personalised medicine

market and regulatory landscape

Over the past several years, there has been continuing interest in the deployment of personalised medicine via the development of companion diagnostics/therapeutics. The leading edge of this discipline is in the cancer personalised medicine arena where a number of therapeutics are associated with a diagnostic entity that serves to stratify those patient populations who can benefit from the given therapeutic. Not only does this ensure optimal treatment options for patients but also streamlines costs associated with expensive therapeutics whose effects may be sub-optimal in some patients, along with the challenges of toxicity and other adverse responses.

I n this article, we present the current state of the cancer personalised medicine marketplace and recent actions from the regulatory authorities, European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), that are now providing much-needed guidance and newly introduced procedures to the vendors offering products into this space. Select Biosciences has been tracking the personalised medicine marketplace for a number of years and published its first market report on this topic in 2007. Our most recent market report on this topic was published in July 2009 entitled *Select Biosciences MicroRNA Diagnostics, Therapeutics, and Cancer Personalized Medicine 2009*.

Ever since, our industry coverage has focused on the various sub-segments of personalised medicine – à la cancer personalised medicine, and personalised medicine driven by microRNAs as stratification elements. We present some of our industry analysis focused on cancer personalised medicine, while ERA Consulting Group addresses the newly introduced procedures available for interacting with the regulatory authorities, offering companies the chance to gain regulatory acceptance of their biomarker development strategy for use in companion diagnostics and therapeutic development.

ERA Consulting Group specialises in regulatory affairs and product development consulting servic-es and has been focusing on characterising the regulatory requirements for biomarkers that can be validated as tools for personalised medicine.

In January 2009, the EMA issued a formal qualification process outlined in the guidance document EMEA/CHMP/SAWP/72894/2008. This procedure provides a much-needed framework and opportunity for companies to engage with the European regulatory authorities to obtain 'buy-in' on biomarker development. ERA encourages companies to interact with the authorities at all levels and seek regulatory advice as early as possible in biomarker and product development strategies, thereby reducing regulatory risk at later stages.

In the US, the FDA has modified its approach to facilitating and accepting biomarkers into drug development. Its introduction of the biomarker qualification process, Voluntary Exploratory Data Submission (VXDS), provides companies with the opportunity to discuss biomarker development from an early stage. Advice on study design and data on samples can be obtained through formal processes for integrating biomarkers into drug development and eventually into clinical practice.

While the challenges for gaining acceptance of biomarkers into drug development are evident, the regulatory authorities are increasing their visibility and taking active steps by offering more structured

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Personalised Medicine

Figure 1: Hurdles for personalised medicine development across various therapeutic classes

Therapeutic area impacted	Large hurdles need to be addressed	Hurdles are not that high
Neurodegenerative diseases [Parkinson's, Alzheimer's]	79%	21%
Schizophrenia, depression, other psychological disorders	59%	41%
Breast cancer	19%	81%
Leukaemias/haematological cancers	35%	65%
Other cancers/oncology	48%	52%
HIV infection/AIDS	51%	49%
Cardiovascular diseases	60%	40%
Drug toxicity/adverse drug reactions	50%	50%

● *OncoType Dx21™* from Genomic Health [offered under CLIA exemption as a means for patient stratification based on probability of recurrence of breast cancer and for guiding chemotherapeutic regimens]
● MammaPrint™ from Agendia [US FDA approved as a means for patient stratification based on probability of recurrence of breast cancer]
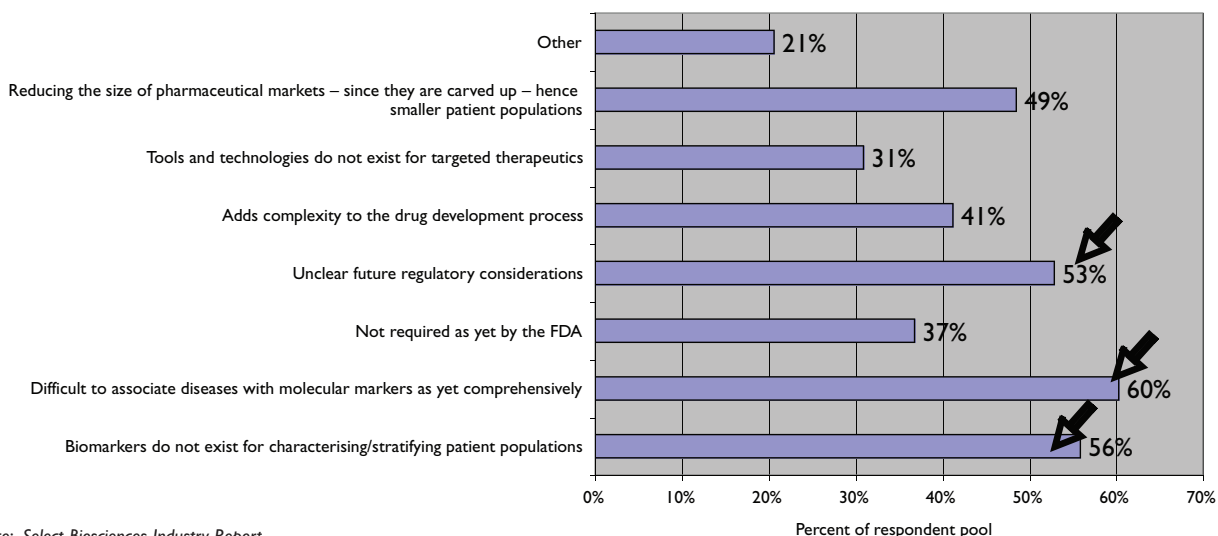● EGFR-targeting therapeutics: Vectibix®, Erbitux® [US FDA approved]

