharmaceutical and lifestyle prevention options	Familion® 5-gene profile	Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Pharmaceutical and surgical treatment options and surveillance	p16/CDKN2A	Guides surveillance/preventive treatment based on susceptibility risk for melanoma
Purinethol® (mercaptopurine)	TPMT	Guides adjustment of dose in treatment of acute lymphoblastic leukemia: Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe Purinethol toxicity from conventional doses. ³¹
Tamoxifen	Estrogen receptor	The estrogen and progesterone receptor values [in breast cancer patients] may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial. ³²

Source: Personalized Medicine Coalition

Personalized Medicine, still suffers from the lack of the optimum diagnostic for this therapy seven years after it was first launched.¹¹ This is a reflection of the very same trial and error approach to personalization that the new therapies seek to replace in the prescribing context. One of the hardest decisions to be made in the personalized context is “when is personalization actually appropriate for an individual therapy?” Being the first to throw their hats into the personalization arena, it is likely that Genentech’s and Roche’s learning experiences with Herceptin, Avastin and Tarceva, respectively, have helped them to understand the process necessary to make that decision and are helping to guide and embed the complex investment matrices essential in the decision whether or not to choose a personalized medicine route.

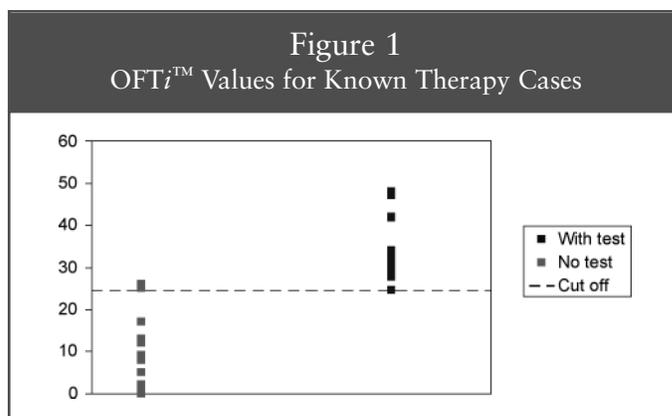
THE DECISION FRAMEWORK IN PERSONALIZED MEDICINE

A key question, then, for those companies who have not yet acquired the same level of experience, is “What exactly are the decision processes essential to guide early commercial commitment (i.e. the commitment to market a therapy alongside a theranostic) in Personalized Medicine?” Such decision processes will be required if incumbent companies are to anticipate the needs of a converged business model implicit in PM and respond in sufficient time to retain their leadership positions.

Although not all “personalized medicines” may require diagnostics,¹² most targeted therapies are likely to depend upon new or existing diagnostic testing methods to determine their appropriateness in terms of prescribing and/or dosing decisions. In theory, the decision of whether or not to undertake development of a diagnostic at the post-Phase 2 clinical trial setting should be simple: review the data collected on efficacy and/or adverse events and decide if the validity is sufficiently high to justify the increased investment to develop a diagnostic all the way through to the market. In reality, however, the “go/no go” decision relating to development and commercialization of a companion diagnostic is not a simple one and it exposes a series of primary dilemmas.

The Timing Dilemma

A question we are often asked by pharmaceutical therapy teams contemplating the opportunities of personalization is, “How late in the therapy development cycle can make the decision to personalize a therapy?” This most frequently arises when the therapy profile is not yet finalized or there is a need to await the outcome of Phase 3 trials to determine the role a theranostic might play in optimizing the efficacy and adverse event (AE) profile. We have come to realize that this is a primary dilemma between the needs of the pharmaceutical model and the needs of a diagnostic, since the former requires flexibility on its Personalized Medicine commitment as late as possible, and the latter requires a long runway, preferably in excess of 3-5 years, to



adequately embed diagnostic standards into clinical guidelines and underpin provider confidence and use.

