Pharmaceutical Regulatory Affairs: Open Access
ISSN: 2167-7689
Mercanoglu and Ozer, Pharmaceut Reg Affairs 2015, 4:1
DOI: 10.4172/2167-7689.1000134
Mini Review Open Access

Is It Right Time to Construct New Radiopharmaceutical Development Strategies?

Guldem Mercanoglu[1]* and Yekta Ozer[2]
[1]Biruni University, Faculty of Pharmacy, Turkey
[2]Hacettepe University, Faculty of Pharmacy, Turkey

21st Century's Pharma Market

Research oriented pharmaceutical sector, as in European countries, is the key sector in many world economies. Data provided by European Federation of Pharmaceutical Industries and Associations (EFPIA) for the 1990-2012 periods has been shown in Table 1 [1].

In 2012 R & D investment in Europe reached to €30,000 million despite being affected by the 2010 crisis. Again in 2012 when pharmaceutical sales data was evaluated, it is observed that 41% of the worldwide sales were made in North America and 26.7% in European countries. Still another important data in Pharmaceutical industry between the years 2007-2011 new product launch rates in the United States and Europe were 62% and 18%, respectively. When this data is evaluated, it is clearly seen that research-based pharmaceutical industry will be one of the most effective players in global economy [1].

The term drug basically refers to two concepts: "original" and "generic". Original drug is an international term used for unique new drugs, which were developed as a result of long research and clinical studies; have proven to have a positive effect on a particular disease and based on a patented molecule [2].

In many countries original drugs, are protected with patent and data protection rights for a certain period of time. During this time, another drug company is not allowed to manufacture a similar drug. Thus, the original drugs manufacturers can meet the R & D investment and create resources for new research [2]. Together with the expiration of the original drug's legal protection, pharmaceutical companies can release drugs similar to the original drug. These drugs are called generic drugs [2].

Generic drugs, with proven bioequivalence and without million dollars research expenditure, are introduced to the market with proven efficacy and safety based on the original drug. Therefore, generic drugs are much cheaper than original drugs.

Comparison of Original and Generic Drug Development Processes

New product development processes vary from industry to industry, and hence, there is no general and standard method applied to all industries and companies.

In order to develop a new product, the basic concept of new product development process is shown in Figure 1 [3].

	1990	2000	2011	2012**
Production	63.010	125.301	205.622	210.000
R & D expenditure	7.766	17.849	29.192	30.000
Employment (units)	500.879	534.882	700.010	700.000
R & D employment (units)	76.126	88.397	115.695	116.000
Pharmaceutical market value at ex-factory prices	41.147	86.704	160.603	163.000
Pharmaceutical market value at retail prices	64.509	140.345	235.017	238.500

Values in € million
**estimates

Table 1: Pharma Market Data [1].

In this basic structure it was met with a multistage product development pipeline. Traditional product development process consists of five sequential steps (Figure 2) [3].

In this basic process the key issues need to be dealt with are: Which projects to develop? In what order? What are levels of resources to assign?

In order to answer these questions in the product development pipeline, there needs to be query and go/kill checkpoints at the lower stages. The Stage-Gate model developed by Robert G. Cooper refines the basic framework. In this model, gates between stages control the process and serve as go/kill checkpoints for the project. These gates also serve a quality-control checkpoint and help determine the resource commitment the project receives from the company (Figure 3) [3,4].

Due to the unique structure of pharmaceutical industry, the legal authorities have defined the stages and gates in the process of new drug development. These stages and gates are summarized in Figure 4.

When the original and generic product definitions given above

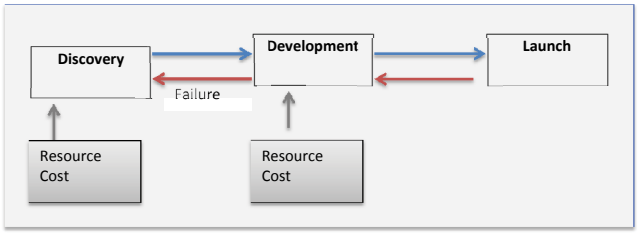

Figure 1: Basic concept of new product development [3].

