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Medicines discovery in the 21st century: the case for a stakeholder corporation

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It is widely accepted that biopharmaceutical companies have, in recent times, failed to deliver large numbers of new medicines to patients and have simultaneously failed to deliver large financial returns to their investors. We argue that addition of different business constructs with wider stakeholder ownership and/or control offers a way to improve returns from the great advances in medical science and drug discovery processes. Governments and other payers for medicines, the academic institutions engaged in bioscience knowledge creation, patient advocacy groups, venture philanthropists and charitable foundations can come together with commercial profit-centred businesses to develop corporate constructs that mutually benefit all of the stakeholders. A rebalancing of the social and financial motives in medicines research can arrest recent productivity decreases of the sector.

Historical success

The pharmaceutical and biotechnology (biopharma) industries have had enormous societal impact during earlier decades. New medicines researched and developed by the industry have played a considerable part in increasing longevity and improving quality of life.

The pharmaceutical industry has historically been very successful in achieving 'double bottom line' impact through the creation of both financial value and social value. Recently, increasing emphasis has been placed on financial performance. The change in balance might suit investors in the short term, but – as shown by recent events in the financial services industry – if the imbalance becomes too great, the industry as a whole will lose its social legitimacy. This is already a major problem for pharmaceutical companies because there is great and growing public mistrust of large firms, which could lead to a reduction of support for bioscience and the direct or indirect subsidies that businesses rely on.

Present challenges

The economic realities of the 21st century are forcing a reappraisal of previously successful business processes and operating structures, and it is clear that the existing business model for the discovery of new medicines is unlikely to yield optimal translation of the great advances in biological knowledge into benefits for patients.

There is a major dislocation between the financial objectives of the owners and the commercial objectives of the business. It takes 12–20 years to translate a bioscience idea into a pharmaceutical product. With very few exceptions, funders of large and small businesses in this space do not have a 20-year perspective; therefore, the longitudinal process involved in producing a drug cannot be optimally accommodated within one vertically integrated business structure funded by this impatient equity. To shorten the timeframe for return on investment, pharmaceutical companies are reducing in-house research capacity and are changing their status from 'research and development' to 'search and development' organizations. This creates a large 'translation gap' between organizations creating the knowledge that forms the basis of new medicines and the commercially funded innovation process that brings new medicines to patients.

Robert Jones has summarized [1] the accepted pharmaceutical sector business model of the second half of the 20th century:

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- 'Investing heavily in research and development (R&D) for new medicines, based upon a sophisticated and increasing understanding of the body's chemical pathways and how chemical interventions could affect disease processes;
- Patenting the resulting products and selling at producer-determined prices into markets managed by largely price-insensitive national healthcare systems;
- Re-investing the business profits in R&D to discover the next wave of medical interventions. Patent protection did not mean extensive market monopoly as competing incremental innovations usually fragmented market share quite early and, in so doing, spurred ever more innovative efforts by originators'.

He avers that 'some unwritten 'contracts' underlay this process':

- Buyers (national healthcare systems) did not challenge drug pricing, or attempt to interfere with the competitive dynamic of the R&D process, so long as drug-acquisition did not create undue stresses for health budgets;
- Manufacturers invested substantially in ever-new R&D facilities, programmes and alliances; recognising that only a continued stream of products that actually made people feel better could justify their evident profitability;
- Shareholders tolerated the allocation of profits to long-term speculative drug development in the expectation that net margins would still be sufficient to drive above-average equity growth and dividends.'

In recent times, many changes in the chain that drove the process have fatally damaged the established business model, resulting in an increasing misalignment between the social and financial returns in the new medicine creation process. These changes include:

- Passive drug purchasers have become aggressive price-seekers.
- Society has become increasingly intolerant of risks associated with new medicines and lost sight of a reasonable balance between risk and benefit.
- The revolution in biology-based knowledge (including emerging understanding of the human genome) has increased costs but so far failed to improve attrition or to deliver increased numbers of medicines to patients.
- Medical knowledge in 'non-commercial' disease areas has caught up with that on widespread diseases suffered by wealthy patients.
- Vastly enhanced access to knowledge of medical advances has raised patient expectations.
- R&D costs have escalated at a much greater rate than general inflation.