The answer to the question, in reality, is that the group developing the therapy cannot wait as long as possible in the development lifecycle to arrive at a personalization decision but rather needs to be assessing the possible commercialization of a test well in advance of the certainty that the therapy will be approved based on successful conclusion of the Phase 3 clinical trials. Development and proper launch of a companion test so that the therapy is fully market enabled from Day 1 of launch takes anywhere from 3-5 years.¹³ This calls for new processes to better align and more readily converge these two disparate timing needs.

The Patient Reservoir Dilemma

In the “one size fits all” therapy model the aim is to develop a therapy which has relevance to as broad a patient base as possible while exposing patients to as few adverse events as possible. This fifty year old model has historically served us well and has seen the launch of many first in class therapies with significant welfare benefits, for example, cholesterol lowering statins like Lipitor and Crestor, or H2 antagonists, like Zantac and Prilosec.

However, this same model has also entrenched the concept with many in the industry that the larger the patient reservoir, the better, since it results in a larger target market from whom to obtain the greatest return on investment. This “investment pool” criteria sought by teams in early R&D is further supported by the experiential evidence that as new drug classes mature, the patient reservoir actually increases as the therapeutic benefit begins to extend to patients previously not diagnosed or not epidemiologically identified. Thus, in the “one size fits all” model, the critical decision formula is “What is the greatest percentage of patients we can treat with this therapy?” The problem with this criterion, however, is that the overall percentage to whom the therapy is prescribed does not reflect a corollary benefit gained from use of the therapy by everyone within that pool. It is presently estimated that the percentage of patients receiving therapy for which it is actually efficacious can fall within a range from 50-100%.¹⁴ Furthermore, even the leading products in a class rarely capture 100% of the market, with a typical 30-40% market share by value and significantly

less in terms of the actual patient reservoir captured being the usual outcome of a concerted marketing and education program.¹⁵ Thus, this focus on “more is better” is no longer a useful predictor of good return on investment in a personalized therapy world where you are targeting patient responder groups which may be as small as 8% of the overall patient reservoir but aiming to treat almost all of the patients appropriately diagnosed.¹⁶ Stated more bluntly, the traditional rules of competition are challenged in this new paradigm and a better and more accurate decision framework is needed to make relevant Personalized Medicine decisions.

The Labelling Dilemma

The primary gatekeeper in the United States healthcare market is the FDA, regulating the approval of both novel therapies and diagnostics¹⁷ for use in the United States. Their requirements are manifest in the drug and test submission processes and have resulted in the requirement for significant corresponding industry resource to interface with the FDA, help guide clinical trial strategy and analyze and compile data into extensive submission documentation.

By its actions and words, the FDA has indicated that they believe there is significant benefit in a shift, where appropriate, to therapies targeted by diagnostics.¹⁸ As a consequence of this, we can most likely expect an accelerated evolution of drug and test approval policies aimed at specifically supporting personalized therapies. In our view, regulation of Personalized Medicine converges around the therapy and diagnostic indications for use on their respective labels. In particular, how a specific test is mentioned in the therapy label and how a therapy is referred to in the diagnostic label clearly reflects both FDA thinking and the demonstrated clinical utility of a test as demonstrated within the clinical trials of the related therapy. The dilemma facing therapy teams today is not merely the need to understand the regulatory idiosyncrasies of diagnostics but more importantly to attempt to anticipate how the FDA will evolve its position over the regulatory lifecycle until the drug is actually approved and launched, which could be as much as 5-6 years away if the pharmaceutical company is only commencing Phase 2 clinical trials. In short, the existing regulatory paradigm with Personalized Medicine is also challenged, making investment decisions on the “one size fits all” versus personalized route all the more challenging.

The Strategy Dilemma

All of the examples of personalized therapy we have on the market today are there by virtue of product design, meaning either that the therapy was made clinically relevant by a diagnostic upon the analysis of Phase 2 or 3 clinical results or it is a therapy which was aimed squarely at a particular set of patient responders. In essence, Personalized Medicine has to date been an R&D led process, providing commercial teams within the pharmaceutical industry with the need to climb the marketing learning curve very quickly.