Source: Select Biosciences Industry Report

platforms for companies to engage with them. Later in this article, we will focus in brief on the steps involved in such newly-introduced procedures, an outline of data package required towards gaining formal regulatory acceptance of biomarkers into drug development strategies and as tools in companion diagnostics.

As part of its industry analysis, Select Biosciences has assessed the various challenges in the development of personalised medicine-based therapeutics. There are hurdles – technical, legal, regulatory, commercial and socio-political – that need to be addressed in the context of personalised medicine and these hurdles serve as challenges to the industry. **Figure 1** classifies the various therapeutic areas potentially addressable by personalised medicine according to hurdles that need to be addressed as part of personalised therapeutic development. In our industry analyses, we have deployed market surveys of worldwide industry participants as a means to map the qualitative and quantitative market metrics. By looking at the distribution of participants from the market respondent pools, we can address how a given parameter distributes across the industry. The percentages in **Figure 1**, for instance, reflect the position of the respondent pool *vis-à-vis* various therapeutic areas – and we observe that in the three areas where the hurdles are not that high – ie breast can-

cer, leukaemias/haemato-logical cancers, and across the oncology space, current product offerings are already on the market. Cancer personalised medicine is therefore at the leading-edge of the broader personalised medicine marketplace. As part of our industry tracking, we have also evaluated the macro challenges that exist in the personalised medicine space – these impact the field broadly rather than being restricted to a given disease/therapeutic class. **Figure 2** presents the data (the size of each bar is proportional to the penetrance of that particular challenge into the personalised medicine industry community). As can be observed, there are three major messages from these data: [a] Unclear regulatory considerations (from the EMA and FDA) are a challenge to the personalised medicine industry development; [b] In many cases it is difficult to associate diseases comprehensively with molecular markers; and [c] Biomarkers do not exist for characterising/stratifying patient populations. More details on the aforementioned guidance from the regulatory authorities, presented later in this article, seek to address the concern voiced by the personalised medicine community and begin to offer a more structured platform for overcoming the regulatory concerns of the community. The difficulty to associate diseases with molecular markers/biomarkers that exist and the paucity of such markers is an area of

Figure 2: Major challenges identified by participants in the field of personalised medicine

	Percent of respondent pool
Other	21%
Reducing the size of pharmaceutical markets – since they are carved up – hence smaller patient populations	49%
Tools and technologies do not exist for targeted therapeutics	31%
Adds complexity to the drug development process	41%
Unclear future regulatory considerations	53%
Not required as yet by the FDA	37%
Difficult to associate diseases with molecular markers as yet comprehensively	60%
Biomarkers do not exist for characterising/stratifying patient populations	56%

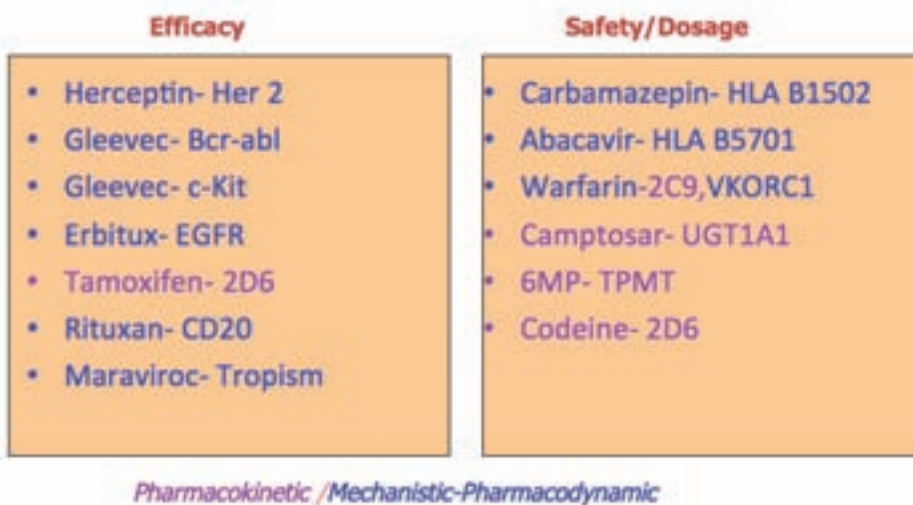*Source: Select Biosciences Industry Report*

