Company profile

Pacific Biomarkers, Inc.

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Pacific Biomarkers, Inc. is a recently incorporated, wholly owned subsidiary of Pacific Biometrics, Inc. (PBI), a specialty clinical trials laboratory. Pacific Biomarkers was created to provide biomarker testing services for clinical drug development, specifically in the areas of ligand-binding assays, multiplexing and immunogenicity testing, in a regulatory-compliant environment.

It is widely recognized that the drug-development paradigm is rapidly changing. The one-size-fits-all blockbuster model is moving towards a model of targeted therapeutics, also referred to as 'personalized' or 'stratified' medicine [1,2]. Targeted medicine requires the use of clinical biomarkers to test for treatment response (both safety and efficacy) and guide selection of an appropriate therapeutic (FIGURE 1). Although the market size for new drugs may shrink under this model, the overall economics are considered to be favorable [1] because:

- The total market size, in fact, may not be reduced significantly compared with empirical medicine because the improved efficacy/safety profile will drive increased patient compliance and market share
- Development times are expected to be reduced for targeted drugs, resulting in an effective increase in patent life
- Targeted drugs with clearly superior efficacy/safety profiles can command premium pricing relative to 'old-style' drugs
- Targeted drugs may present a barrier to generic entry because of increased complexity of drug–diagnostic combinations

The key to the success of the targeted medicine model is the use of clinical

biomarkers. These can include genomic, proteomic, biochemical, imaging or other biomarkers that are informative about treatment response. It is expected that many biomarkers will be analytes that can be assayed using ligand-binding assays on conventional or multiplexed platforms. Importantly, many clinical biomarkers will be novel analytes discovered during the drug discovery and early drug development process that will require development of novel homebrew assays not available from commercial *in vitro* diagnostic (IVD) manufacturers. Thus, there is a rapidly evolving and growing market opportunity for laboratories that are expert at custom assay development, validation and testing in a regulatory-compliant environment.

A recent market report predicts that the global market for biomarkers will grow by a compound annual growth rate of 18% over the next 5 years, reaching US\$12.8 billion in 2012 [101]. The fastest-growing segment of the market is the application of biomarker testing in clinical trials, which will grow by 23.5%, reaching US\$1.8 billion by 2012 (FIGURE 2). The report highlights the rapid transformation of the industry as biomarkers assume a central role in both drug development and healthcare delivery [101].

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Figure 1. Utility of clinical biomarkers.

At present, there are relatively few vendors with an established reputation in the provision of clinical biomarker services, and currently no dominant players. It is important to note that the key concept here is 'clinical biomarker services'. There are numerous startups that have focused on biomarker discovery or on new diagnostic technologies that take advantage of advances in genomics and proteomics [2]. However, these companies generally have no expertise in the provision of biomarker testing for clinical drug development and most are not CAP/CLIA-certified laboratories. Several of the large central laboratories and global contract research organizations (such as Covance and MDS) and combination clinical/central laboratories (such as LabCorp and Quest) have recently announced the establishment of biomarker testing services, and we can expect rapid expansion into this new market segment. The laboratories best positioned to enter this market are those that have a strong science base, established expertise in specialty testing and strong relationships with the scientific/clinical teams at both pharma companies and diagnostic manufacturers.

Pacific Biomarkers, incorporated February 1, 2008 as a wholly owned subsidiary of Pacific Biometrics, Inc.

(PBI), will leverage the 19-year reputation of its parent as a specialty laboratory with significant scientific and technical expertise in providing esoteric testing services for clinical drug development. PBI has traditionally focused on specific therapeutic areas, notably metabolic and musculoskeletal diseases, whereas Pacific Biomarkers will offer services across all therapeutic areas where biomarkers are required. Assay services will be highly customized, involving noncommercial reagents and, in many cases, proprietary methods.

Types of biomarkers

The term 'biomarker' is often used but there is sometimes confusion about its precise meaning. The FDA recently defined biomarkers as 'measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans' [3]. This is a useful operational definition because it encompasses a broad range of types of biomarkers, and includes both predictive/preventive biomarkers and those that are useful as surrogate end points in monitoring the safety and efficacy of drugs (FIGURE 1). Biomarkers that have utility in drug development broadly fall into one of two categories: IVD assays and imaging technologies.

In vitro diagnostic assays

In vitro diagnostic assays are laboratory tests that are performed on clinical samples such as serum, urine or solid tissue. A wide variety of technologies are used, including:

- Ligand-binding assays; that is, immunoassays. Most of these are based on the ELISA format. Immunoassays remain the workhorse for clinical biomarkers;
- Multiplexed immunoassays. Many ELISAs are now performed in a multiplexed environment, which means that panels of tests are conducted simultaneously on the same sample. Technologies include Luminex® and Meso Scale;
- Gene and protein microarrays. Gene microarrays are well established in early drug discovery and development work. The recent approval of the Roche Amplichip® and the FDA's recommendation to perform genetic testing to guide warfarin dosing have pushed gene arrays into the diagnostic spotlight [102]. Protein microarrays are also making steady progress [4];

- Mass spectrometry and nuclear magnetic resonance (NMR). Mass spectral methods are making inroads into clinical drug development and diagnostics, but are still constrained by the need for sample preparation methods that can reduce the background noise from high-abundance proteins. NMR techniques have proved remarkably robust for the analysis of plasma lipoproteins [5].

