Review

Hypothesis for changing models: Current pharmaceutical paradigms, trends and approaches in drug discovery.

Domenico Fuoco, *PharmD. PhD.*

Drug Discovery Research Unit, McGill Nutrition and Performance Laboratory. McGill University. Place Vendome. 5252 de Maisonneuve, Montreal, H4A 3S5, Canada. Fax: 514.504.2077

domenico.fuoco@mail.mcgill.ca

Abstract

Despite the increasing availability of chemicals, the number of New Drug Approvals (NDA) from the Food and Drug Administration (FDA) remains unchanged. The number of chemical structures available online via web-based open source applications will reach the symbolic 1 billion in the 10 next years. However, for no apparent reasons, the number of NDA accepted yearly has not changed in the past 25 years. One of the emerging paradigms of *Big Pharma* is that the more we know about molecular mechanisms and cell signaling pathways, the less we understand how to use this knowledge to make New Chemical Entities (NCE). Moreover, the annual number of pharmaceutical patents collected in the OCSE database has virtually not increased. Unexpectedly, the number of patents originating in the USA is decreasing significantly, while Asia is doing very well. The comparison between the number of NCEs and the American investment in Research and Development (R&D) in the last 35 years shows that to obtain a new drug blockbuster, the total investment is *quasi* 4 USD billion. One of the peculiarities is the inverse relationship between the investment in R&D and the continued shortfall in productivity. A main reason for this decline is that the quality of scientific reasoning done by experienced chemists is too often replaced by *Big Data*. It is time to change the role of chemistry in *Big Pharma* and to re-position it as the central science to progress and to lead to much needed innovation.

1.0 Introduction

Analyzing the total number of new drug approved (NDA) by Food and Drug Administration (FDA) and the number of new chemical entities (NCE) is clearly evident that *Big Pharma,* starting from the 2000, is in a generalized identity crisis. The main reason is attributing to the difficult of their financial arms to get new revenues from the same market-share (due to the losing of patent protection of their most important blockbusters) [1]. This fact breaks out with the changing in the global ranking of the top 20 companies (one time called *Big Pharma*), now reduced to the top 10, due to the drastic "synergistic acquisition" imposed by the boards to do cash (and debt, of course!), cutting redundant employees and closing chemical plants in Europe and North America on the pretest of the high cost of restructuration imposed by environmental political parties.

On the 22nd September 2014, *Merck KGaA* announced the acquisition of the *Sigma-Aldrich*, becoming the most important world fine chemicals player. In the next weeks, if *Pfizer* will buy *AstraZeneca* to move in UK and *Valeant* will put the hands over *Allergan*, we'll see the end of what we have known until now about the function and structure of a research and development (R&D) department in a pharmaceutical company. This situation is ongoing since long time and as known as the new paradigm which pharmaceutical companies are facing to "move from a hierarchized silos compartment to a dynamic strategic collaboration with everyone and everywhere helping by information technology [2]".

This new concept is called *Collaborative drug discovery* (CDD) and represents the best practices for all researchers in this field. In this approach the driven force to lead to pharmaceutical innovation is the bioinformatics. The question is simple: this new pharmaceutical trend alone can bring *Big Pharma* back to the golden years*?* And again, what is the place for medicinal chemistry*?*

1.1 From central information to science in translation

Chemists are the first scientists we think when we speak about classification sets and data collection library. Since 1881, the Beilstein database is the most important example of this fact and it is also the oldest scientific catalog of the history, covering data recorded back in time until 1771. In 1869, Dmitri Mendeleev has tremendously impressed the world with his visual representation of the chemistry information of the Nature with the 'Period table of Elements' that until today is the most notable example of a scientific dataset collection. Between 1945 and 1980, chemical database have grew in independent way according the politics of multinational company that they belong to and also more important those database were library of paper catalogs. Since the 80s, industrialization of computers have changed all those existing physical library for more usable magnetic and optic support, passing form huge halls of book to just one office room library. Until 1990 those database were an asset of private chemical enterprise and data were jealously stored under key. With the expansion of the Web and the constantly growing up of data coming from academics and public

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institution, we have seen the born of public consortium of database and a new trend in collaboration between public and private company to share information and assets. Such background led the American national institute of health (NIH) to support the born of *PubCHEM*, the most important database available on-line via web-based open source application (*Fig 1.A*) [3]". In 2009, Hohman *et al.* advanced a new paradigm about the use of open source philosophy in drug discovery and in biomedical research in general. They stated that: *"a community-based platform that combines traditional drug discovery informatics with Web2.0 features in secure groups is believed to be the key to facilitating richer, instantaneous collaborations involving sensitive drug discovery data and intellectual property* [4]*"*.