In contrast, the strategy led process behind “one size fits

Table 2
OFT_iTM Scores for Presently Marketed Therapies
Personalized v. Non-Personalized

Drug	Related Theranostic	OFT _i TM Score
Herceptin	Her2	30
Campath	CD 52 antigen	34
Prozac33	No test	27
Zantac	No test	6
Metrogel	No test	18

all” product targeting within most pharmaceutical companies sees a therapy area team identify key areas of unmet clinical need on which it wishes the R&D teams to focus resources. In order to reformulate this process to enable it to embrace the opportunities which might present under a Personalized Medicine strategy, the strategy team needs to understand the likely return on investment of a personalized versus non-personalized strategy.

Unfortunately, there is little material published on this and few relevant role models to help steer the way. Business analyst teams are thus presently not enabled to compare the net present value of one strategy over another. As a result there remains a considerable dependence upon R&D to decide whether or not a therapy should be personalized. This dependence process undermines the very “strategy led” processes presently existing within most pharmaceutical companies.

The Competitive Dilemma

A final primary dilemma facing pharmaceutical teams is an anticipation of the market place itself. Three years ago, conference debates on Personalized Medicine intimated that personalization made sense in oncology but was also likely to be relevant outside of areas where patient groups were small. We are now three years further on and the advent of marketed or near market drugs utilizing a personalization strategy outside oncology is now a reality.¹⁹

Furthermore, research in neurology, diabetes and cardiology also points toward the likelihood that by 2015 most primary therapeutic areas will have experienced a Personalized Medicine product launch of some dimension. For pharmaceutical teams still operating solely under the marketing concepts of the “one size fits all” drug model, the personalization of these therapy areas will require a steep learning curve to understand how their non-personalized therapy might fare against a primary competitor’s personalized therapy with equal marketing muscle. To use an apt analogy, this is the equivalent of selling Walkmans into a market and a primary competitor starts selling the iPod. Although the iPod may only be focused on a few customers at the outset, if it becomes the standard approach to mobile personal music systems, then the sellers of the Walkman will find themselves trying to compete against a powerhouse design with a lesser product of their own.

THE SOLUTION TO THE DILEMMAS

While we can continue to add to the list of dilemmas exposed by the convergence of test and therapy, what is clear is that the way strategic investment decisions are currently made for the “one size fits all” therapy model are hampered when it comes to defining where Personalized Medicine might be relevant or more clinically and financially rewarding. What is needed is the ability to define and build new decision matrices which learn from and improve upon the 7-8 year experience of the first movers and new entrants into the PM market and embed it as early as possible in drug development, potentially at the proof of concept stage, if possible.

To address this overall issue, we have used a Case Based Reasoning (“CBR”) methodology to help define the critical elements necessary to be considered in assessing a Personalized Medicine scenario much earlier in the therapy development process.²⁰ Using the CBR methodology we analyzed the differences between those therapies already on the market which were and were not personalized in order to determine which factors were most determinative of outcome. Recognizing that, as stated above, the final decisions on test commercialization may need, in some circumstances, to be left until the Phase 3 clinical outcome data is completed, such a method allows pharmaceutical teams to assess the likelihood that an individual therapy under development will fit closer to a PM strategy than a “one size fits all” therapy model much earlier in the development life cycle.

Furthermore, the determination of whether a PM strategy is needed, and is viable in terms of return on investment (“ROI”), has to date not been standardized across the pharmaceutical industry or across projects within individual pharmaceutical companies. We postulate that this same method allows for a standardized decision process to be readily adopted across groups within the same company as well as across the industry.

