International Organization
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Globalization and development: The critical role of pharmaceutical and biomedical analysis

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Introduction

This paper considers pharmaceutical and biomedical analysis in a global context – how it is both being shaped by and helping to shape some of the major forces of globalization. We experience globalization as the increasingly unhindered and rapid flows of goods, capital, services, labour and information around the world; and the increasing integration of national industries into global ones. One of the strongest driving forces of this globalization is the revolution in information and communication technologies, which is now reaching some of the poorest and most remote locations in the world.

But with the rapid pace of change that we are experiencing, we need to ask whether the world is ready for the new global forces that are re-shaping it. And, in particular, I would like to focus on an aspect of globalization that is proving particularly challenging - namely "liquidity ".

Zygmunt Bauman is one of the world's foremost thinkers and writers on modernity. In his book on 'Liquid Times', Bauman observes that modernity has passed from the 'solid' to the 'liquid' phase.[1] That is, structures, institutions and patterns of acceptable behaviour can no longer keep their shape for long – they decompose faster than the time it takes for them to be cast and set. One example of this is that regulatory systems of all kinds – whether dealing with flows of finances, goods or information - find it difficult to keep up with the pace of change.

Bauman comments[1] that this difficulty is compounded by the increasing separation of power and politics. Power that once rested with the nation state is now moving to the politically uncontrolled global space; while politics is unable to operate effectively at the planetary level since it remains local and rooted in national interests.

The changing world of pharmaceuticals

The world is changing rapidly in ways that are affecting:

- ***where*** PBA is practiced
- what ***kinds of materials*** are the subject of investigation
- what sorts of ***analytes*** are addressed
- the sorts of ***people*** to whom the results are communicated

In particular, the world's health is changing – and this includes aspects of health related to economics, age and disease burden. The world is changing with regard to the pharmaceutical industry - especially concerning the locations of R&D, production and consumption and the types of products; and there are a number of critical concerns about "health security", especially regarding the fact that we are increasingly living in a dirty world and a fake world.

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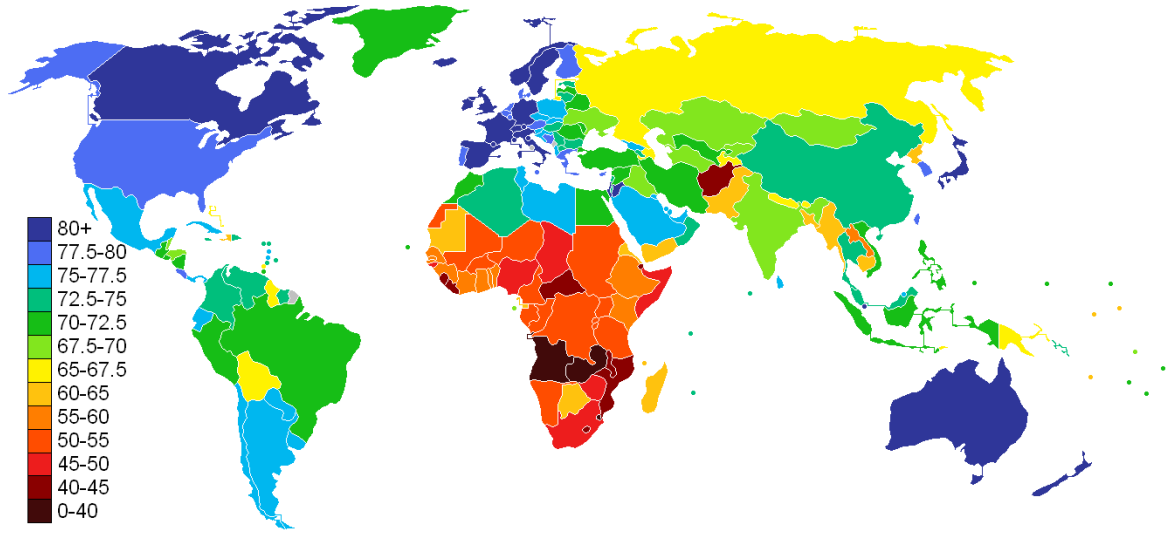
In the whole of human history, global average life expectancy at birth remained at no more than about 30 years until around 1900 – but in the last century global average life expectancy has more than doubled. However, this massive improvement in life expectancy is not evenly distributed around the world – and as the chart shows (Box 1), the biggest gains have been in the high-income countries, so that a girl born today in Japan can expect to live to more than eighty, whilst one born in some parts of Africa will only expect to live to about half that age.[2]