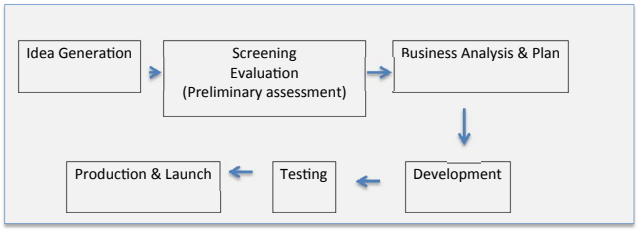

Figure 2: Traditional drug development process.

***Corresponding author:** Guldem Mercanoglu, Biruni University, Faculty of Pharmacy, Turkey, Tel: +90216 5780000; E-mail: guldemiko@gmail.com

Received January 16, 2015; **Accepted** March 02, 2015; **Published** March 09, 2015

Citation: Mercanoglu G, Ozer Y (2015) Is It Right Time to Construct New Radiopharmaceutical Development Strategies? Pharmaceut Reg Affairs 4: 134. doi:10.4172/2167-7689.1000134

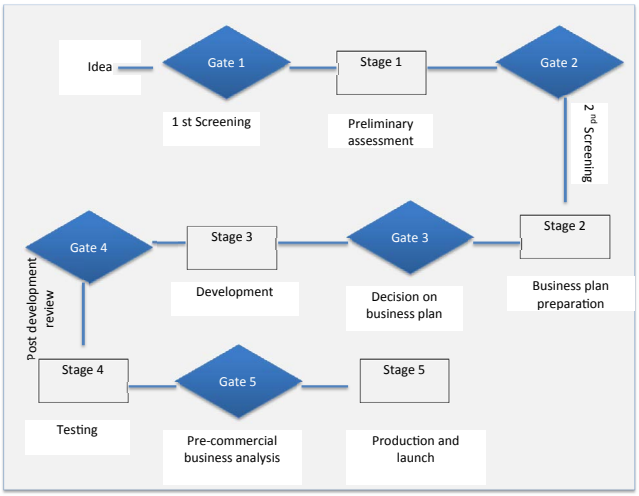

Figure 3: Stage-Gate drug development method.

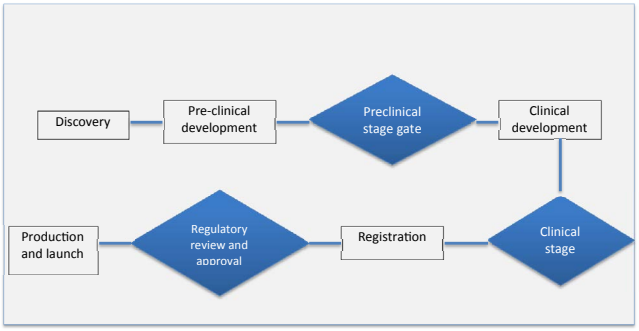

Figure 4: Basic pharmaceutical drug development process.

are evaluated, the drug development stages for these will emerge spontaneously. Considering that the efficacy and safety of generic drugs is the same as the originals, the "clinical development" stages of new product development are obviously not applied. Instead of this step, it must be shown that the biological activity of the generic product is identical to that of the original product. This is referred as "bioequivalence" study and it corresponds clinical development stage in new pharmaceutical development. Since this step, which is the longest step in new drug development (10-12 year), is missing, the generic drug development process shortens and the product launches early. The "clinical development" which is the most costly step in the development of new drugs decreases the development cost. And this is the main reason why generic prices are lower than the original product.

New Concepts?

Industry perspective

Most of the time the rules are laid down by the regulatory authorities and in an industry where the development stages are standard, the presence of players should be questioned with the following two questions:

1. Why do companies produce new products in the market where only 100 of the 100,000 new product candidate molecules can pass to the stage of clinical evaluation; where only 2 of the 10 drugs entering the market return a profit; and a new drug development costs between $600 million to $1.2 billion around 6-12 years? [5] Why do they finance R & D?

2. What creates the differences between companies in terms of productivity in such an industry that the stages of new product development are to a large extent the same? How is it possible?