THE OPTIONS FOR TESTING INDEX™ (OFTI™): A DECISION SUPPORT TOOL FOR PERSONALIZED MEDICINE

Specifically, in designing OFTI (Options for Testing index),²¹ we identified and leveraged a number of known factors and assessed their importance in therapies already on the market—both stand alone and targeted—to help validate the correctness of our choice of factors. We determined that OFTI needed to provide support in the following additional critical areas and the means to:

- Assess the likely requirement for a test to support a therapy being placed on the market for the first time or for a therapy already in existence and/or on the market.
- Reach this determination prior to major investment being made in the development and commercialization of the test.

- Make the determination of the need for a test to support the therapy at an optimum time before launch of the therapy, to enable sufficient test adoption in the marketplace for maximum ROI.
- Enable forecasting of potential changes in test requirements as post-launch factors can significantly influence this decision, i.e. the very real possibility that subsequent label changes for a therapy initially approved for use without a test may mandate or make reference to a test as has recently happened with warfarin and previously Strattera.
- Utilize a method of analysis sufficiently simple to enable understanding and buy-in from those responsible for strategic decision making and to aid adoption across both development teams and within the industry.
- Ground the method in real world numbers with no bias towards any one particular factor.

The concept of OFTI is straightforward, asking “What factors, beyond Phase 2 clinical data, were most likely to determine whether the decision to personalize a therapy was correct?” Use of CBR enables us to analyze the effects of a number of factors on the outcome of particular therapies by correlating a metric to the factor being considered (input) with a metric pertaining to the outcome being considered (outcome) which then allows us to predict the likely outcome of an unknown case by analyzing the input factors. Through the use of CBR analysis, we determined four factors that clearly differentiate the success of those therapies regarded as “targeted” (those utilized with a diagnostic) and those which fit the “one size fits all” paradigm. The following factors are paramount in considering whether or not to invest in the development of a companion diagnostic at the pre-Phase 3 stage.²²

Drug Label

As the regulatory agency responsible for reviewing and approving new therapies and diagnostic tests, as well as approving labeling requirements, the information on how the FDA decides to include the test in the therapy label shows a high correlation to the positive outcome of the decision to develop a test.

On a categorical scale, consideration must be given to whether the label 1) requires the use of a test in the “Indications for Use” section of the label; 2) recommends use of a test either as a prerequisite for use of the therapy or to monitor the patients condition/dosing during use of the therapy, 3) suggests or mentions a test relevant to prescribing decisions that could be used before or during therapy use or 4) mentions a test or condition in the context of therapy.

Excluded Population

The size of the patient population who carries the relevant genotype or subgroup biomarker also correlates to a positive outcome of the decision to develop a test. Whether or not the therapy only works (or only works optimally) for a small percentage of the population is inversely proportional

to the overall value of having a test. Thus, if a therapy is projected to work best in 70% of the target population, then the population which would otherwise be excluded if a test was available to target that group would be 30%. This latter number is utilized within the *OFTi* method.

Severity

The severity of the adverse events can range from a black box warning concerning a condition that may be tested and a high rate of serious adverse effects on a condition that can be tested to varying rates of serious adverse effects on a condition that would not ordinarily be tested. The method utilizes a categoric scale based on descriptions consistently assigned to individual marketed therapies by the FDA.

Sales

What are the projected yearly (or current, in the case of a presently marketed therapy) sales and relative market position of the therapy? The method relies on the analysis compiled by Grabowski, et al. on over 120 therapies which allocate deciles to the market position captured.²³ This analysis consistently shows that first in class or highly clinically differentiated therapies are rewarded with a higher market share than those that enter fourth in class or other “me too” compounds relying only on convenience as a differentiating market factor.

CALCULATION OF *OFTi*TM: THE OPTIONS FOR TEST INDEXTM

Once values for these four factors are obtained, an *OFTi* score for the therapy under consideration may be calculated and compared to values calculated for therapies where the test/no test decision has already been made.

