Biopharma 21

A position paper on the healthcare ecosystem in the 21st century

July 2013

HBio
Hellenic BioCluster

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Healthcare is Changing

Healthcare is in a state of widespread change and reorganization. Some call it “the perfect storm” with major patent estates being lost, significant cuts in R&D impacting our ability to fill up drug pipelines at an appropriate pace, payers and patients demanding cheaper medications and regulators becoming more stringent.

These developments impact all major stakeholders who are working to understand and adjust to the emerging trends. Many of the structures, relationships and procedures that have served us well in the past are being re-assessed in the light of these changes. Furthermore, as a drug's success in the marketplace will increasingly depend on the drug maker’s ability to prove its additional benefit over existing pharmaceuticals, stakeholders are exploring unconventional partnership models that only a few years ago would not have been considered at all.

This change and ‘fluidity’ that we are all currently experiencing, creates opportunities for all, including the Greek healthcare community which, despite being relatively small in absolute size and fragmented in nature, includes a number of very innovative members with a strong regional and notable international role.

These organizations agree that it is vital to understand the emerging ecosystem, place their stake in it and chart a course for the future that serves patient interests well, supports international collaborations where these are feasible, and takes advantage of their unique competences.

Understanding and predicting the future is no easy task, yet some key signposts and trends already exist that allow us to posit scenarios for how the healthcare ecosystem of the near future may develop. Through a number of meetings involving prominent individuals of the community, Hellenic Biocluster (HBio) members have identified a number of ‘trends’ that we believe are shaping developments and can help define strategic choices, guide investment and identify beneficial collaborations to be sought at the operational level.

Trend 1
Non-Traditional collaborations

Recent years have seen the announcement of a number of collaborations between organizations that haven't been 'typical partners' in the past and by new entrants seeking to apply platform technologies in the healthcare space.

Collaborations between HMOs and IT, biotechs and Electronics, Pharma and payer organizations and even coalitions of game playing aficionados solving hard protein folding problems are seeing the public light and creating significant interest.

We expect this trend to continue and increase as actors in the space are exploring new roles and the creation of solutions on which the new healthcare system will depend. In particular we expect a lot of activity in areas such as risk-sharing, patient compliance, product differentiation, integrated therapies, super-generics development and mobile- and e-health.

Appropriate business models and investment tools will also be developed in support of these collaborations.

Trend 2
From isolated therapies to integrated treatments and personalized medicine

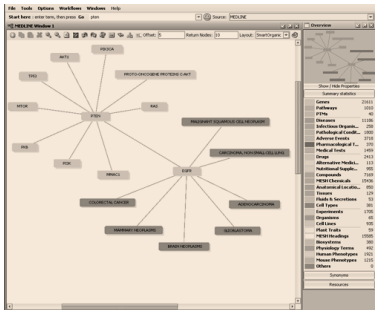
We are witnessing a shift form isolated components to integrated treatments. In the future it will no longer suffice to create isolated 'healthcare components' (such as drugs, diagnostics or delivery devices) and then seek to combine them to provide high quality healthcare. Integrated treatments will require the combination of drugs with delivery devices, monitoring with prevention and compliance systems from the design and development stage rather than once these components are in the market.

We expect that in an analogy to other industries where the components themselves are of little value until combined into an end product, increasingly stakeholders will seek to address the

'total health status' of patients combining prevention with therapy and post therapy monitoring in an integrated 'treatment program'. This will moreover seek to combine population with personalized data in a continuous feedback loop system with the goal of increasing the population health status as a whole.

Personalized medicine is an area of specific interest where we expect integrated treatments to contribute. The era of personalized medicine will require development and adoption of novel technologies that will allow for individual determination of response to targeted treatment. For example, multi-analyte diagnostic platforms should provide information on the patterns of metabolic changes affected by chemotherapy protocols and allow doctors to decide the optimal solutions without waiting for the clinical outcome (which may prove wrong). The same is true for the treatment of psychological disorders, a huge and extremely personalized health market itself. In addition, in the personalized treatment of cancer, the classification for treatment planning experiences a drastic paradigm shift moving from standard morphological classification to molecular classification by cellular genomics.

The road to personalized medicine will necessitate the move of some molecular diagnostics from the laboratories to the primary care units and the physicians' office, the so called point-of-care testing. This makes collaboration with various engineering disciplines necessary, e.g. electronics and micromechanical engineering and creates new challenges in the areas of instrumentation design and manufacturing.



Trend 3

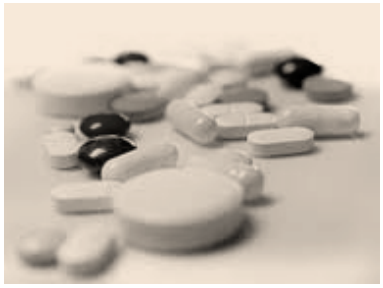
From Symptoms to Mechanism of Action

As our understanding of genes, pathways and biological processes expands, we are driven to use this knowledge to better manipulate the benefit-risk equation of drug development.

Increasingly, important stakeholders such as the regulating authorities, the payers but also care givers and patients themselves demand that medications are developed, approved and used on the basis of a good understanding of the underlying biological processes of disease and the effects of drugs on these, rather than some statistical analysis of observable symptoms. Furthermore, it is no longer sufficient for drug developers to show efficacy in some disease model but rather a clear benefit over the existing standard of care. Nor is it sufficient to show efficacy in some surrogate biomarker as the Avandia (Rosiglitazone) case illustrates. Adding to the above, the need for proactive management of risk and identification of opportunities together with pressure on patent practices are further catalyzing change in this direction.