The importance of adopting the collaborative business model to increase the potential for innovation is reflected in the fact the dominant paradigm in drug discovery for the last 30 years has been the target-centric model or the one-to-one: "one Target, one New Chemical Entity (NCE) approach [5-6]".

2.0 Reasons for a crisis

If we analyse the phase III clinical trials of *Big Pharma* of the last 10 years we can observe a number of failures three fold time bigger than the previous decade (table 1) [24-26].

The result is clear since 1996 ("*The golden years"* for the pharmaceutical companies in term of maximum results of New Drug Approval from FDA), number of new approved drug is going down (figure 1.B) [24-26].

- One reason is the fact that "targets can be hypothetically associated with certain diseases which does not mean that they represent suitable intervention levels for new drugs [7]".

- Another one reason is the great level of validation required by a new hypothetically model.

- The uncontrollable growing up of scientific journals more than 135.000 in 2013 has led to a constant rise in data, from peer-reviewed journals and public consortium around the world. During the experimental phases of a model validation, this mole of data is, paradoxically, becoming an obstacle. Now, researchers are questioning about credibility of some authors, of some not-profit labs or if not even the whole system [8-9].

- In the era of personalized medicine those facts can be a serious misunderstanding about what medicinal chemists are doing. Dr. Tunis of *J&J* proposed, in 2007, to the UK government to give back money for all those patients with a bad answer to anti-cancer chemotherapy. That's ridiculous! It is not that the pharmaceutical concept beyond the personalized medicine that thousands of medicinal chemists around the world are building up [10].

- Translation of new, cutting-edge science into successful drug development program happens more slowly than anticipated (e.g. "genome hype) [11].

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- Sticking to old paradigms, novel approaches such as modeling and simulation have been neglected.[http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085549.pdf]

- The decline in total number of pharmaceutical intellectual properties (*Fig. 1.C*) [http://stats.oecd.org/Index.aspx]

The shocking paradigm emerging from this results analysis is: *More we know about molecular mechanisms and cell signalling pathway, less we understand how to use this knowledge to make new drugs*.

Despite the impressive amount of information available for free, the trend in the number of NDA is still the same. 1996 was the only year, in the last 35 years, with an extraordinary number of approvals (156). Since 1980 the year average is less than 100 and the prediction for the future is not optimistic. Analysts are questioning about this discrepancy between the greatest level of information that we have and the difficulty to translate those knowledge in new drugs. One of the answer is in the always more strictly regulation and procedure standardisation that FDA impose to *Big Pharma* to protect the collectivity.

Table 1. Success rate of a Phase III Clinical Trial to get a positive final review from FDA as New Drug Approval (NDA).

Success rate	40%	34%	22%	18%
Period	1999-2003	2003-2007	2007-2011	2011-2014

3.0 The current driven forces to drug discovery.

3.1 Bioinformatics

Since the early '90 the investments in bioinformatics operated by all sort of chemical enterprises have been constantly growing up. Bioinformatics is an open scientific field that to be hold up need large computer networks hanger (called *GRID)* and dedicated energy facilities with power back-up (called *APS*), more than a performant software with ultra-fast rendering capacity and several web-based applications for the final end-user and all those devices have to be connected in real-time [12].

The apotheosis of this fascinating period was in the June of 1993 when Itzstein *et al.* introduced the first drug entirely done on a computer (Zanamivir) and so the chemiometrics science done on computer became a proper science [13].