Based on our CBR analysis of over 20 different therapies, it is clear that use of an *OFTi* score provides the means to differentiate between those therapies that require a test and those that do not (Figure 1). The upper value of 25, above which a personalized strategy should be considered, was calculated as the midpoint between the mean *OFTi* value for therapies not using a test and the mean *OFTi* value for therapies using a test. Equally, a lower value of 18 was used to represent the upper 95% confidence limit for therapies without a test (Table 2). This suggests that above a score of 25, a personalized therapy strategy should be considered, and that below a score of 18, a non-personalized strategic route may be the most optimal.

In this way, *OFTi* also highlights an “amber zone” between 18 and 25 which is defined as the overlap between the lower 95% confidence limit on the mean for therapies with a test and the upper 95% confidence limit for therapies without a test. This we believe still suggests the need to give significant consideration to a PM route today. In particular, the team should consider the probability of a shift in any one of the four values or future market conditions (perhaps as a result of more market research) and how that shift would shift the *OFTi* calculation towards

or away from a “one size fits all model.”²⁴

To illustrate the method and its utility in the strategic decision-making process, we have described and scored four potential scenarios below:

Scenario 1: In dialogue with the R&D team, it has been determined that the therapy currently entering Phase 2 clinical trials is likely to work optimally on 65% of the target patients with the original unmet clinical need. In addition, the R&D team has identified a number of adverse events which would require specific provider education and for which the FDA may recommend, but not mandate, the use of a theranostic. The therapy is likely going to be second into the marketplace with a different mode of action and clinically differentiated features to the market leader. Reviewing and ranking the four factors described above, an *OFTi* score is calculated at 23.76.

Although the *OFTi* score does not exceed the upper point of 25, it falls into the upper part of the amber zone suggesting the need for the team to consider the impact of a PM strategy and perhaps conduct further market research regarding the implications of including a test within its present clinical trial and marketing strategy. Provided a contingency theranostic program is developed, they would then plan to make a final assessment of the test commercialization decision based on the outcome data post-Phase 3.

Scenario 2: A second therapy is also being considered by the same therapy team, but this one works on 75% of the target patients with the original unmet clinical need. In addition, the R&D team has identified no real adverse events which would require specific provider education and, therefore, the FDA is unlikely to mention a theranostic in the label. However, the therapy is very likely going to be the fifth one into the marketplace with no clinically differentiated features to the present market leaders. Reviewing and ranking the four factors described above, an *OFTi* score is calculated at 30. In this scenario, the *OFTi* score suggests that this therapy could fare better if it was commercialized with a theranostic. In this instance, the PM strategy could be considered a primary market differentiator helping to reposition the therapy as 1st into its own patient sub-group rather than 5th into the overall market.

Scenario 3: A third therapy is also being considered by the same therapy team, this one also working on 75% of the target patients with the original unmet clinical need. The therapy is likely to be second into the marketplace with a different mode of action and clinically differentiated features to

the market leader. However, the nature of the drug is such that the commercial team is asked to consider the possible impact of adverse events occurring only after 12-18 months experience with the drug in the marketplace. Were these adverse events known today, they would lead to a test being recommended to monitor dosing of the therapy. Reviewing and ranking the four factors described above, an OFTi score is calculated at 23.

Although the OFTi score does not exceed the upper point of 25, it is sufficiently close for the team to consider the impact of a PM strategy and the possibility of including it within its present clinical trial and marketing strategy. The team should also consider the impact on the reputation of the company of including a PM strategy as an option. Provided a contingency theranostic program is developed, they would then plan to make a final assessment of the test commercialization decision based on the outcome data post-Phase 3.

Scenario 4: A fourth therapy is also being considered by the company, this one also working on 75% of the target patients with the original unmet clinical need. The therapy is likely to be second into the marketplace with a different mode of action and clinically differentiated features to the market leader. In addition, the R&D team has identified no real adverse events which would require specific provider education and, therefore, the FDA is unlikely to mention a theranostic in the label, even though a test is available on the market. Reviewing and ranking the four factors described above, an OFTi score is calculated at 13.

