Bio-business in brief: the paradox of being a drug company

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Companies must show a profit to survive. But medicines should essentially cure people, which would automatically decrease the sale of drugs, thereby decreasing the profits of the drug companies. How does one resolve this contradiction? Currently, many companies are pursuing the profit motive first, with health care as a second priority. We list two dozen reasons that could underlie an increase in the revenue for a drug company. About half of them are ethical reasons, and the other half unethical. We discuss some of these reasons with examples. A change in the drug discovery paradigm may be warranted to resolve this contradiction.

Biopharma companies live by the same financial logic as other companies: the stock market expects them to show double digit growth each year. This holds for public companies, and by extension, there is an expectation that private companies would show similar kinds of growth. But therein lies a paradox: medicine should cure a person and thereby decrease the demand for more medicine. Furthermore, the idea of making money out of people's miseries is distasteful. So how can a company fulfil these contradictory demands of simultaneously curing people and also selling more drugs?

We digress briefly to first describe the current process of drug discovery and development. Since India has yet to produce a widely used scientifically tested drug, we use the process as it happens in the United States as an example. The National Institutes of Health (NIH) and other government bodies fund basic research. Companies may also fund basic research, either in government labs or universities, or within the company. Such research forms the basis for the advancement of knowledge which in turn is the basis for many new drugs to be developed. The next steps – applied research such as target identification, screening of candidate molecules and animal studies – take place almost solely in companies. Once a compound is deemed ready for clinical trials, these may be conducted by companies or by public institutions such as the NIH. Either way, the molecules (and results of the trials) belong to the company. Regulatory review is also paid for by the company. The company has therefore undertaken significant R&D expenditure and prices its drugs to reflect these costs. A generic drug, on the other hand, primarily reflects manufacturing costs, since there is little by way of R&D costs in producing a generic.

Since a company that has developed a novel drug may have spent hundreds of millions of dollars, it is therefore under considerable pressure to recoup that expenditure and show a profit. We list the various possible scenarios that could lead to an increase in sales of a drug. We have also classified which of these seem to us to be ethical and which do not, while acknowledging that there could be a spectrum of opinions on some issues. Of the 24 reasons identified as possible causes for an increase in sales, half are – ethically speaking – above board. However, the other half of the reasons are less defensible. We list here these reasons, with a discussion of some of them.

We first address the ethical increase in drug sales. The broad categories identified are as follows.

Demographic changes: There are two possible demographic reasons for an increase in drug sales. One, the population increases, and therefore needs more medicine, and two, there is need for greater medication because of a longer average lifespan, especially while ageing. There is no doubt that globally both these phenomena are happening, although specific countries have a declining population.

Issues of access: One of the most important ways to increase access to medicines is through a drop in their prices. Competition leads to some reduction in prices and generic pricing to even more. Our own patent laws in the 1970s made generic drugs available not only to Indian patients but also those in several other countries, and therefore agencies such as Medecins Sans Frontieres, for instance, take great interest in the price of drugs in India (www.doctorswithoutborders.org). The well-known 'Hatch-Waxman Act' of the United States of America (USA) – formally known as the Drug Price Competition and Patent Term Restoration Act – brought in generic pricing for users in that country in 1984. One notes that a drop in prices might lead to an increase in revenue even for the 'innovator companies' in case the drugs are now affordable by more patients.

Another initiative with a similar effect is that of differential (Ramsey) pricing in different markets. Amongst others, an organization of medical students and teachers across 25 universities in North America, Universities Allied for Essential Medicines (UAEM), have lobbied with universities such as Emory and Yale to license their research in a manner that enables low-priced access to the resultant medicines in sub-Saharan Africa[1]. These and other initiatives enabled HIV/AIDS patients in South Africa to access drugs at a fraction of their cost in the richer countries.

A major factor that would lead to greater access to medication is greater purchasing power, and the growing middle class in India and China has certainly been in the eye of many an international company. Greater access could also happen because of more health insurance, companies reaching new locations, more physical infrastructure such as metaled roads, etc. We have not seen data on whether, in India or globally, the latter trends are contributing to the increased revenues of the biopharma companies.

Improved medicines: Yet another reason for increased sales relates to the intrinsic quality of the drugs. There are different categories of improved medicines. For instance, medicines could be developed for conditions for which there were none earlier, but this author does not have a feel for the productivity of this kind of drug discovery in general. For the specific case of tropical diseases such as malaria, the Medecins Sans Frontieres has estimated that only 1% of the drugs launched between 1975 and 1999 were for such diseases[2]. There has not been a large increase in the availability of such drugs in recent years, and therefore one presumes that they are not mak-

ing a significant contribution to the pharma industry's profits at this point. A different category is that of drugs developed under the Orphan Drug Act (of the US) meant to stimulate drug development for diseases affecting less than 200,000 patients in the US. This incentive has worked so well, and companies have made so much money from these diseases, that the Act has become controversial (http://query.nytimes.com/gst/fullpage.html?res=9C0CE4DF1F3EF933A0-5757C0A966958260).