The answer to the first question is actually hidden in the second one. Although medicines constitute only a small part of healthcare costs with, on average, 16.6% of total health expenditure [1]; the Institute for Healthcare Informatics (IMS) predicts that by the year 2016 with an increase of nearly $250 billion from the $956 billion recorded in 2011, the pharmaceutical market will reach nearly $1,200 billion [6]. Pharmacy is one of the world's most profitable industries. During the last 30 years, the industry has spent billions of dollars on research and billions in return. In 2006 alone, the pharmaceutical industry introduced 31 major drugs and sold $643 billion in products worldwide- a 7 percent increase over 2005 sales, according to the drug market research firm IMS Health. U.S. sales beat the national average with growth of 8.3 percent (up from 5.4 percent growth in 2005) [7]. All these show that pharma industry is one of the biggest industries in the world.

Personally, it can be found an answer to the second question by evaluating the findings of an Innovation Excellence Study [8] conducted by Arthur D. Littele in 2005. This study helps to evaluate the productivity of new product development by each sector. The new product development productivity of an industry is measured with the ratio of inputs into outputs. For example, when the output is "five-year sales from new products as a percentage of company sales", input would be "research and development spending as a percentage of company sales". The results are quite remarkable for pharmaceutical industry: "the top 25% pharmaceutical companies are 31 times more productive in new drug development than the bottom 25%" [8]. Then the next question should be asked: "What are these high productivity companies doing so differently?"

Because of the differences in product development pipeline, the answer to this question will be given for original and generic drug separately:

Original drug development process

Two giants of the pharmaceutical industry; Pfizer and Elly Lilly is worthy to discuss two different systems developed it.

In 2001 Eli Lilly designed and piloted Chorus, an autonomous experimental unit dedicated solely to early-stage drug development. The system uses "early-stage, truth-seeking" approach [9]. Bonabeau summarizes the underlying philosophy of this approach: "When development costs are high and failure is common, companies should structure research to seek truth first, success second." [9].

In this model, the new drug development method is late stage oriented, and the organizational goal is "seeking success". However the method suggested was early stage oriented, and the organizational goal was "seeking truth". The organizational strengths of both methods and approaches are summarized in Table 2 [9]:

When the new drug development process is considered, Figure 5 [9] displays the stages of the process and their effects on time and cost. As can be clearly seen from the figure, "clinical development stage" has the greatest impact on launch.

In a success-seeking program, expensive and lengthy large-scale manufacturing and long-term animal studies are often initiated before critical data from the early-stage safety; and efficacy studies are available. For example, if the purpose is to develop of sustained release tablets of the active substance, the initiation of clinical trials does not

Early	Late
Organization Goal	
Seek truth	Seek success
Organizational Strength	
Establish novel products' promise lack thereof	Take products to market
Organizational Approach	
Reduce risk	Maximize value
Maintain loyalty to the experiment	Maintain loyalty to the product
Focus on scientific method	Focus on commercialization
Operate with low fixed costs, low capital requirement	Operate with high fixed costs, high capital requirement
Work in small, experiment-based teams	Work in large, product-based teams
Emphasize testing	Emphasize refining

Table 2: Organizational Characteristics of Stages [9].

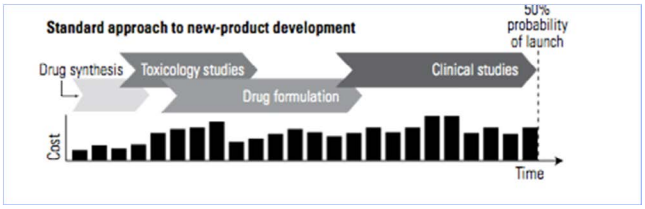

Figure 5: Impact of drug development stages on time and cost [9].

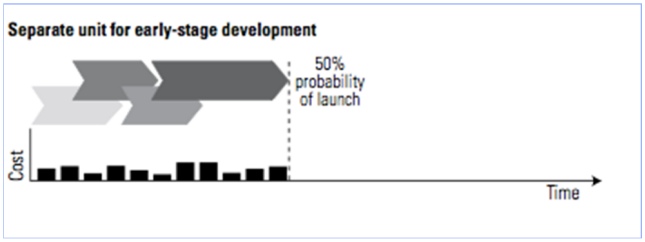

Figure 6: Impact of early-stage method on time and cost of the process [9].

require the completion of drug formulation stage. The active substance can be administered in repeated doses so as to mimic the sustained release effect. And thus, not only the transition to clinical trials is accelerated, but also the cost is reduced (Figure 6) [9].