Despite these changes, investors have continued to expect large, rapid and growing financial returns on their investment.

One current pharma strategy is to focus only on new medicines that are predicted to yield high financial returns. This is mirrored in smaller companies. Most venture-funded biotech businesses do not plan to achieve end-to-end operations from research to the marketplace and have their focus on the pharmaceutical companies as their customer. Their research agenda, therefore, is also largely driven by the present-day commercial strategy of the pharma companies.

Another current strategic response of pharma companies seeking to maintain returns for shareholders is to 'exit research to create value' (which is the title of a report from Morgan Stanley, January 2010). Morgan Stanley's analysis suggests that, 'on current market economics, the industry should reallocate the bulk of small-molecule research invested capital to in-license external assets post phase IIa, especially in therapeutic areas with high attrition rates (Gastro-intestinal, CNS, Cardiovascular and Respiratory)'. This strategy seems to have a mid-to-long-term flaw because it relies on current market economics to determine research strategy. Today's research spend will bear fruit in a future, very different, marketplace. The future marketplace is unlikely to be rich in opportunities for in-licensing because the generation of these would need present-day research investment, which is reducing.

The natural pose of profit-centred organizations is to believe that the paying customer should drive the product focus. Pharma companies controlled by their marketing functions are, indeed, narrowing the disease focus of their research divisions to those areas in which they believe the customer of the near-term future will pay. As large companies merge, the diseases that fit within strategic areas of operation become ever less diverse. This results in a considerable under-exploitation of the rapidly growing knowledge base by the current business equity holders.

Many good projects are stopped because they no longer fit the strategic direction of the company (e.g. GSK's decision in February 2010 to exit a large proportion of its neuroscience drug discovery). Other scientifically sound projects are unfundable in failing biotechs and yet more are in academia, where their supporters probably do not have the multidisciplinary skills to maximally extract value and the funding for setting up and sustaining spin-out companies has, with few exceptions, essentially dried up.

The future of small-molecule drug discovery is under increasing threat. Funders are applying more of their resources to the later stages of the process to get more rapid return on investment, and venture capitalists are more reluctant than ever to fund early ideas. Parts of the translational gap are being addressed by various organizations enabling clinical science advances, but in the preclinical part of the drug discovery process, the gap is increasing, despite the excellent efforts of UK of organizations such as the Wellcome Trust, MRCT and CRT.

It is widely recognized that, during the past two decades, R&D productivity in the pharmaceuticals business sector has declined or, at best, remained static, with only 21 new drugs approved in the USA in 2008 [2]. This is despite great scientific and technical advances in every stage of the R&D process and despite the very large annual investments by biotech and pharma companies ($28 billion and $65 billion, respectively; see 'Biotech 2008: A 20/20 Vision to 2020' at http://www.baybio.org/pdf/Breakfast_Plenary_2020.pdf and Profile: Pharmaceutical Industry 2010' at http://www.phrma.org/sites/phrma.org/files/attachments/Profile_2010_FINAL.pdf). There is clearly no shortage of invention in the biopharma space, as evidenced by analysis of the number of patent filings. There is, however, a failure in translating this invention to large numbers of socially and commercially important new medicines. It seems self-evident that the lack of productivity must result from a systemic failure of the prevalent biopharma business models.

In addition to the visible failure of output of the pharmaceutical industry in terms of new medicines, the industry's major educational role has, in the opinion of the authors, been compromised. For more than half a century, the pharmaceutical industry has provided 'quaternary' education in the multidisciplinary process of the discovery of new medicines, particularly small-molecule (affordable) medicines, but this activity is seriously threatened by the major restructuring that is now taking place, Alternative routes are needed to provide training for the next generation of researchers to engage in medicines research to avoid the loss of this important knowledge base. Local and national governments want high-quality employment and to sustain and develop the skill sets capable of contributing to the high-value knowledge economy. 'Quaternary education' includes vocational training, fellowships and mentorship of staff: it both builds upon and complements academic education.