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Indeed, bioinformatics made it possible to work on such big amount of data, as well as very fast in a little while, it was unimaginable fashion just 10 years ago. Different definitions of bioinformatics are available according the specific role that authors want introduce over it. To better understand this role and also quantify the relevant position accredited to the bioinformatics by chemical enterprises, the method chosen herein is the evaluation of the historical development of chemical library database (figure 1.A), better than to be focus on the number of journals already ranked in that field, or the number of publications or the direct investment in informatics infrastructures (people working on it or the economy generated by the time). The most promising methods to analyse those entire large database are the data mining [14] and the pattern recognition [15].

3.2 Coping the Nature

Historically, the majority of new drugs have been generated from natural product (secondary metabolites) and from compounds derived from natural products. During the past 15 years, the pharmaceutical industry research into natural products has declined, in part because of an emphasis on high-throughput screening of synthesis libraries. With the result that there is substantial decline in New Drug Approvals [16]. Firms involved in drug discovery must hit the target not only accurately, but very quickly and very profitably. In the 1987, an excellent golden year of NDA, the amount of drug as natural product (or natural product derived was more than the 80% of the total) and those proportions is still the same today [16].

There is a difficult to discover drug candidate form natural product?

Historically, screening of natural materials for biological activity has worked well. Considering only polyketide metabolites, just over 7000 known structures have led to more than 20 commercial drugs with a *hit rate* of 0.3%, which is much better than the 0.001% hit rate for HTS of synthetic compound libraries [16].

3.3 Drug repositioning

Drug repositioning is a growing approach to drug discovery powered by the necessity to get more *"approved medical uses"* for the same drug, possibly approved from FDA for another indication and close to lose intellectual protection, or already out of the market, because considered an old medicines. In the past, drug repositioning was driven by serendipity as well as with the off-label use done by physicians. However, there are ongoing efforts to conduct drug repurposing systematically. Examples of old drugs that are still interesting for new medical propose are tetracycline [17]. In more than 60 years of their history tetracyclines have been using as antibiotics and in the last 20 years apart for that also as anticancer as well as for neuroprotection [17].

In 1980, the registration of patents coming only from USA represented above the 75% of total number of intellectual copyrights in the world. In the 2013 the patents production form USA is less

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the 35%, but the global number is almost unchanged. The decrease in patent production form USA has been replace by the increase in registration coming from other countries, once totally out of the World Trade Organization, and now, very active to gain market share as global players (China, India, Brazil, Singapore, Russia and Iran).

3.4 Super resolution microscopy for Single Molecular Detection (SMD)

Since its debut way back in the 16th century, microscopy has proven to be one of the best techniques for the study of molecules and sovra-molecular phenomenon. The advances that were discovered in single molecule imaging have led to advances in super resolution microscopy as well. Super resolution microscopy can be used to image structures that are smaller than the diffraction limit of light and as cannot be easily resolved. It had been observed that fluorescent molecules stochastically blink. By controlling this blink, it is possible to use different fluorophores to get a high-resolution image of the object of interest [18].

The first analytical chemistry study of single molecules was in 1961 by Rotman using a claster of immobilized enzymes [19]. In the 1980s the object resolution was pushed until the single nanometer-scale by the introduction of scanning tunneling microscopy (STM) and atomic force microscopy (AFM). Example of this new technique can be found in material science as well as for biological structure characterization [20].

Despite the fact that every laboratory has easily access to this incredible technology, it is very difficult to explain how it is possible that the number per years of New Chemical Entities is remained the same in the last three decades.

4.0 Possible solution of the crisis

This large number of data coming from genomics, proteomics and metabolomics sciences, combinatorial chemistry and automated high-throughput screening (HTS) has led to a new trend in drug discovery: "the critical discourse between experienced chemists and biologists and the quality of scientific reasoning are sometimes replaced by the magic of large numbers [7]".

The great availability of a large number of compounds (or much better active fragments of those) exposed to the large amount of hypothetical targets (the biggest results introduced by genomics and proteomics science) had given us many *hits* that theoretical would rice many *leads* and so far many active pharmaceutical ingredients (commonly called *drugs*). It has not gone well.