Early-stage method reduces both the time to launch and costs. Another benefit is the launch probability of the product being developed. The evaluation of the results of high focused small clinical trials that aim at evaluating the efficacy and safety of the active substances which will in turn further reduces the likelihood of failure in the phase by providing launch probability.

In the Model-based drug development method used by Pfizer, the researchers use computational tools such as MATLAB® and SimBiology® to support model-based drug development. The aim is to organize phase II studies, since the phase II clinical studies is the longest and most costly stage in the drug development pipeline. This method prevents the deficiencies that will occur in late-stage studies. This system is computerized simulation software used in earlier phases of drug research and also connects systems of biology and pharmacokinetic-pharmacodynamic (PK/PD) modeling to the clinical research. With this model aimed at increasing research productivity late stage failures can be prevented [10].

Generic drug development process

Especially in an increasingly competitive environment, aggressive methods such as "patent clusters" that are used to extend the duration of exclusivity of the original drug have caused manufacturers to develop different products rather than pure generic. These products, known as "Brand generic", are reformulation and re-invented products. These products are sometimes also allied with new drug delivery methods. The value added qualities of these products is also an important feature that needs to be taken into consideration.

According to a study by Prašnikar et al. [11] the development of a new generic product takes approximately 59.2 months during which the longest phases are registration (mean 19.5 months), laboratory development (mean 15.3 months) and development of technology (mean 12.6 months), respectively (Figure 7). These phases were also the stages with the biggest standard deviation.

In the study, the parameters that affect these phases were examined and the results were as follows:

1. If the Active Pharmaceutical Ingredient (API) is developed internally, basically due to the prolonged phase 2, API will be longer than time to market outsource. In the case of developing API internally, phase 4, registration, shortens. But, in this case the number of deficiency letters from the regulatory authorities will be higher than the externally developed.

2. Similarly, in the product formulation phase, the formulation can either be developed internally or be outsourced (complete formulation licensed or technology bought). In internal development especially phase 2 and 3 take longer, whereas the registration phase, phase 4, takes shorter time. The main reason is that when the formulation phase is outsourced, the API development phase is outsourced as well. This, of course, significantly reduces the required internal resources for formulation development, in particular production and research and development capacities.

The researchers evaluating the overall study results concluded that [11];

• There is a positive relationship between the number of strategic alliances a generic pharmaceutical company enters and its rate of new product development.

• There is a positive relationship between incorporation of new product development tools and techniques (e.g. design techniques, organizational techniques, manufacturing techniques and information technologies) and the time-to-market in the generic pharmaceutical industry. These results are in consensus with other studies [12-18].

In April 2011, Kenneth Frazier, the CEO of Merck, announced his firm growth strategy as expanding in emerging markets through partnerships, rather than acquisitions. This strategy was put to use in establishing an equal joint venture between Merck and Sun Pharmaceuticals of Mumbai, India to sell branded generic drugs in emerging market [19].

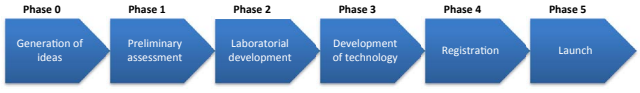

Figure 7: New product development process for generic pharmaceutical companies.

What about Radiopharmaceuticals?

Radiopharmaceuticals are radiolabeled drugs used for diagnostic and therapeutic purposes.

Due to the radioactive nature of this group, it has been produced as magisterial product and used locally for years. Today, still marketing authorization is not required for the local usage of some of these products.

In 2000, the Food and Drug Agency (FDA) obliged Radiopharmaceutical production facilities for licensing and good manufacturing practice (GMP) compliance. After this, the marketing authorization for radiopharmaceuticals became mandatory. Similarly, in the 2000s radiopharmaceuticals began to be licensed as same procedure as pharmaceutical products by EMA in Europe.

Despite being considered as pharmaceutical products and taken under the protection of license after the 2000s, the approval of radiopharmaceuticals is still slow [20]. Between the years 1999-2004 two of the oldest and largest industry players invested $150 million to R & D studies, however, they did not get new radiopharmaceutical approved by FDA.