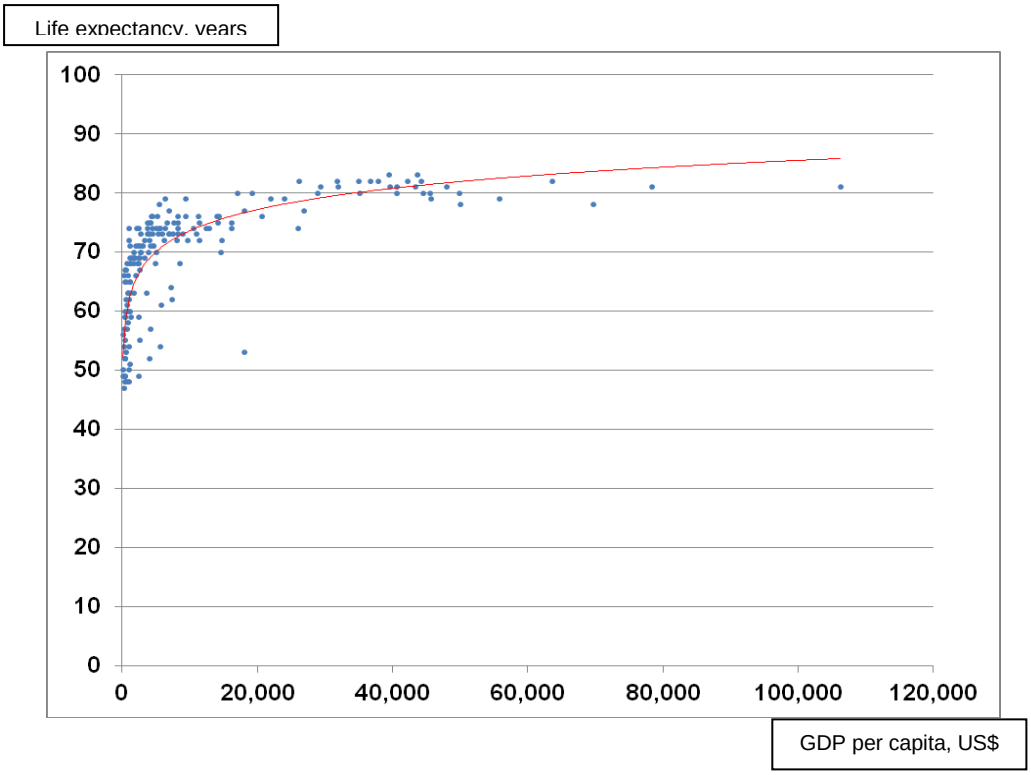
Box 1 Life Expectancy at Birth by Country: 2011 Estimates



There is a relationship between life expectancy and the wealth of populations, as illustrated by the Preston curve[3] (Box 2), which plots the average life expectancy for a country against the country's average gross domestic product (GDP) per capita.[4] The relationship is clearly not a straightforward linear one – beyond a certain wealth, more money does not buy greater life expectancy in high-income countries (HICs), but below this point it does seem that having more money makes a big difference. And in this regard, it is notable that some of the low- and middle-income countries (LMICs) have been demonstrating dramatic rates of growth in their economies in recent years. So much so, that it is clear that we should really stop talking about "developing" and "developed" countries: It is predicted that the sum of the GDPs of all the developing and emerging economies will overtake the sum of all the advanced economies within the next couple of years.[5]