Imaging biomarkers

Imaging technologies continue to increase in resolution and will become ever more important as the basis for biomarkers in drug development and diagnostics. Techniques include:

- Ultrasound-based technologies. These are broadly used in multiple therapeutic areas, most notably oncology and cardiovascular disease. Coronary intravascular ultrasound and carotid intima-media thickness have recently been much in the news [6,7];

Figure 2. Growth of the market for biomarkers over the next 5 years.

The market is divided into three segments: biomarker discovery (Discovery), molecular diagnostics (Mol Dx) and clinical trials (Clinical trials). **(A)** Compound annual growth rates for each segment, 2007–2012. **(B)** Annual revenues for each segment in 2007 and 2012. Data from [101].

- MRI, functional MRI, computed tomography and positron emission tomography scanning. These methods have developed into very powerful tools, especially when combined with molecular probes, which can provide real-time analyses for disease-modifying drugs, especially for oncology and CNS diseases [8,9].

Pacific Biomarkers focuses principally on ligand-binding and multiplexed assays, which among the IVD assays currently have the greatest utility for monitoring drug response. Gene microarrays are expected to play an increasing role in stratifying patients into treatment groups based on genetic risk and drug-response profiles, but will not be discussed further here.

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The need for clinical biomarker services

The provision of highly customized biomarker assay development and clinical testing services presents an evolving opportunity in the drug-development sector because of the changing drug-development paradigm, as already discussed. For the purposes of this article, 'clinical biomarker services' comprises:

- Novel biomarker assay development and testing
- Immunogenicity testing for biologic drugs
- Multiplex testing

These three areas are related because, in the majority of cases, they each involve 'ligand-binding assays', which are immunoassay formats based on a variety of technology platforms, most commonly ELISAs and various automated and/or multiplexed platforms with fluorescence or electrochemiluminescence detection.

At present, much of the focus in clinical biomarker services centers on biologic drugs. This is because biologics are frequently, by their very nature, highly targeted towards specific disease-related molecular targets. The drug targets themselves or closely associated disease markers serve as surrogates for drug

response during development. Moreover, all biologics require assessment of their immunogenicity during preclinical and clinical evaluation, leading to a dual requirement for the development and validation of an assay for a drug-associated biomarker that is informative about efficacy and an assay for anti-drug antibodies that evaluates safety (immunogenicity testing).

A survey of publicly available databases indicates that the number of biological product candidates and preclinical research and development programs may exceed 1000. These programs are roughly evenly divided between antibody-based and non-antibody-based approaches. The latter include peptides, fusion proteins, oligonucleotide-based drugs (aptamers, RNAi, etc.), adenovirus vectors and other nonprotein-based biological products.

Based on the above information, there may be as many as 2000 clinical trials with immunogenicity testing potential. Since the FDA and other regulatory agencies have mandated immunogenicity testing for all biologic drugs [10], this represents a significant market. Although there is increased use of 'fully humanized' biologics, it is unlikely that immunogenicity testing can be avoided because even fully humanized drugs can still elicit anti-drug antibodies [10]. Moreover, the expected approval path for bio-generic or bio-equivalent drugs ('biosimilars') in the USA and Europe will likely open the floodgates for immunogenicity testing, further increasing the size of this market.

Currently, most immunogenicity tests are being performed in-house at the biopharma/biotech companies because outside vendors with demonstrated competence in this area are sparse and sponsors have been reluctant to outsource. However, there is a general expectation that there will be an increasing trend to outsource these assays and thus there is a large untapped market for immunogenicity testing by contract laboratories.

The two other markets that will be addressed by Pacific Biomarkers are novel biomarker assay development/testing and multiplex testing. These markets are

similar or greater in size than the immunogenicity market. Requests for immunogenicity testing are often accompanied by requests for biomarker assay set-up and validation, for reasons already discussed. Moreover, biomarker testing is often required in multiplex format in order to reduce sample volume requirements and contain costs when testing for large panels of markers.