What is the source of this problem? The cost and duration of diagnostic radiopharmaceuticals development is $100-200 million and 8-10y, relative to pharmaceuticals, for which $600 million to $1.2 billion over 10-12y [20]. Compared to multibillion annual sales, the annual sales of best-selling imaging radiopharmaceuticals are in approximately $400 million range [20]. When considering the most commonly used FDA-approved 3 radiopharmaceuticals developed between 1980-1990, current R & D costs expected to be supported by revenue from these products. Here is the main problem: Wıth reimbursement rates of $100– $200 per dose, the necessary revenue to cover these costs may be possible with the use of 1 million dose of these products.

Aside from the financial aspects of the business when the profiles of industry players are considered; except for two major players of the industry, which are also players in pharmaceutical industry (Schering and Covidien); it is observed that the other players are also medical device manufacturers (like Siemens, GE, Iba, AAA). The domination of new drug development process of these players comes from the tradition of medical device manufacturer, which has unique principles must be considered as well. Indeed, when the business models are examined, it is observed that business strategies of these companies are recruiting small companies with molecular patents.

Seeing this gap in the radiopharmaceutical industry, professional institutions such as National Institute of Health (NIH) or the National Cancer Institute (NCI) have undertaken the task of bringing new players into the industry. These institutions through websites are sending open invitations to either active substance (API) or finished product and/or technology manufacturers for participation in clinical trials of new radiopharmaceuticals. The clinical studies are being funded by these institutions, and according to the results of the studies institutions apply for the marketing authorization of the new drug. During the preparation of the application file both API manufacturers (as type II Drug Master File (DMF)), and finished drug (as type I DMF) or technology manufacturers (like machine producers) (as type III DMF) add their own sub files.

By this way; while clinical trials, the longest and most costly stage of new product development are financed by institutions instead of these companies that cannot afford the finance of this huge amount; on the other hand, all of these companies can be licensed with a single application. After the expiration of data concession, these producers are free to apply for generic product license.

As a result, the launch of the new product as early as possible is provided. Moreover, companies without financial power to perform these studies will become the manufacturer of radiopharmaceuticals as a regulatory aspect. But most importantly, this process establishes strategic partnerships and ensures information networking for the foundation of strong future radiopharmaceutical manufacturers.

The first benefit of this practice was harvested in 2011 when big 99 Mo (Molybdenum) crisis occurred. 18F labeled tracer of Sodium Fluoride was approved as alternative product and given into the market in a short period of two years. This was a turning point. After this point, more than 6 new 18F labeled radiopharmaceuticals (18F-FLT, 18F-Dopa, 18F-flourbetapir, 18F-flourbetapen, 18F-flourmetamol, and 18F-MISO) approved either by FDA or EMA within three years.

Regulatory Perspective

According to the FDA's 2004 report, new molecular entities and biologic license applications submitted to the FDA have decreased over the last decade [21]. Whereas, a peak (both in submission and approval) has been observed in 1996, the number of approvals for 2003 was almost half of the 1996's (Figure 8) [21].

As discussed earlier, the traditional drug development process can be summarized in four stages: discovery, development (preclinical and clinical), regulatory review and approval for marketing, production and launch together with post marketing safety surveillance. Through the discovery phase, lead drug candidate(s) are identified for further assessment in humans. Extensive preclinical testing is conducted in animal models to establish proof of the concept. Safety pharmacology and toxicology profiles are established and dose-screening studies (minimum 2 different doses) are conducted. The cost of pharmacological and safety part alone can reach 0.4-0.5 million $ [22]. In addition, several years of discovery and preclinical development is needed to reach to the clinical phase. On the contrary, the estimate of success to reach the stage of regulatory review is about 25% [23,24]. Increasing this to 33% would produce up to a 50% overall cost savings. This bottleneck, the decision to remove the candidate from the clinical phase pipeline, can produce cost saving and permit the evaluation of alternative candidates. However, the decision to remove candidate from the advanced clinical phase pipeline with huge amount of investment is not easy. Some more steps are needed to support this

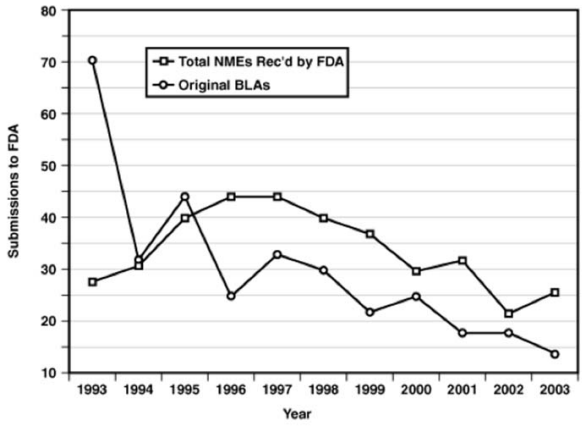

Figure 8: Ten-year trends in major drug and biological product submissions to FDA [21].