But economics is clearly not the only factor involved in the dramatic increases we have seen in average life expectancies during the last hundred years. If a set of Preston curves is plotted for the last century covering different time periods (Box 3), it is seen that in any one time period there is a similar trend for the relationship between life expectancy and GDP per capita, but between each succeeding time period there is an overall increase in life expectancy.[6] So in constant dollars, the same amount of wealth seems to buy more life in a later period. However, economists like Easterlin[7] have concluded that the steep decline in mortality during the 20th century had its origin not directly in wealth but in technical progress – where 'technical progress' is defined broadly as the sum of scientific advances, the diffusion of these technologies to different countries and the capacities of countries to undertake, apply or adapt the technologies for local use. And it is clear now that much of the variation between countries in their average life expectancies results from very substantial variation in their rates of technical progress- for example, this explains much of the differences in improvements seen in infant mortality rates.[8,9] So the diffusion of technical knowledge that comes from research turns out to be a key factor in determining human lifespan and reducing early mortality – truly, we can say that "ignorance is fatal".[10]

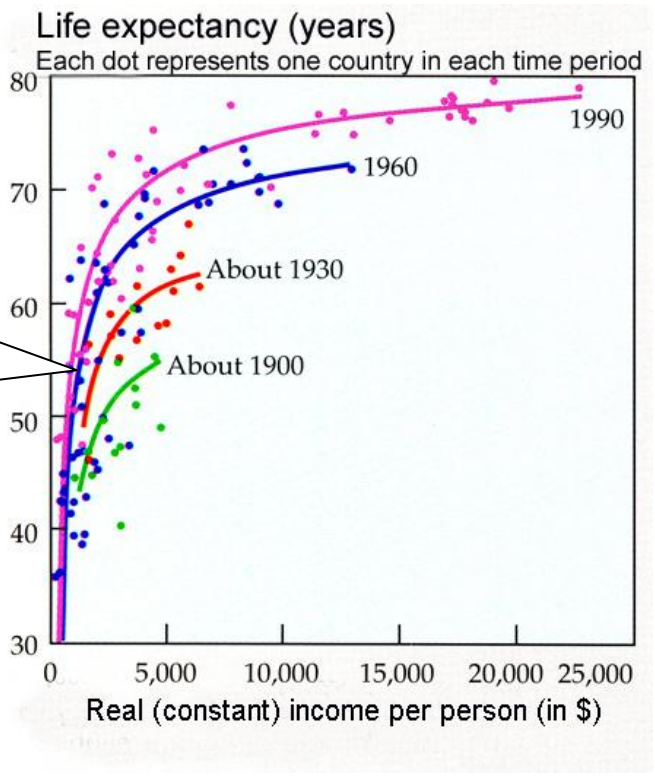
Box 2 Preston curve: Life expectancy vs GDP per capita 2009



Box 3 Preston curves 1900-1990

20th century mortality decline had its origin in technical progress.[7]

Much of the variation in country outcomes results from very substantial cross-country variation in the rate of technical progress.[8,9]