active investigation. In fact in the academic litera-ture in the past several years, there are tens of thousands of biomarkers that have been described. Only a few of these markers can be validated, how-ever, in that their association with a biological phe-notype (disease) is strong, robustly-detected using commercially-available assays, and their frequency in the target patient population is significantly high such that they can be effectively used as *bona fide* biomarkers. These are significant hurdles from a scientific perspective, notwithstanding the regula-tory and economic barriers for deployment.

For these reasons, there are currently very few companion diagnostic-therapeutic combinations that have made it to the drug label – ie, providing prescribing guidelines to the physician. **Figure 3**

Figure 3: Dawn of personalised medicine: tests recommended/required in US drug labels

Efficacy
- Herceptin- Her 2
- Gleevec- Bcr-abl
- Gleevec- c-Kit
- Erbitux- EGFR
- Tamoxifen- 2D6
- Rituxan- CD20
- Maraviroc- Tropism

Safety/Dosage
- Carbamazepin- HLA B1502
- Abacavir- HLA B5701
- Warfarin-2C9,VKORC1
- Camptosar- UGT1A1
- 6MP- TPMT
- Codeine- 2D6

Pharmacokinetic /Mechanistic-Pharmacodynamic

Source: US FDA Presentation at Select Biosciences European Biomarkers Summit 2009 (EBS2009), Barcelona, Spain, November 2009. 2D6 and 2C9 refer to the cytochrome P450 drug metabolising enzymes (CYP450 DMEs)

Figure 4: Cancer personalised medicine market segmentation by biomarker studied primarily in current research efforts

Source: Select Biosciences Industry Report
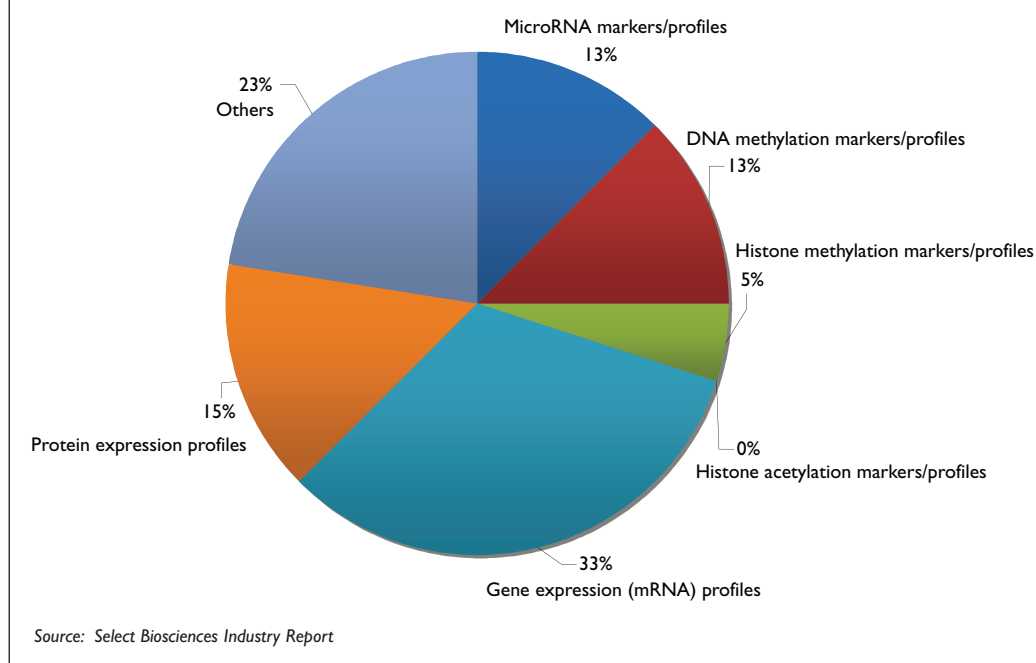
presents the tests recommended/required in the drug label in the US market (ie, these labelling actions have been driven by the US FDA).