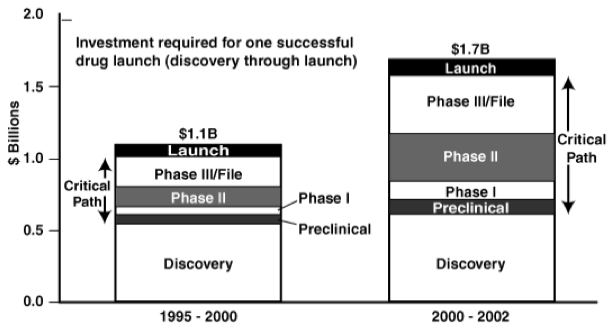

Figure 9: Total investment cost for launching a drug product [21].

"go-no go" decision making process. In their 2004 report "Innovation or Stagnation" FDA defined this step as "critical path" (Figure 9) and developed an action plan called "Critical Path Initiative (CPI)" [25]. The CPI represents a framework for facilitating the entire drug discovery and development process from inception to approval.

Within that framework, two new steps are worthy to discuss here. The first one is introduction of Exploratory Investigational New Drug (exploratory IND) application that is based on micro-dosing concept. Parallel with FDA; European Medicine Agency (EMA) also introduced this concept as "phase 0" studies in 2004 [26]. This micro-dosing concept lowers the threshold for human studies by: 1) reducing costly pre-clinical toxicity and pharmacological studies, 2) allowing the assessment of preliminary PK/PD in humans early in the development timeline, 3) evaluating multiple compounds from the same class, and 4) evaluating pharmacologic effects and /or mode of action of compounds observed in humans at earlier stages. This will in return allow earlier go-no-go decisions and enhance the pool of selected therapeutics that will proceed to the more costly clinical trial phases of development [22].

The second step is the identification of medical imaging and imaging biomarkers as potential clinical development tools to facilitate medical product development by FDA [21]. Important actions taken for this step were: 1) In May 2005, with collaboration of National Cancer Institute, industry and academia; FDA organized a workshop to identify the path for routine use of new imaging techniques in the product development, 2) since all the participants in this workshop indicated the limited availability of PET radiopharmaceuticals as a significant drawback for the incorporation of imaging biomarkers in early phase studies, the FDA published "Critical Path Opportunities Report and List" as a follow-up. This list included more than 40 critical path collaborations and research activities with FDA participation. 3) Parallel with this, in December 2006 "The Biomarkers Consortium" was launched with the goal of accelerating the delivery of successful new technologies, medicine and therapies for prevention, detection and treatment of diseases. The consortium determined "the use of (18F)-fluodeoxyglucose (FDG)-PET in non-Hodgkin's lymphoma and in non-small cell lung cancer" as the first project for funding [27]. 4) In the subsequent years, FDA partnered with Society of Nuclear Medicine (SNM), Radiological Society of North America and National Cancer Institute (NCI) to facilitate broader use and predictive power of investigational PET radiopharmaceuticals in multicenter clinical trials with investigational and approved drugs. Under this partnership, many workshops have been conducted for the standardization of imaging clinical trials and manufacturing requirements of the PET radiopharmaceuticals. 5) Recently, in December 2009, the "Current Good Manufacturing Practice (cGMP) for the Production of PET Drugs" was published [28].

As a summary, when we consider all these steps undertaken by the regulatory authorities, two important points are observed. First, both the new regulations such as exploratory IND applications, and collaborative efforts with professional institutions reshaped the drug development process by improving the development stage, which is considered as a critical path. Second, FDA's recognition of medical imaging biomarkers as critical to medical product development has lead to the use of radiopharmaceuticals in the area of drug development. Many large pharmaceutical companies have started to invest in small animal imaging equipment in order to use in their drug discovery and development programs. When the length of time needed for the development of radiopharmaceutical is taken into account, incorporating imaging probe into the drug development means the development of new imaging probe at the same time. By this way, the probe will be available for imaging studies in the clinical phases and human approval and validation of the radiopharmaceutical will not be required. Furthermore, this generates new players in the radiopharma market.