New medicines could also be developed that are significantly more effective than the currently available ones. Unfortunately, drugs developed in recent years have often not represented significant medical advances. The Food and Drug Administration of the US (FDA) has estimated that of the over 1000 drugs it approved between 1989 and 2000, only 25% were better than those already in the market[3].

Another manner in which medicines could be more effective is through personalized medicine, where a drug is approved only for use in a defined set of people. Although much discussed, this practice has not yet contributed significantly to drug approvals[4]. During drug development, a candidate drug may fail trials due to a large percentage of 'non responders', that is those for whom the drug is of no use. If, however, it is possible to identify a segment of the population that will respond, the trials can be designed to test only in that segment. This enhances the chance of the drug being approved, but for a smaller set of users than the general population. Apparently only one drug, BiDil, has been approved by the FDA, for a specific subpopulation, African Americans (http://www.fda.gov/bbs/topics/news/2005/new-01190.html). As the drug development pipeline dries up, and with it the chance of 'blockbuster' drug revenues, companies may be more willing to pursue drugs that have small user populations.

Change in disease prevalence: Increased incidence of diseases – such as many cancers – for which there is no cure despite much research could be yet another cause of increased sales. This author has not seen statistics as to whether the incidence of such diseases is increasing, in specific countries or globally.

Finally, another situation of potentially large drug sales is that of a totally new disease or a pandemic. In recent decades, we have mercifully been spared a pandemic of the type that killed tens of millions after World War I. However, should this happen, and should a drug with even partial efficacy be available, there would be such a huge jump in demand that manufacturers would find it difficult, if not impossible, to supply adequate amounts in a reasonable timeframe.

Having considered the several ethical reasons for increased drug sales, we come now to issues that are at the very least distasteful, and often unethical.

Aggressive drug sales: General over-prescribing has become common, and entire books have been written about this[5,6]. Whereas Abramson, for instance, writes about the situation in the US, the middle class everywhere feels in the grip of too many tests and medicines. Other than routine over-prescribing (including sometimes unwarranted higher doses), there are now cases of diseases being defined for slightly abnormal but not dangerous conditions. Thus, slightly higher than the recommended blood pressure (above 120/80 but below 140/90) is now defined as pre-hypertension which apparently requires medication[7]. And after the rock-

Table 1. Potential causes of increased revenues of the therapeutic biopharma companies in the global marketplace. We assume that the companies are selling 'medicine', that is therapeutics

ETHICAL
Demographics
The population increases and therefore needs more medicine
People live longer and need more medicine, especially as they age
Access
The price of drugs drops significantly, through competition or generic pricing
Different (Ramsey) pricing in different countries
People have greater purchasing power
People have greater health insurance or relatively low cost access, as through government clinics
Health care becomes available to here-to-fore under-served populations, for reasons of physical access, as by better public transport, companies marketing in new areas and so on
Improved medicines
Medicines become available for conditions for which there were none, including for tropical diseases and orphan diseases
Medicines are developed that are significantly better than best current options
Personalized medicine
Change in disease prevalence
More widespread diseases such as cancer, for which, despite much research, there are inadequate options
People come down with unknown, new diseases
People are sick due to an unexpectedly large spread of disease, as in a pandemic*
UNETHICAL
Aggressive drug sales
General over-prescribing
Prescribing higher doses than required
'Medicalizing' a condition unnecessarily, and manufacturing diseases
Medicine is pushed for conditions that could be attended to through non-medical methods, as by behavioural changes
The drugs are ineffective, or of low efficacy, but are aggressively marketed anyhow
Low quality of drugs
Drugs with known or suspected negative side effects reach the market and/or continue to be marketed after problems are noted
Sale of counterfeit drugs
Other reasons
An unreasonable increase in the price of drugs
Innovator company pays off generic company to deny customers the benefit of low-priced drugs
Spending more on marketing than on research, which is reflected in the cost of the drug
Other uses of medicine, as for the meat industry or for cosmetic purposes**

*Sales of drugs for precautionary stock-piling, as by a company to a government, would be acceptable in some situations.
**Whether or not there is an ethical transgression likely to vary with the case.

eting sales of viagra, female sexual dysfunction, a previously unheard of condition, is being defined as a condition that – of course – requires viagra too[8].

Separately, medicine is pushed even though behavioural changes would suffice. John Abramson recounts how, for cardiovascaular disease, patients were initially advised more physical exercise, no smoking and less eggs and red meat in their diet. This led to a dramatic reduction in death from this disease with a 50% reduction between 1970 and 1990. However, subsequently this advice was sidelined in favour of the use of stents and clot-busting and cholesterol-reducing drugs. Therefore despite this medical 'progress', the annual rate of decline of the death rate from heart disease actually decreased in the 1990s!