Note from **Figure 3** that various therapeutics are 'associated' with a given biomarker(s) – the US FDA recommends or mandates genotyping of patients across the given biomarker(s) and this information can then be used by the physician in therapeutic administration or dosing decisions. It is interesting to note from **Figure 3** how few therapeutics are currently subject to biomarker testing. This is a growing space and we expect the number of therapeutic/biomarker combinations to increase in part because of the recent active role taken by the EMA and FDA in providing regulatory clarity to the industry.

Our industry analysis has included understanding the types of biomarkers currently penetrant across the personalised medicine field – more specifically, we have evaluated the quantitative penetrance of various classes of biomarkers in cancer personalised medicine including microRNA expression profiling and epigenetic profiles of key cancer-associated genes. The data are presented in **Figure 4**.

Note from the data that the most penetrant biomarkers currently in cancer personalised medicine research activities are protein and mRNA expression profiles, but note also that microRNA and DNA methylation (epigenetic) profiling are making a small, but measurable, impact in this space. Over time, as more diseases are associated with microRNA profiles (up/down-regulation of specific microRNAs), this will be a driver for the increased utilisation of microRNA profiling in cancer personalised medicine. In fact, Rosetta Genomics (Rehovot, Israel) has developed three microRNA expression profile-based tests for cancer, and is in development of a fourth test for colorectal cancer based on microRNA expression profiles in serum samples.

In the past, the regulatory landscape was less conducive for focused interactions regarding biomarker development. However, recent advances from both the EMA and the FDA are opening doors for companies that are ready and willing to engage with them on this topic. The new frameworks and structured formal procedures now in place will pave an easier route to gaining acceptance of new biomarkers, thus providing new and exciting market opportunities for vendors in the personalised medicine space. These recently published guidelines issued by the authorities clarify regulatory expectations, outline a procedure for companies and detail the data packages required.

Figure 5 outlines, in brief, the steps involved in the

EMA Biomarker Qualification procedure. This formal procedure not only offers companies a route for gaining regulatory acceptance of their biomarker, but also encompasses a broader scope for obtaining regulatory advice on additional novel methodologies, including imaging methods or other drug development tools.

A Qualification Opinion can be gained on the acceptability of a biomarker in a research and development context (non-clinical or clinical studies), based on the data package submitted. If the amount of data is not sufficient to achieve the formal Opinion, a Qualification Advice based on the evaluation of the scientific rationale and preliminary data submitted, identifying gaps that need to be filled to gain the formal Opinion is provided.

The specialised group (Qualification team) appointed by the EMA is composed of selected key opinion leaders from the EMA experts' network. The procedure is highly interactive and involves several opportunities for both teleconferences and face-to-face meetings throughout the procedure. Prior to adoption of the Qualification Opinion a public consultation step is implemented for a set time period of six weeks to allow the scientific community to give their views. It should be noted that the content for release to the public domain will be agreed with the company prior to publication.

The Qualification Advice and Opinion route can take approximately 100 and 190 days, respectively. As more companies go through this procedure, since its introduction in January 2009, the outlined timetable may be modified depending on the data packages submitted.