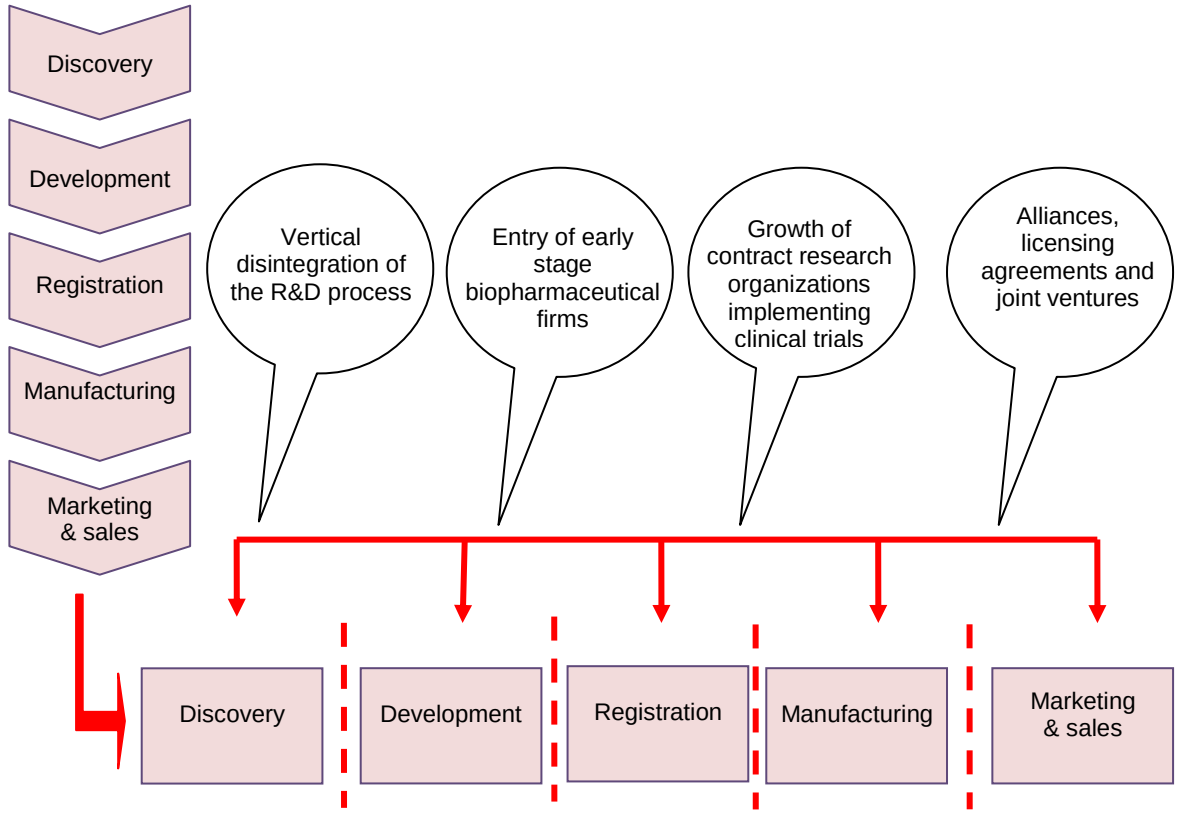
Advances in medicine and public health have been a very major part of this technical progress. But this was not always the case. It took a combination of the better science and better regulation that began during the second half of the 19th century to ensure that sick people are offered medicines that

are safe and effective.[11,12] The evident impact on health during the last 100 years has been enormous. And during that time pharmacy has grown from being a cottage industry practiced in local communities to being a global industry which not only contributes massively to health but also to national and global economies and will soon have sales exceeding US$ 1 trillion per year.[13,14] The biopharmaceutical research industry is one of the most research-intensive and in a number of countries invests tens of billions of dollars every year.[15]

The pharmaceutical industry is moving sideways, East and South. Paradoxically, we have seen in recent years a combination of two countervailing trends - mergers and acquisitions, which from the early 1990s began to take place on a scale unprecedented in the entire history of the pharmaceutical industry;[16] but simultaneously there has a shift from 'vertical' to 'horizontal' structures, including the separation of research from development.

The various functions of the pharmaceutical industry were traditionally all located within the same company, but these vertically integrated supply chains are breaking apart into component activities that can be outsourced.[17,18] There are now numerous stages at which outside agents are taking over specific functions and we are increasingly seeing alliances, licensing agreements and joint ventures along the whole value chain (Box 4).[19,20,21]

Box 4 Pharmaceutical industry value chain: Shifting from vertical to horizontal industries



The separation of research, development and manufacturing is reshaping the character of R&D around the world – and it is not at all clear that this is for the better in the long term. As one recent, detailed study put it: mergers may have achieved cost reductions and addressed short-run pipeline problems, but so far there is little evidence they have increased long-term R&D performance or outcomes. And there is a persistent problem with R&D productivity. Indeed, some in the pharmaceutical industry itself have characterised this as a 'crisis' (Box 5).

Box 5 Pharmaceutical R&D productivity: what the industry says

Although mergers and acquisitions in the pharmaceutical industry might have had a reasonable short-term business rationale, their impact on the R&D of the organizations involved has been devastating.

LaMattina (former President of Pfizer Global R&D)[22]

Without a substantial increase in R&D productivity, the pharmaceutical industry's survival (let alone its continued growth prospects), at least in its current form, is in great jeopardy.