One of the most important "metrics" to measure efficiency of a pharmaceutical company is the number of developmental candidates or leads produced, the time taken to advance candidates through the pipeline and the incremental change in value of the portfolio over time. The problem is not the

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volume of compounds being produced and the number of projects in the early discovery research phase, but the quality of those compounds and the diversity of approaches taken [20].

In 2002, Oprea proposed for a data set of one million compounds tested via HTS, it is possible to obtain at least one that can reach the market. In this moment PubChem has 75 millions of chemical entities in his database, so we can obtain 75 new drugs theorically has maximum for this data set or we can search for different questions in the same data set and obtain 75 new drugs every time? *And where is the place for the serendipity?*

"One in a million compounds (or more) from those initially tested via HTS has the probability to reach the market [21]*".*

A paradigm that a medicinal chemist should never forget is the famous statement of the Noble Prize for the Medicine of 1988, Sir James Black: *"the most fruitful basis for the discovery of a new drug is to start with an old drug* [22]*".*

The only solution available and practicably is put again medicinal chemistry in a central position in the R&D departments of *Big Pharma.*

Apart academic speculation and technically the paradoxically result of all the factors mentioned above is that:
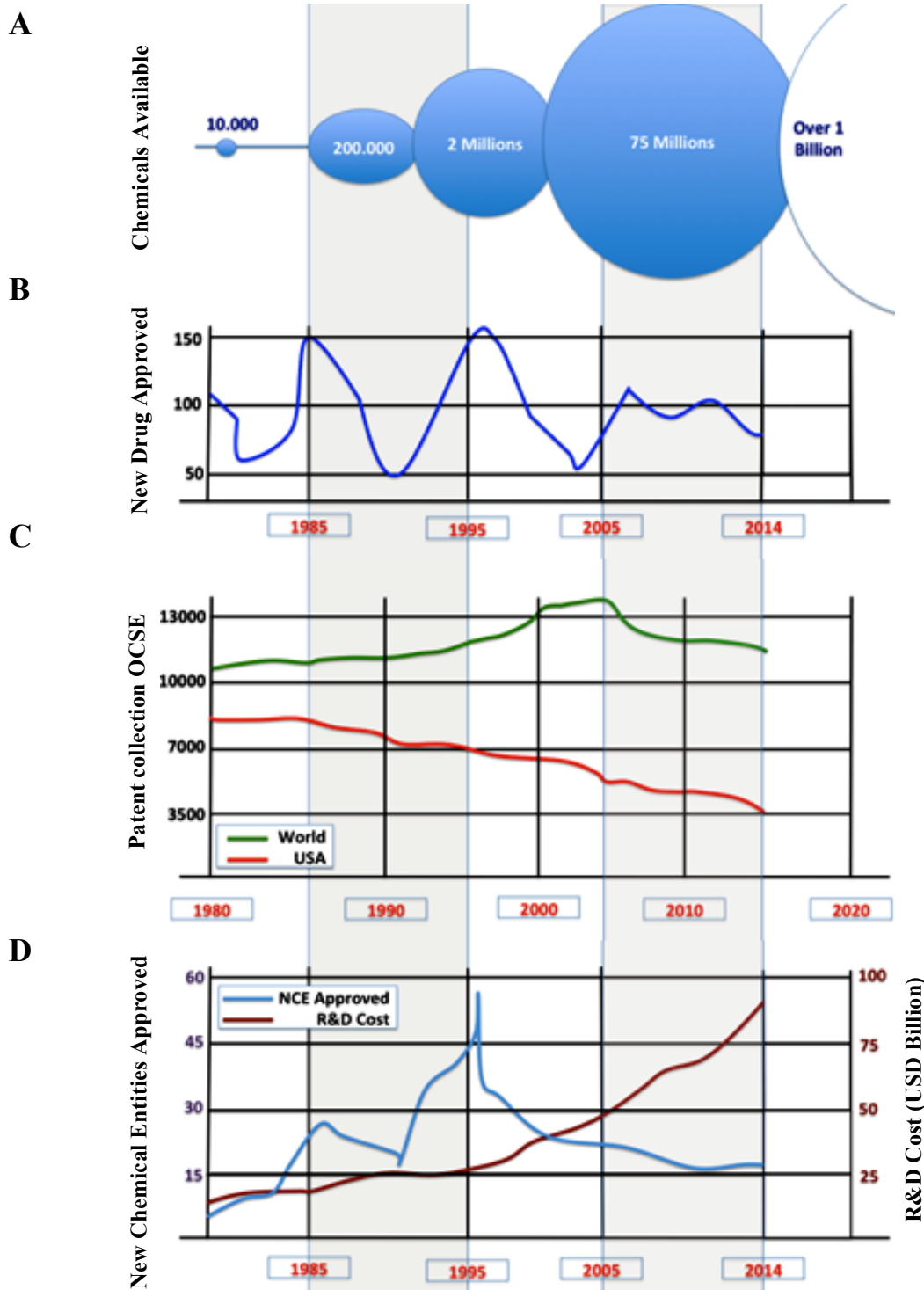
The trend in NEW approved yearly by FDA is remained the same in the last 35 years. The greatest amounts of information available via database as well as the greatest number of journals and new technologies introduced by the post-genomic revolution have left unchanged the capacity to produce innovation.