The OFTi score suggests that a PM strategy would not be the optimal one since the therapy will probably be perceived to have a strong clinical utility and providers are likely to accept for the overall population. Although the therapy may not work optimally on a small percentage of patients, it is probably more efficient to rely on empirical clinical knowledge to aid patient treatment than to implement a screening program for all patients.

Investment decisions are made throughout the lifecycle of a novel therapy in development and are a constantly changing target. The decisions are always complex and multi-factorial and no attempt should be made to simplify or underestimate the task R&D and corporate investment teams make. However, there is a need to adopt new methods to help address the evolving clinical paradigm in PM and to embrace the different dynamics emerging in the personalization of therapy. OFTi is put forward only as an aid to these teams to help standardize their investment decisions. It is also sufficiently flexible to revisit as additional or more concrete information becomes known or to extrapolate on the post-marketing impact on decisions

which need to be made today.

More importantly, however, is that although OFTi has been designed to rely on currently known or predictable factors, certain of these factors are still moving targets; for example, the likelihood of a test being recommended for use by the FDA in the therapy label. While we acknowledge that this is a limitation of the method, it is also its most compelling quality since the process of scoring itself using the OFTi method will encourage and foster extensive debate and the need for more rigorous fact finding regarding the very pertinent and important backdrop of market differentiation issues.

CONCLUSION

The pharmaceutical industry has great concerns about the potential commercial dependency of a drug on the performance and adoption of a companion diagnostic. These concerns are justified since the history of diagnostic tests is frequently one of underutilization and, more often than not, inappropriate use in clinical practice. Such underutilization is not, as is commonly believed, confined to esoteric or rarely used tests but also applies to mainstream tests targeted for use in primary care. For example, in one review of studies, creatinine kinase tests for hypertension and 6-month hemoglobin A1c (HbA1c) tests in diabetics were requested less than a third of the times it was deemed clinically appropriate for such tests to be done.²⁵

Of equal concern is the increasing pressure on the diagnostic industry, which has never had to put forth comparable levels of investment in the validation and launch of diagnostics as is typically invested for drugs. Historically a high volume, low cost business, the diagnostic industry has not yet provided a solution to the potential investment required to undertake the clinical trials necessary to obtain FDA approval for highly clinically significant diagnostics as well as the market development investment necessary to ensure they become standards of care within 2-3 years of launch. We empathize with this hesitancy on the part of the diagnostic industry in the absence of any indication that the currently outdated reimbursement scheme for diagnostic tests will be changed, thereby resulting in increased reimbursement levels for tests.

Yet PM today requires us to work within these limitations in order to ensure that, for example, a new targeted therapy for arthritis reaches the patients it was intended for and does not languish because the test on which it relied failed to achieve parallel market adoption. If the decision to commercialize a test alongside a therapy is left until after phase 3 results such an outcome is probable. Being able to address that investment decision much earlier in the drug development cycle will serve both the therapy and the test better and help keep pace with the first movers and new entrants into the PM space.

To revisit our Walkman/iPod analogy; consider how different the team inside Sony may have behaved had they been empowered with a method to allow them to look outside

their own technical paradigm of cassettes and CDs to the miniaturization of hard drives and reflect that what made the Walkman such a “must have” item in the first place was as much to do with its fit with customer behavior rather than

merely the usefulness or longevity of the technology. Had Apple not undertaken such an “outside the box” review, perhaps it would not have reinvented itself as a new entrant into the market space it virtually owns at present.