Along a slightly different line, several biologics have only marginal efficacy, and yet may be promoted with vigour. Thus, Herceptin works for only about 35% of the 20% of the breast cancer patients who over-express (by 2- or 3-fold), the Her2 epidermal growth factor receptor[9]. This means that a mere 7% of breast cancer patients benefit. Furthermore, the benefit is often counted in terms of the few months that the patient remains progression-free (http://www.medicalnews-today.com/articles/109363.php). Much is made of each new drug in the market, but it is important to get a sense of the actual benefit in each case.

Low quality medicines: In their attempts to have a new drug approved, pharma companies have in the past suppressed negative results from clinical trials and only put forth the positive results. In the past, this has led to drugs being approved with known or suspected problems. Similarly, if a drug is in the market and a problem is identified, it is not necessarily brought to the notice of the regulatory authorities in a timely manner. Neither of these is defensible, and the FDA has been accused of being incapable of protecting the health of Americans[10]. So, too, the extreme example of an ineffective drug – an inactive or actually harmful substitute for the real thing – a counterfeit.

Other reasons: There are several other reasons that are ethically questionable, that do not fall in the categories of aggressive drug sales or low quality medicines. An unreasonable increase in the price of drugs is one such. A good example of over-priced drugs is provided by replacement enzymes from Genzyme, prescribed for patients whose bodies do not make the requisite enzymes. Cerezyme, for Gaucher's disease, is priced at over US$ 200,000 per person per year (http://money.cnn.com/2007/03/13/news/companies/genzyme/index.htm), difficult to justify even in a prosperous nation such as the US, even if most of the payment is made by an insurance company.

A similar outcome accrues when an innovator company pays a generic company to delay the introduction of a generic version of its drug (http://www.ftc.gov/opa/2008/02/ceph.shtm). Doubtless both companies benefit, but patients lose out as they are forced to pay the higher price for some more months or years.

On a different note, a fundamental problem with the current profit-driven drug discovery paradigm is that two- or three-fold more money is spent on marketing than on research[11]. Large advertising budgets are considered normal for regular commercial activities, but do not make as much sense when viewed through the lens of patients paying more of their hard-earned money to stay healthy.

And finally, the use of medicines for reasons other than improving health can have potentially dangerous side effects. Thus, the widespread use of antibiotics in a routine fashion in the meat industry contributes to antibiotic resistance, a danger to everybody. And to use a highly toxic substance such as botulinum toxin for cosmetic reasons is to take unnecessary risks. The aggressive promotion or adoption of such uses is not ethical.

The list of reasons for increased sales, both ethical and unethical, are summarized in Table 1. We have expanded upon only some of these issues, and only briefly. However, it is not our contention that accusations of unethical practices are to be laid solely at the doors of the drug companies. Let us take a quick look at the role of government.

For the sake of argument, let us ask why the government should concern itself with the health of its citizens. In India, many are unemployed. Their sickness or early demise does not result in loss of man-days at work, and therefore has no direct impact on the economy. Furthermore, the government does not provide healthcare to all of these people through its own clinics or hospitals, and therefore does not incur any direct cost when a poor person falls sick. Therefore, at stake is not an economic argument but a moral one. The Indian government is not merely *by* the people and *of* the people but also *for* the people. Good health is one of the most fundamental needs of any individual, and failure to ensure it is to unconscionably abrogate a fundamental duty. National governments and international organizations have potentially strong tools of policy in their hands. They must use common sense and either existing or new legal methods to ensure the good health of all. A strong infrastructure for preventive and other forms of primary healthcare would go a long way in taking care of the health of its citizens.

Conclusion

So where do we go with this analysis? On paper at least, there seem to be as many unethical as ethical reasons for the increased sale of medicines. Ways need to be found to reinforce the latter and decrease the former. Reorganizing the entire drug discovery process, especially by having a new means of funding R&D so that it is not included in the final cost of the drug[3], might reduce the pressure on a company to show huge annual increases in revenue, the cause of many if not most unethical practices.

1. Chokshi, D. A., *PLoS Med.*, 2006, **3**, 723–726.
2. Nathan, C., *Nat. Med.*, 2007, **13**, 304–308.
3. Hubbard, T. and Love, J., *PLoS Biol.*, 2004, **2**, 0147–0150.
4. Sinha, G., *Nat. Med.*, 2006, **12**, 983.
5. Abramson, J., *Overdosed America: The Broken Promise of American Medicine*, Harper Perennial, New York, 2004.
6. Angell, M., *The Truth about the Drug Companies: How they Deceive us and What to do About it*, Random House, New York, 2004.
7. Elliot, W. J. and Black, H. R., *Nat. Clin. Pract. Cardiovasc. Med.*, 2007, **4**, 538–548.
8. Tiefer, L., *PLoS Med.*, 2006, **3**, 436–440.
9. Goetz, M. P., Toft, D. O., Ames, M. M. and Erlichman, C., *Ann. Oncol.*, 2003, **14**, 1169–1176.
10. Frantz, S., *Nat. Rev. Drug Discov.*, 2005, **4**, 5–7.
11. Gagnon, M.-A. and Lexchin, J., *PLoS Med.*, 2008, **5**, 29–33.

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