Currently, investors in medicine research frequently drive companies to make short-term

decisions that are detrimental to the long-term value of the companies and at the same time do not maximize societal health benefits.

Future opportunities

Future demand for new medicines will grow dramatically as under-developed economies 'emerge' and the number of people aged over 65 increases substantially in the years ahead. IMS Health predicts that the global market for pharmaceuticals will pass $1 trillion by 2013 [3]. Despite this prediction, there is a crisis of confidence in today's pharmaceutical companies, and this is driving the changes described above.

The creation of a new medicine takes 10–20 years from idea to the pharmacopoeia. Organically self-sustaining, vertically integrated businesses (not using the financial engineering route of mergers and acquisitions) therefore require their shareholders to have a patient view of return on investment. Investors in biopharma businesses have become less patient over time. The ownership structure is a key issue. Not only do investors need to invest for the 15 years of the development process but also, because an independent biotech might not become sustainably successful until multiple projects have been concluded, the timeframe for achieving a self-sustaining portfolio of assets can be much more than 15 years.

Organizations focused on the paying customer will be complemented by those whose strategy is led by researchers that would be likely to adopt a different approach. This would be to identify the key needs of the patients of the future and trawl their research knowledge to identify opportunities to address these future needs. Indeed, an organic process of vertical integration in which researchers progressed their discoveries through development and to the marketplace describes the development of many of the companies that dominated the pharma landscape of the 20th century. This development was achieved while retaining the capacity for effective research into new products and was only possible because the equity owners were patient and focused on long-term success.

Vertical disintegration [4] allows the possibility of sustainability to be achieved in somewhat less time by research-based businesses as their outputs form the inputs for the 'search and development' organizations to bring to the market.

The future marketplace for pharmaceuticals will have a very different shape to that of recent decades. The treatable patient population is now acknowledged to be globally dispersed and in many cases cannot pay the full cost of producing the medicine. In addition, it is now recognized that the patient population is not homogeneous. Thus, it has been possible for some diseases to be genetically sub-typed (cancer is a good example). The individual patient's response to a drug is also genetically sub-typed. These stratifications increase the potential power and accuracy of clinical studies but reduce the likelihood of future blockbuster drugs where one size fits all. Again, the ability of patients to pay for the research and development of these stratified medicines is in doubt. R&D funding structures must be diversified to reflect these marketplace changes.

There is a need to rebalance the 'pull' from the market and the 'push' from new ideas. For effective and productive pharmaceutical research, a variety of business models should be available to enable exploitation of both: it is clear that future patients will not be best served by simply continuing with today's biopharma business models. Other forms of ownership structure are necessary to complement the activities of the current publicly traded equity ownership forms. There are a significant number of successful privately owned businesses in the sector. In general, businesses owned by families or by charitable foundations have enjoyed long-term survival through a range of economic climate changes; examples include Roche, NovoNordisk, Leo, Ferring, Grunenthal, Chiesi and Almirall.

Current annual academic research spend on biosciences has been estimated at $200 billion. There are encouraging signs, especially in the USA, that universities are taking the initiative to drive their assets to commercialization, and the purchase by Yale of the former Bayer research facility is an example.

For too long, the important stakeholders (future patients and the governments and health insurance companies who pay for medicines) have ceded responsibility for the desired innovative outcomes in medicines research to a relatively small number of biopharma companies and their shareholders.

There is considerable scope for multiple forms of social capital to contribute to expansion of the innovation dividend.