ENDNOTES

1. <http://money.cnn.com/news/newsfeeds/articles/prnewswire/NETH03027092007-1.html>
2. On 25 June 2007, Roche announced a tender offer to acquire Ventana for \$75 dollars per share in cash in order to combine both companies' expertises in in-vitro diagnostics, cancer and virology to enhance both of their positions in the area of personalised healthcare. <http://www.roche.com/pages/downloads/company/mr070627r.pdf>

On July 12, 2007, Ventana's Board dismissed Roche's \$3 billion bid for the diagnostics specialist Ventana as “inadequate.” http://www.pharmaceutical-business-review.com/article_feature.asp?guid=06AF9FBD-6947-4B33-A648-A9278695C9A5. Roche digs in for takeover battle. <http://www.reuters.com/article/mergersNews/idUSWEA409820070626>. Ventana finally capitulated to Roche in January 2008 based on a per share offer of \$89.50. <http://www.labtechnologist.com/news/ng.asp?n=82685-roche-ventana-companion-diagnostics-breast-cancer-personalised-medicine>.
3. United States Department of Health and Human Services, “Personalized Health Care: Opportunities, Pathways, Resources”. <http://www.hhs.gov/myhealthcare/goals/index.html>
4. See, for example, the ABA Biotechnology Subcommittee, 2nd Annual Symposium, “Potential Physician and Manufacturer Liability in Personalized Medicine,” Mollie Roth, JD, Dr. Stirling Puck and Dr. Robert Nussbaum.
5. Roth, Mollie, JD, “Personalized medicine: using effective partnering for managing the risk of legal liability,” *Personalized Medicine*, 4(3), 329-339 (2007); Evans, BJ, “Finding a Liability-Free Space in Which Personalized Medicine can Bloom”, *Clinical Pharmacology & Therapeutics*, Vol 82 (4), October 2007.
6. Pickering, Lulu, PhD, “Companion Diagnostics: Enabling Personalized Medicines in Cancer,” *Spectrum Reports, Biomarkers and Diagnostics*, 3-4 (Oct. 27, 2006).
7. “Except from the bubble year, 2006 was the highest year ever for the industry,” said Keith L. Brownlie, speaking at this week's biotech symposium hosted by industry trade groups Pennsylvania Bio and BioNJ. <http://www.bizjournals.com/boston/othercities/philadelphia/stories/2007/10/15/story1.html?b=1192420800%5E1533578>
8. Ancarani, Fabio, “Strategic Alliances and Customer Interactions in Convergent Industries,” SDA Bocconi-Bocconi University Graduate School of Management, Milan, Italy.
9. Roche's Humer Insists He Will Win Ventana, <http://www.pharmalot.com/2007/10/roches-humer-insists-he-will-win-ventana/>. Ventana indeed finally capitulated to Roche in January 2008 based on a per share offer of \$89.50. <http://www.labtechnologist.com/news/ng.asp?n=82685-roche-ventana-companion-diagnostics-breast-cancer-personalised-medicine>
10. Lieberman, Montgomery, *First-Mover Advantages*, Strategic Management Journal (1988).
11. Dr. Pamela M. Klein, an executive at Genentech, the manufacturer of Herceptin, stated that the company was continuing to explore how to best identify patients appropriate for use of the drug, NY Times, June 12, 2007.
12. For example, BiDil® (isosorbide dinitrate hydrazaline) was personalized for “self-reporting” black Americans with heart disease.
13. See Keeling Peter, Role of the Opportunity to Test Index in Integrating Diagnostics with Therapeutics, *Personalized Medicine* 3(4), 399-407 (2006).
14. Ridge, J, “Reimbursement and coverage challenges associated with bringing emerging molecular diagnostics into the personalized medicine paradigm,” *Personalized Medicine*, 3(3), 345-348 (2006); Alliance for Human Research Protection, citing Dr. Allen Roses, then worldwide vice-president for genetics at GlaxoSmithKline.
15. The Quantity and Quality of Worldwide New Drug Introductions, 1982-2003, Henry G. Grabowski and Y. Richard Wang, *Health Affairs*, 25, no. 2 (2006):452-460.
16. <http://www.huliq.com/37106/test-identifies-patients-who-benefit-from-targeted-drugs>.