Since the publication of FDA's Critical Path Initiative (2004), significant progress has been observed in facilitating radiopharmaceutical development. Moreover, there is no doubt that regulatory authorities and professional institutions, as in the construction of basic development stages, will be the major force in re-shaping these stages.

References

1. The European Federation of Pharmaceutical Industries and Associations EFPIA (2013): Pharmaceutical Industry in Figures. Key Data efpia.
2. AIFD (2008) What is an original drug?
3. Kirkpatrick D (2010) New product development: From Idea to Market. Business and Employment.
4. Cooper RG (1990) Stage gate system: A new tool for managing new products. Business Horizons 44-55.
5. DiMasi JA, Hansen RW, Grabowski HG, Lasagna L (1991) Cost of innovation in the pharmaceutical industry. J Health Econ 10: 107-142.
6. IMS Institute for Healthcare Informatics (2012) The global use of medicines: Outlook through 2016. Parsipanny, NJ: IMS Institute for Healthcare Informatics pp. 10.
7. (2012) Industry Overview: Pharmaceuticals and Biotech. WETFEET.
8. Georg B (2005) Innovation Excellence 2005: How Companies Use Innovation to Improve Profitability and Growth. Arthur D. Little.
9. Bonabeau E, Bodick N, Armstrong RW (2008) A more rational approach to new-product development. Harv Bus Rev 86: 96-102, 134.
10. Piet G (2012) MathWorks® User Story. Pfizer Uses Model-Based Drug Development to Help Reduce Phase II Attrition Rates. Math works, pp. 1-2.
11. Prašnikar J, Škerlj T (2004) New product development process in generic pharmaceutical companies: determinants of the time-to-market. Proceedings of the Fifth Asia Pacific Industrial Engineering and Management Systems Conference.
12. Gonzales FJM, Palacios TBM (2002) The Effect of New Product Development Techniques on New Product Success of Spanish Firms. Industrial Marketing Management 31: 261-271.
13. Bonner JM, Ruekert RW, Walker OC (2002) Upper Management Control of New Product Development Projects and Project Performance. J Product Innovation Management 19: 233-245.
14. Cooper RG (1979) Dimensions of Industrial New Product Success and Failure. J Marketing 43: 93-103.
15. Cooper RG (1994) Debunking the Myths of New Product Development. Research Technology Management 37.

16. Griffin A (1994) PDMA Research on New Product Development Practices: Updating Trends and Benchmarking Best Practices. Journal of Product Innovation Management 14: 429-458.

17. Droge C, Jayanth J, Shawnee VK (2002) The Ability to Minimize the Timing of New Product Development and Introduction: An Examination of Antecedent Factors in the North American Automobile Supplier Industry. J Product Innovation Management 17: 24-40.

18. Spaulding AD (2002) The New Product Development Practices of the North American Confectionery Manufacturers: Determinants of New Product Development Time. OAI, pp. 205-227.

19. (2011) Mercks Growth Strategy: Cohabitation over Marriage. Knowledge @ Wharton.

20. Nunn AD (2007) The Cost of bringing a radiopharmaceutical to the patient's bedside. J Nucl Med 48: 169.

21. USFDA (2004) Challenge and Opportunities Report March 2004.

22. VanBrocklin HF (2008) Radiopharmaceuticals for Drug Development: United States Regulatory Perspective. Current Radiopharmaceuticals 1: 2-6.

23. DiMasi JA, Grabowski HG (2007) Economics of new oncology drug development. J Clin Oncol 25: 209-216.

24. DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: new estimates of drug development costs. J Health Econ 22: 151-185.

25. FDA (2004) Critical Path Initiatives.

26. Committee for Medicinal Products for Human Use (CHMP), EMEA (2004). Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose.

27. Harapanhalli RS (2010) Food and Drug Administration requirements for testing and approval of new radiopharmaceuticals. Semin Nucl Med 40: 364-384.

28. Guidance on PET Drugs (2009) Current Good Manufacturing Practice (cGMP). USFDA.