In recent years, several supra-governmental organizations, governments of emerging economies and venture philanthropists have begun to alter the picture, often in public–private partnerships with biopharma companies [5]. The new world of venture philanthropy is emerging, as successful business leaders – e.g. those of the Bill and Melinda Gates Foundation (www.gatesfoundation.org) and the Milken Foundation (www.fastercures.org) and Sergey Brin (http://dailyqi.com/?p=2841) – turn their attention to achieving social goals using the gains from their business success. Their funds are used not only to fund specific medicine discovery projects but also to analyse business processes and to promote public policy changes to ensure that the future patient remains at the centre of the agenda.

Total funding for R&D into new products for 31 neglected diseases is growing rapidly and in 2008 was $2.96 billion. 88% of this came from public and philanthropic donors [6]. More effective ways are required to achieve greater social and commercial value from intellectual property assets; for example, patient advocacy groups frequently form charitable foundations to promote the discovery of new medicines for particular disease areas. There is an increasing desire to ensure that the academic research funded by these organizations is translated into real innovations that benefit patients. CRUK's establishment of CRT to promote this translation is a good alternative business construct.

INMedD (www.inmedd.org) is a social enterprise that aims to address the market failure, taking projects that are not fundable by their current owners and moving them forward to a position where sufficient risk has been removed to enable investment for onward development. Removal of the need for profit distribution enables inclusion in the portfolio of those projects that are expected to make a significant social but not large financial return. INMedD provides an integrating focal point and drive for collaboration between the many stakeholders in new medicine creation (Fig. 1).

There is a clear opportunity in the biopharma sector for interested stakeholders to pursue ownership models that emphasize the 'stewardship' role [7] of company owners. This can be achieved by enlightened shareholders in publicly quoted companies, by foundations or by various forms of mutual ownership or social enterprise. In the latter case, efficiency gains can be achieved by reduced cost of capital (smaller return on investment acceptable) and decreased attrition ('failures' because of lack of projected profitability are reduced). In addition, social enterprises might be well positioned to drive open innovation [8] models because they can remove the perception of exploitation of one collaborator by another, which often introduces a barrier in such models.

The stakeholder approach [9,10] to medicines research is not just a moral imperative but a healthcare and commercial necessity. There is great opportunity for governments and other payers for medicines, the academic institutions engaged in bioscience knowledge creation, patient advocacy groups, venture philanthro-

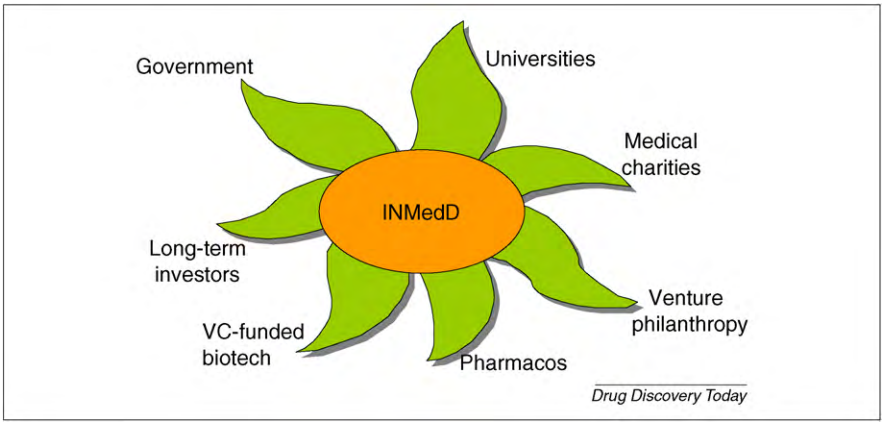

FIGURE 1

Focus for productive partnership between stakeholders.

pists and charitable foundations to come together with commercial profit-centred businesses to develop corporate constructs that mutually benefit all of the stakeholders.

Conflict of interest statement

The authors are bioentrepreneurs and independent advisers to medicine discovery businesses and are currently planning an institute for new medicine discovery (INMedD), which will harness public, private and philanthropic funding to translate novel bioscience into commercializable new candidate medicines.

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