Paul et al (Lilly Research Laboratories, Eli Lilly and Co)[23]

There has been much written in the last few years about whether innovation in the pharmaceutical industry is declining. The number of new molecular entities registered as drugs has certainly fallen back from the peak seen in the 1990s. At the same time, R&D costs have been rising steeply for many years and the overall productivity of investments in pharmaceutical R&D has therefore been diminishing very substantially in countries like the USA.[24,25,26,27,28,29]

Meanwhile, in tandem with all this internal restructuring, pharmaceutical R&D is globalizing – especially moving East and South, expanding substantially in what have become known[30] as "innovative developing counties" like India, China and Brazil.[31,32,33,34]

- Brazil has enacted new patent and technology laws to encourage innovation and, together with large increases in investments in R&D and new strategic developments such as the fostering of drugs and biopharmaceutical development at FIOCRUZ, this is giving a big boost to Brazil's position as a global player.[35,36]
- India has long been known as the "pharmacy of the developing world", producing cheap versions of known drugs for markets in low- and middle-income countries.[37] More recently, Indian pharmaceutical companies have begun an intensive innovation drive to create new molecules.[38,39]
- China has invested heavily in R&D infrastructure and many multinational companies have been establishing operations there. They are now shifting their focus from late-stage drug development and R&D outsourcing to setting up a second wave of more fully integrated R&D capabilities.[40,41]

As a region, Africa has the weakest capacities for drug production – but efforts to change this are now under way, with a commitment by the African Union to strengthen both pharmaceutical innovation and production[42,43] and new initiatives such as the African Network for Drugs and Diagnostics Innovation established in the last few years by the World Health Organization.[44]

At the end of the 20th century, 90% of the world's pharmaceutical production was concentrated in high-income countries and there was little or no production capacity in several regions, including Africa and parts of Asia and Latin America.[45] But that picture has begun to change rapidly in the last decade and more and more production is moving to cheaper locations in LMICs.[46,47]

A recent UN report[48] shows that more than half of African countries have some pharmaceutical manufacturing capacity. But except in South Africa, local production is currently limited to final formulations manufacturing and few local producers have so far managed to meet WHO pre-qualification requirements. The UN report also notes that other regions are also developing their capacities – e.g. Bangladesh has a growing local pharmaceutical industry.

The report makes a number of policy recommendations that will help to make affordable essential medicines more accessible. What I want to highlight in the present context is the emphasis put on ***quality assurance*** and ***regulation***, both of which need to be underpinned by strengthening analysis capacities.

At the same time that R&D and production are moving, pharmaceutical markets are also growing very rapidly in these countries.[49] So for example, in the current five year period to 2015, the Compound Annual Growth Rate or 'CAGR' for pharmaceuticals is predicted[50] to be less than 3% in North America and Western Europe, but the Asia-Pacific and Latin American regions are seeing CAGRs of 11-16%. In fact, there is now a whole group of countries that are becoming known as the "pharmerging markets". They are already being classified into three tiers – China in a tier of its own with a huge growth rate of its pharmaceutical sector –for example it grew by 26% in 2008. In Tier 2

are Brazil, Russia, and India – Brazil, for example, has had a consistently high pharmaceutical growth over the last few years and was at 20% in 2008 – and then there are another 17 countries in Tier 3 which have recently begun showing very high growth rates of their pharmaceutical markets. Taken together, these pharmerging markets are going to be accounting for around half of the total world growth in pharmaceutical sales in the next few years.[51,52,53]

The need for pharmaceutical and biomedical analysis

We live in a dirty world – and not necessarily a world that is becoming any cleaner. In particular, strong vigilance is needed in three areas, to do with pharmaceutical contaminants in the environment, in food and in pharmaceuticals themselves.

Just to take a few brief examples:

Environment and food

A recent report illustrates some of the key features of environmental contamination by pharmaceuticals: despite a 2006 ban by India on the use of diclofenac in cattle, and some progress seen since then, the latest evidence shows that the ban is being circumvented by illegally using, for veterinary purposes, diclofenac manufactured for human use. Several species of vultures that feed on the carcases of dead cattle are endangered as a result.[54]

Problems of contamination of food and the environment with pharmaceuticals are widespread throughout the world. A recent report in *Nature*[55] concerns high levels of pharmaceutical ingredients in treated effluent from wastewater-treatment plants and in effluent downstream from pharmaceutical factories with examples coming from India, the USA, and the European Union. It is important to recognise that there has been a systematic failure, at both national and global levels, to deal with these problems. As the Nature report observes:

- It has been assumed that water-quality standards and companies' desire to avoid wasting valuable pharmaceuticals would minimize the extent of bioactive compounds released by factories into wastewater, and ultimately into rivers. The report says: "***A string of studies suggest otherwise.***"
- "The discovery has prompted calls for more effective oversight of the industry. The USA and Europe do not have regulations limiting the concentrations of pharmaceuticals released into the aquatic environment in either municipal wastewater or in effluent from manufacturing facilities." The report concludes: "***People think drug release is regulated, but it is not.***"

Pharmaceuticals

Another area of very serious concern is the contamination of pharmaceutical products themselves with harmful ingredients (Box 6). For example:

Box 6 Examples of contamination of pharmaceutical products

Nigeria: In 2008 dethylene glycol (DEG) was found to have been used in *a* baby teething mixture called *'My Pikin'.* There were 84 deaths reported. The source of DEG was traced to batch of what was supposed to be glycerine, sold by by a local unlicensed chemist. This is not an isolated case – in the last 20 years, contamination of medicines with DEG has caused hundreds of deaths of children and adults in several countries around the world.[56]

China: In 2008 melamine, a trimer of cyanamide, was found in infant formula. 300,000 infants and young children were affected. There were only 6 deaths reported but many believe this was a gross under-estimate. Investigations showed that the practice of using melamine to boost the nitrogen content on analysis was in fact very widespread. There was a huge scandal when the story finally reached public attention; a number of people were jailed and 2 were executed.[57]

UK: In 2011 all stocks of the non-prescription painkiller Nurofen Plus had to be recalled after the contents of some packets that had been sold were found to have been substituted with antipsychotic and anti-epilepsy drugs.[58]

There are a number of important lessons to be drawn about drug and food safety in a globalized world: [59]

- The problem is often only identified when large numbers of people or animals are affected and there are numerous deaths.
- Deliberate contamination may be widespread but escape detection in poorly regulated markets.
- The contaminated raw material may cross national boundaries and be used in more well-regulated markets.
- It is not clear that regulatory organizations currently have the capacity to deal with the problem.
- There is a need to develop cooperative programs to detect and limit these global outbreaks.
- The veterinary and medical communities need to develop proactive global approaches to this global problem.

In the world of fake drugs, profit is a very powerful driving force. It is estimated that counterfeit drug sales are worth US$75 billion globally this year. A 1,000 dollar investment in fake drugs can return $30,000, which is 10 times the typical profit from the same investment in heroin. So we find that counterfeit medicines are estimated to constitute more than 10% of the global medicines market, ranging from an average of 1% in high-income countries to 10- 50% in low- and middle income countries. It remains a big challenge even in well-regulated pharmaceutical markets like that in the USA, because c. 40 % of drugs in USA imported and c. 80 % of active ingredients in US drugs come from overseas sources.[60,61,62,63,64,65]

These types of fraud have been made very much easier by the use of the internet as a source of pharmaceutical products. A recent case illustrates some of the typical global characteristics of these crimes – with production, supply and payment chains operating across several countries and making it very difficult for national enforcement agencies to catch and successfully prosecute the perpetrators.[66]

The true extent of the problem is very difficult to measure, but the evidence suggests that a very large fraction of drugs available over the internet do not comply with national drug regulatory requirements.[67]

WHO assessments[68] have shown that a very wide range of drug types are involved, and a whole range of faults from little or no active ingredients to substitution with potentially harmful substances. It is clear that there is no simple solution and that

- the problem has reached a global dimension and needs a global approach.
- but in many places there is absence of, or weak, drug regulation

If the movement of pharmaceuticals is globalizing and if R&D, production and consumption are all expanding East and South, there is also going to be a need to localise the analysis of pharmaceutical preparations in these countries – not only as an aspect of the R&D and production processes, but also at the national levels in terms of ensuring the quality of drugs at the registration, procurement and distribution stages.