17. Laboratories licensed under the Clinical Laboratory Improvement Amendment rules (CLIA) may develop tests, including genetic tests, for use in-house, solely by that laboratory. Although the FDA has always maintained that it could regulate these “homebrew” tests as devices, it has historically not done so. Within the last few years, the FDA has begun to increase oversight of genetic homebrew tests and has stated in a recent draft guidance document that some laboratory developed tests indeed constitute “test systems” that are subject to FDA regulation as Class II or III medical devices. See, FDA, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (Sept. 7, 2006).
18. See, for example, the Critical Path Initiative, the FDA's effort to stimulate and facilitate a national effort to modernize the scientific process which includes an initiative to standardize microarray data analysis — a critical component for developing personalized medicines — through readily available RNA samples. <http://www.fda.gov/oc/initiatives/criticalpath/> In March 2005, the FDA released its Guidance on Pharmacogenomic Data Submissions and the associated Manuals of Policies and Procedures (MaPPs), available at <http://www.fda.gov/cber/gdlns/pharmdtasub.pdf> “The move toward personalized medicine is likely to redefine the way phase 2 trials are designed”, stated Dr. Janet Woodcock, the FDA's Deputy Commissioner and Chief Operating Officer, “specifying different doses of a drug for the way people metabolize a drug, and identifying the sub-populations that are most likely to benefit from a new drug in trial.” <http://www.biotechnologyhealthcare.com/journal/fulltext/3/1/BH0301009.pdf>
19. In September 2007, Pfizer launched Selzentry CCR5 for use in treating HIV and in the same month Vanda submitted a new NDA to the FDA in September for Loperidone, an investigational atypical antipsychotic for the treatment of schizophrenia.
20. Originated by the US Navy, CBR first appeared in commercial tools in the early 1990's. It is of particular use to decision makers when there is a wide body of previous situations (analogues) which can be called on to determine both values for decision variables and decision tree frameworks - by comparing it to the known value or behavior of something similar. Wong, SH, *Pharmacogenomics and Proteomics*, AACCC Press, pp. 69-78 (May 2006).
21. OFTI™ is the subject of a US patent application.
22. Labeling, target populations and adverse event rates and severities were taken from US package inserts for chosen therapies. The 2006 sales data for chosen therapies (or most recent year if 2006 data were unavailable) were taken from company financial reports.
23. Grabowski, H, “Patents and New Product Development in the Pharmaceutical and Biotechnology Industries,” Duke University Department of Economics (2002), Paper 02-25.
24. Validation of the model involved calculating OFTI scores for a number of therapies and then determining the accuracy of the value in predicting whether a test was required for a given therapy. The cutoff of 25 (rounded from 24.6) gave a sensitivity of 100% and a specificity of 85% resulting in an overall accuracy of 91%.
25. The Lewin Group: The Value of Diagnostics Innovation, Adoption and Diffusion into Healthcare (2005), see also <http://jama.ama-assn.org/cgi/reprint/280/23/2020.pdf>
26. Kaiser Family Foundation. Conversations on Health with Sidney Taurel, May 10, 2006. www.phrma.org/about_phrma/ceo_voices/kaiser_conversations_on_health_with_sidney_taurer
27. Perlegen Sciences. News Release: Companies Usher in New Era of Personalized Medicine in Metabolic Disease. April 12, 2005. www.perlegen.com/newsroom/pr/2005/2005_04_12_MCC-555_Joint_Press_Release.pdf
28. Keeling, P, Fear of Theranostics, *Decision Resources*, November (2005).
29. Personalized Medicine Coalition, Collins Presentation. www.personalizedmedicinecoalition.org/programs/francis_collins_pmc_presentation.pdf
30. *Id.*
31. The Lewin Group: The Value of Diagnostics Innovation, Adoption and Diffusion into Healthcare (2005).
32. Rogers, E., *Diffusion of Innovation*, 5th Edition. Free Press, NY, USA (2003).
33. We note that Prozac exhibits a score that would suggest a personalized approach would be optimal for the drug. In light of the current black box warning, we believe that a review of the testing recommendations is called for.