We therefore expect to see increased activity related to the creation, organizing, accessing and use of mechanism of action (MoA) knowledge both at the research and the commercial ends of the market.

Systems Biology approaches and novel experimental technologies offer a great promise in this respect. To this extent, high throughput and multiplexed phosphoproteomic technologies (Mass Spec and xMAP-based) together with well-established pharmacogenomic and pharmacogenetic measurements hold promise for quantifying MoA experimentally and acquiring a better understanding of how drugs target cells in the human body. Platform technologies, collaborations, procedures and regulatory requirements will evolve to address this challenge at an increasing pace as this MoA knowledge is shown to be put to good use.



Trend 4
Generics on the rise

As market pressures are forcing companies to seek growth opportunities outside their traditional sectors, the boundaries between the novel therapeutics and the generics markets are blurring. Big pharma are increasingly looking at their generics offerings and strategies, while traditional generics companies are looking to add value to better fend off increasing competition amongst themselves and the big pharma companies.

This is creating the need for solutions that address issues such as product differentiation to provide clear additional benefit over existing pharmaceuticals, risk/side-effect reduction and repositioning so as to render orphan and rare diseases more interesting for treatment development. For example:

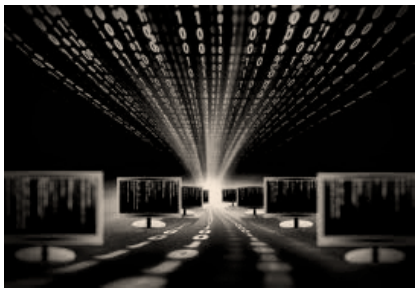
- Modifications of the active API can form the basis of exploitation of different crystalline forms, hydrates or solvates, switching from one salt to another or, less commonly to a different ester.
- Modified release formulations provide improved patient compliance by reducing the dosage frequency through maximizing the period in which plasma concentrations of drug are kept above the minimum level for efficacy and/or to avoid excessive peak plasma concentrations that might give rise to unwanted effects. Modified delivery formulations deliver improve compliance by providing more convenient administration.
- New routes of delivery
- Fixed dose combinations: With combination therapy increasingly becoming a standard of many treatment paradigms across a range of indications, many pharma companies are trying to capitalize on this growing trend by developing fixed dose combinations (FDCs), which can also act as a generic defense strategy.

Trend 5
Clinical trials and new approval models

In the recent past the need to understand disease at the molecular level - including the need for a better understanding of targets and biomarkers - is driving the shift of clinical research and drug development away from the traditional linear process of clinical trial phases. The realization that most diseases are multi-factorial is further compounding this shift towards multi-target therapies and as a consequence new clinical trial practices.

These new clinical trial practices will need to address a number of socioeconomic issues and shifting parameters such as the aging population, increased costs of drug development and research, raising costs of primary and secondary healthcare, the impact of pharmacogenomics and pharmacogenetics in the development of wide-access individualized therapies as well as the identification of more predictive biomarkers and surrogate markers.

This multiplicity of factors involved will create novel collaborative patterns between industry, academia and the regulating authorities, some of which will focus on the earlier stages of development. As a consequence we expect the role of clinical research organizations to change from one of a sub-contractor to that of an active collaborator who will be engaged sooner rather than later in the development process. Clinical Trials CROs will engage actively in integrating scientific, technologic and basic knowledge emerging from Academia driving early negotiations and discussions with regulators, long before the first PoC study takes place.



Trend 6
Big Data Analytics

Sequencing and related technologies are creating over a terabyte of data for each patient while it is typical for reference genomes to create over 3 million variants. This is a massive amount of data and yet this is not all. Over 2 million scientific publications are added to Medline every year alone and other relevant resources are expanding at similar rates.

Clearly this amount of data cannot be handled by any single team, let alone any single individual. Furthermore, not only is it becoming increasingly difficult to be aware of and hence access

potentially relevant data but even more importantly, even if access is guaranteed, the new challenge is to *interpret* this data and to understand *how to use it* in the right context.

There are a host of technologies in existence and in development that aim to provide access and interpretation of extremely large data sets. Moving forward we expect to see increased activity in these, especially technologies that ensure access to seemingly disparate data and that find non-obvious connections of knowledge that can be put to effective use in specific problem contexts. Inline with our expectation for more non-obvious collaborations, we also expect to see an increase of these between providers of such solutions and the traditional stakeholders of the industry including pharma/biotech companies, HMOs, and healthcare providers.

Novel disciplines, such as information architecture, along with current technological developments, such as the "cloud", can help shape up actual virtual workbenches for researchers providing them access to personalized scientific information, both in terms of automatically pre-selected relevant experimental data as well as machine-monitored scientific publications and information about patents.

Trend 7
Mobile Health

The recent explosion in mobile communications driven by the uptake of devices such as smart phones and tablets is opening up a global mHealth market, which in 2013 will reach an estimated $2bn.

mHealth solutions promise improvements in healthcare system processes, better medical data collection and better patient compliance, not to mention improved access to healthcare in remote or rural areas. Dedicated devices that perform medical functions will utilize mobile technologies offering new possibilities for treatment monitoring and administration. For example the combination of personal lifestyle data with genotypic ad phenotypic data ca support the optimization of disease prediction and prevention in the first place and treatment adjustment during the therapy phase.

The mHealth ecosystem will support healthcare practitioners while software and app developers will assume an increasing role and offer significant product differentiation opportunities to more established companies. Government bodies, payers and pharmaceutical companies are also expected to increase savings and revenues from mHealth.

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