WHO has stated[69] that: “every country, regardless of its stage of development, should consider investment in an independent national drug quality control laboratory”. But at present, of 191 WHO member states only about a fifth have well developed drug regulation; and in many places where some drug regulation activities do exist they often suffer from inadequate resources, absence of training, inefficiency and incompetence.[68]

Another aspect of the changing world of pharmaceuticals that is presenting a major challenge to the analysts is the nature of the analytes themselves.

A significant proportion of the new molecular entities registered as drugs in the last 20 years has been large biological molecules rather than small drug molecules and it is predicted that this proportion will increase significantly in the next few years. The new biologic drugs include a range of proteins, nucleic acids and carbohydrates with a variety of biological activities. Registration of the new types of products is not straightforward: we are dealing here with molecules that are usually produced by biological processes rather than synthesis. They are often high molecular weight, fragile, and have complex structures that can vary in subtle ways in exact sequence, 3-D structure and conformation – all of which can affect biological activity. And, very importantly, the structure may be strongly

influenced by the conditions of production. Over 300 new biologic products have been approved by the FDA in the last dozen years. In 2009 the biologic drug market generated worldwide sales of over US$ 125bn; and because of the high expense of these drugs there is great demand for lower-cost biologics, driving interest in "generic" versions known as "biosimilars or "follow-on biologics". [70,71,72,]

The product approval pathway for biologics runs in parallel to that for small molecule drugs. Small molecule drugs progress via a 'new drug application or NDA, and when patents expire and generics are produced they seek an Abbreviated New Drug Application or ANDA. The equivalent to the NDA for biologics is a Biologic License Application or BLA. A number of early biologics are now off-patent and here the process is still being worked out.[73] But when is a generic biologic equivalent to the originalpaptended version?

- The European Union has a specially adapted approval procedure for "*similar biological medicinal products*." – demonstrates *"comparability*" of the *"similar"* product to an existing approved product.[74]
- Recently the USA introduced an abbreviated approval pathway for biological products shown to be "biosimilar to, or interchangeable with", an FDA licensed reference biological product. [75]

The underlying problem is at least in part an analytical one.[76,77] In the case of a complex biological molecule, there is a large range of analytical techniques available and the choice of which combination to use is going to be very context-specific. How can analysis be used to ensure the functional identity of different batches or of successor biosimilars? The present view[78] is that there is no silver bullet:

- No one analytical technique is sufficient to properly characterize all the ways the structure of a follow-on can vary from that of the innovator product.
- There is consensus that multiple, orthogonal approaches to characterizing a follow-on biologic will be necessary.
- And it is highly likely that some form of clinical trial data will be required to establish that the follow-on product is safe.

The need for a better system for global regulation

In this changing world, it is becoming clear that a much more effective and productive communication interface is needed between the different kinds of actors concerned with analysis and with how the results are used. In particular, there is need for:

- better cooperation and harmonization among analysts working in the different the fields of pharmaceuticals, food and the environment; and
- better cooperation and harmonization between analysts in all fields and policy makers

There is a need to communicate with policy makers in order to create more effective regulation, including analytical methods to support

- Licencing
- Quality of products procured and in circulation
- Counterfeits
- Contamination of the environment and foodstuffs

Effective regulation is not a simple business. It requires a combination of laws, policing and a criminal justice system. Analytical science feeds into all three. It has a crucial role to play, as it

- Sets the position for what is possible
- Sets the practical framework for the timescale and cost of what is detectable
- Sets the limits of what is 'provable' and therefore enforceable by courts

Communication between scientists and policy makers is not always easy and it is vital to use non-technical language and to understand that the two groups need to reconcile very different understandings of issues like 'certainty' and 'risk'. What is needed is communication that creates productive dialogue, leading to decision-making and effective regulation and enforcement. This process needs to involve people working in the diverse but interconnected fields of pharmaceuticals, food and the environment as well as policy-makers and people from an array of national, regional and global organizations.

But there are quite a lot of these. There are diverse organizations that represent groups of professional analysts and different analytical techniques; and there are national and occasionally regional bodies involved in the regulation of registration, quality and enforcement. So, with such a complex array of actors, how is the world going to be able to create a coherent dialogue, reconcile different views and make sense of the field?

Perhaps it's time to consider whether we need a World Organization for Regulation of Food, the Environment and Drugs?

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