The only year with a remarkable result is still the 1996 with 55 NCE. The biomedicines (as are called proteins and nucleic acids derivatives used in therapy) are not changing the capacity of *Big Pharma* in term of drug launch per year. Small molecules still represents the most important chemicals in our therapeutic arsenal.

"There is an inverse relationship between the investment in the drug research and development process and the continued shortfall in in the productivity [23]*".*

It is not easy to calculate the cost to obtain a NCE, because this process is made over a long time (8-12 years) and in different laboratories working in many countries at the same time. Moreover, every laboratory follows many projects at the same time and the entire R&D model is in continuing evolution with new technology and people. We can assume that the final cost supported by Big Pharma for each NCE should be the sum of all those factors mentioned above.

Paradoxically, the R&D cost to get an approved drug is passed form an average in 1980 of USD 300 million to more the USD 3 Billion in 2013. This is a clear indication of a necessity to change the chemical enterprise model of *Big Pharma* [25].

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Figure 1.A.: Number of chemical structures and relative profile information available on-line via web-based open source application. Circles represent the exponential growth of number of chemical structure collect in database since the origin of the internet. **Figure 1.B.:** Number of New Drug Approval (NDA) by FDA yearly. **Figure 2.C:** Number of pharmaceutical patents collected in the OCSE database. **Figure 3.D.:** Comparison between the number of New Chemical Entities (NCE) and the US investment in Research and Development (R&D) in the last 35 years.

Source of data: PhRMA, OCSE, FDA, PubCHEM. Linked-related-web-page are fully reported in the text.

4.1 The central role of Medicinal Chemistry

To reverse all those trends, which are destroying the pharmaceutical enterprise, is pivotal to re-establish the chemistry as the central science to make innovation. Specifically, it is time to change the role of medicinal chemistry in industry that has remained too narrow in the last 35 years. All data produced until now has to be returned to a human dimension to be manage by the beautiful mind of a scientist. To foster innovation, we must enable the most gifted and curious scientist to create organizational structure (like the Period table of Elements) to support the right focus. Following this approach, chemists with a broadened horizon toward chemical and molecular biology will have a crucial role in truly advancing this research field [24-26].

5.0 Conclusion

As has been discussed in this article the results of a pharmaceutical industry are evaluated in terms of patents, discoveries of new molecules (NCE) and new drugs (NDA) put on the market. In the last 30 years there has been a clear decline in productivity and innovation, which instead had remarkably distinct *Big Pharma* in the thirty years from 1945 to 1975. Of course, *Big Pharma* does not lack of economic resources or new technologies for the discovery of new drugs. What was missed is the guidance of chemical-entrepreneurs. The biggest difference between the origins of *Big Pharma* and today can be seen in the composition of the board of directors. Once medicinal chemists will be put in the condition to lead again the pharmaceutical company, and also the Serendipity will do its part, we will return to the golden years of innovation.

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