Guidance on the structure and content of the data package required is outlined in the document EMEA/CHMP/SAWP/72894/2008. ICH E16 also provides some useful guidance and structure applicable to the generation of biomarker data intended to support qualification. In brief, the following keys pieces of information are needed:
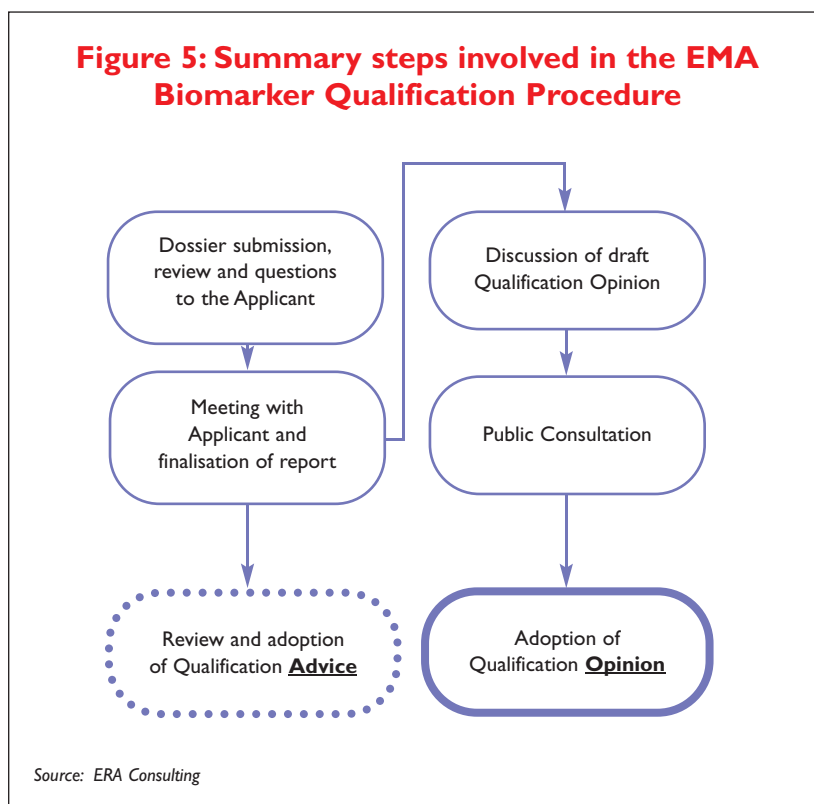
● Disease setting associated with your biomarker(s)
● Intended use of biomarker, its need and impact, how it will be integrated into drug development and regulatory review
● Relevance and adequacy to extrapolate the pre-clinical models to clinical setting
● Details on study design, critical analysis of results, assay validation, statistical plans
● Inclusion of as much supportive data to strengthen the package, such as systematic literature reviews, meta-analysis, study reports
● Gaps (if any, should you only wish to opt for Qualification Advice) that remain and how these will be addressed in future plans/studies.

Prior to entering these Qualification procedures, there are other opportunities to engage with the European regulatory authorities. Advice and input from such groups as the Innovation Task Force and/or the Pharmacogenomic Working Group is often recommended and indeed encouraged prior to entering the EMA Qualification procedures.

The FDA also has a biomarker qualification mechanism, although currently it is still at the pilot stage and is less structured compared to the EMA procedure. The procedure is termed a Voluntary Exploratory Data Submission (VXDS) and involves the submission of an information dossier to the Interdisciplinary Pharmacogenomics Review Group (IPRG) which forms a tailored Biomarker Qualification Review Team (BQRT). VXDSs can be submitted as a stand-alone submission in which case a new pre-IND number is issued or they can be associated with a pre-existing IND in which case no new number is issued and the status of the current IND is not affected.

In principle a VXDS is similar to the EMA qualification procedure in that a dossier containing studies supporting the use of the biomarker are submitted to the regulatory agency which then provides an opinion and/or advice. The key differences are that the FDA procedure does not have formal timelines and currently there is no scope for public consultation.

Figure 5: Summary steps involved in the EMA Biomarker Qualification Procedure

Dossier submission, review and questions to the Applicant

Meeting with Applicant and finalisation of report

Review and adoption of Qualification **Advice**

Discussion of draft Qualification Opinion

Public Consultation

Adoption of Qualification **Opinion**

Source: ERA Consulting

Personalised Medicine

The good news for companies with a global strategy is that there is the possibility of joint FDA-EMA Voluntary Genomic Data Submissions. Although this process is relatively untested at this stage, it should be possible to make a single submission to both the European and US regulatory agencies and receive, hopefully, a unified response. The importance and benefit of biomarkers to optimise both current and new treatments from the patients' perspective is of increasing interest. The opportunity to use biomarkers to select which patients who will be considered to respond best to a treatment should contribute to an increased number of biomarkers that will be verified by the regulators for clinical use.

It should also be possible with the increasing opportunities for interaction on this topic among the regulatory authorities in Europe and the US to expand the use and implementation of new biomarkers in the personalised medicine space. In addition, with the introduction of new Consortia both in European and the US with experts from academia, industry and the regulatory authorities, a more harmonised approach to biomarker development for use in the clinical setting may advance over coming years.

Conclusion

The cancer therapeutics space is driving the development of the personalised medicine field. As more disease-associated biomarkers are identified and validated, this will expand the reach of personalised medicine into many therapeutic areas beyond oncology. Beyond gene expression and protein expression profiles, novel biomarkers are being validated with association with disease, especially microRNAs in various types of cancer. The growth of the number of biomarkers and their utilisation to stratify patient populations is developing in parallel with the new guidance on their validation and usage by the European and US regulatory authorities. A regulatory framework is important,

and the newly introduced procedures provide a clear playing field and platform for various companies seeking to provide content and tools for personalised medicine and we believe will contribute to the growth and development of the personalised medicine field.

Details of this report can be found at: www.selectbiosciences.com/marketreports/MicroRNA_and_Cancer_PM2009.aspx.   DDW

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