In terms of the competitive landscape, the market is fragmented, with currently no dominant players. A survey of publicly available information indicates that close to 40 contract laboratories advertise services in the immunogenicity and/or ligand-binding assay space. The majority of companies offering services in this space are focused on early-stage drug discovery and development services, including animal testing services, with no demonstrated expertise in supporting human clinical trials. Laboratories that offer clinical biomarker services include:

- Charles River Laboratories
- Covance
- MDS Pharma Services
- Millipore-Linco
- Quest Pharmaceutical Services
- Pacific Biomarkers

Pacific Biomarkers' business model

Pacific Biomarkers is a private, wholly owned subsidiary of PBI, a Delaware public company. Pacific Biomarkers comprises the Clinical Biomarker Services business unit, formerly housed in the laboratory at PBI in Seattle, Washington. The biomarker services business is sufficiently differentiated from conventional specialty central laboratory services to merit creation of a new subsidiary. This has enabled a distinct focus to be brought to assembly of the core scientific staff, acquisition of dedicated instrumentation, targeted business development, and unique branding and marketing.

Pacific Biomarkers expects to realize revenues from two principal sources described below.

Clinical biomarker services

This is expected to be the principal source of revenue in the near-to-medium term. The business model for these services is similar to that of the parent laboratory, although there are critical differences:

- Pacific Biomarkers is contracted by pharma and biotech companies to provide testing services on samples collected during clinical trials. In some cases, there are subcontracts from other central laboratories. Unlike conventional central laboratory contracts that can stretch over many years, many of these contracts are expected to be shorter-term;
- Contracted services include assay set-up, validation and testing of clinical samples. Assay set-up comprises either tech transfer of sponsor-developed methods or building an assay from scratch. Deliverables include a completed assay validation report and, where applicable, reportables on tested samples;
- Margins are expected to be better than for conventional central laboratory contracts because most of the testing (with the exception of multiplex testing) are based on in-house-developed homebrew assays, thus avoiding the purchase of high-priced reagents.

An important component of the business model for the provision of clinical biomarker services is partnership with a global central laboratory in order to aggressively market and expand these services on a global basis. A global partner is considered to be critical because:

- Clinical trial services are increasingly required to be global. Services offered by a single location often cannot meet sponsors' turn-around-time requirements, may be cost-prohibitive (due to shipping costs) or may not accommodate sample stability restrictions;
- As already noted, several global competitors have started pushing into this space. While their current capabilities

are limited, they have the resources to build operations that will, in time, be a threat to Pacific Biomarkers.

The parent company, PBI, already has a co-marketing agreement in place with Quintiles Laboratories. This agreement combines the specialty testing expertise of PBI with the global logistics offered by Quintiles and has successfully supported large, multinational clinical trials. It is expected that a similar partnership will be established for Pacific Biomarkers to gain access to global studies.

Development of proprietary biomarker assays

Pacific Biomarkers will look for opportunities where it can take a proprietary position in novel biomarker assays. In most cases, these biomarkers will be proprietary to pharma and biotech companies that approach Pacific Biomarkers to assist with the development of suitable assays. Where appropriate and applicable, Pacific Biomarkers will offer to develop the assays at no charge in exchange for a percentage of the ownership of the assays. Future revenues from such proprietary assays can then be derived from:

- Sale of testing services for these assays to other sponsors (if allowed by the original biomarker rights owner). Sales of these services will be at a premium because the assays are proprietary and not available elsewhere;
- Sale or licensing of the rights to these assays to IVD manufacturers, which in turn will sell the assay reagents to other central laboratories or to the clinical diagnostics market;
- Complete development, approval and sale of companion diagnostics for novel targeted therapeutics.

The development of proprietary biomarker assays represents a significant future upside potential for the company. As the targeted and personalized medicine market continues to evolve and expand, there will be increasing numbers of companion diagnostics and drug–diagnostic combinations coming

onto the market. At present, there is no uniform business model for how these novel biomarkers will be marketed [1,101]. Several models are conceivable, including development and marketing of the companion diagnostic by the drug innovator; development and marketing of the diagnostic by a bona fide IVD company in a collaborative or joint venture structure with the drug innovator; or provision of biomarker testing services by a clinical diagnostics laboratory offering a ‘homebrew’ assay under analyte-specific reagent rules. Pacific Biomarkers therefore expects that there will be multiple revenue-generating opportunities as this market unfolds.

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Future perspective

There will be rapid growth in the requirement for biomarker testing during clinical drug development. Starting in the oncology area, all new drugs will be linked to one or more specific biomarkers that predict response, and such drugs will be co-approved with the biomarkers as companion diagnostics. This same logic will spill over into other therapeutic areas, most likely beginning with neurological and inflammatory conditions for which highly targeted biologics are in the pipeline. Clinical biomarker services will be the fastest-growing segment of contract laboratory services for drug development. There will also be the parallel emergence of next-generation diagnostic companies that will develop and market novel companion diagnostics based on ligand-binding assay, genomic, proteomic and imaging technologies.

Financial & competing interests disclosure

The author is an employee of Pacific Biomarkers, Inc. and of its parent company, Pacific Biometrics, Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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