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Commentary

Drug development and imperfect design☆

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Abstract

Several factors affect or control design of any new object and these could be—cost, time, quality, aesthetics, technology, and strategy. The object designed is never perfect. The article extends this concept to the drug industry and discusses various imperfections. In spite of these imperfections, the drug industry is serving mankind satisfactorily and improving quality of our lives. The discussion leads to steps, which can be taken to make better drug products. Individualized medicines, combination drug products, and targeted drug delivery systems could be some of the options. Natural medicines may guide us to develop "perfect" drug products.

Keywords: Design; Imperfection; Drug industry; Drug development; Drug delivery systems

I recently came across the book by Henry Petroski on designs of objects and imperfection (Petroski, 2003). The concept was intriguing—is there any design which one can be claimed perfect? Wabi–Sabi, the Japanese philosophy, teaches us to value imperfections. Wabi implies rustic simplicity and Sabi is the beauty that comes with age. The commentary here has attempted to apply the same principle of the imperfect design to the discovery and design of new drugs.

1. Factors governing the designing of objects

Several factors affect or control the design of any new object. Management books often refer to a triangle of cost, time and quality. It is claimed that usually one can obtain the best for only two factors of the three. This model is not perfect and we need to add three additional factors as depicted in Fig. 1 to make it more complete. Company management usually has a strategy to design its products mainly for business reasons. For many small companies, a new innovative concept cannot be implemented to develop a "perfectly" designed product due to lack of funding and technology. Aesthetics is also a critical factor for products, helping to ensure consumer acceptability.

2. Drug industry and the imperfect design

Often scientists design drug molecules and formulations and therefore, we may be able to apply the concept of "the imperfect design" to the drug industry. With advancements in chemistry and instrumentation, we can determine the structures of compounds, which can fit on the desired receptors. We can now isolate various active components of various extracts and conduct toxicological and pharmacological tests to determine the most active moiety. Medicinal chemists may derivatize active moieties. In designing and selecting drug molecules, typical reasoning has often been simple—administer the most active ingredients to the patients. Formulators then develop pharmaceutical formulations using the active ingredient.

A staff writer of The Star Ledger (New Jersey) discussed the statistics on the number of drugs approved per year since 1990 (Jordan, 2007) as depicted in Fig. 2. The average and the median values for the number of drugs approved are 28 and 27, respectively. Merck pulled their painkiller product Vioxx from the market in 2004 and in 2005 and 2006, only 20 and 17 drugs, respectively, were approved by FDA. The pharmaceutical industry is facing a major problem of dry pipelines in spite of spending about 40 billion dollars on research and development. We observe late stage failures in clinical trials even though thor-

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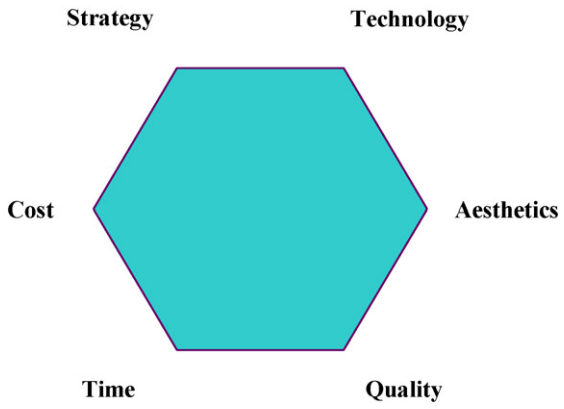

Fig. 1. Factors affecting the designing of an object.

ough research is conducted in selecting the drug molecule for further development. Research on Torceptrapib, Pfizer's heart pill, was halted due to deaths and other cardiovascular problems in the clinical trials. It was a major set back for Pfizer and the drug industry, in general. What went wrong when the scientists at Pfizer designed Torceptrapib?

It is a dream of every medicinal chemist to invent a perfectly designed molecule, which has very high potency and is devoid of all side effects. Do we have such a drug for any indication? The answer is simply—No. There is no drug molecule, which is effective in every patient and has no side effects. How much time and money should one spend in designing a perfect drug molecule? Management and patients would like to see drugs brought to the market as soon as possible. Patients may desire to have a "not so perfect" molecule today when they need it rather than wait (perhaps it may be too late) for a perfect drug to be designed later.

If the design of a perfect molecule is unattainable, one may question the withdrawal of drugs from the market due to potential life-threatening side effects for a few individuals, thus depriving those individuals who actually may benefit from the drug. One way to solve such a problem is to identify individuals who likely would show undesired and life-threatening side effects and this is achievable only by close monitoring of patients. This includes routine examinations and biochemical analyses to produce databases of similar types of patients. With the advancement of genetic engineering, it may be possible to identify

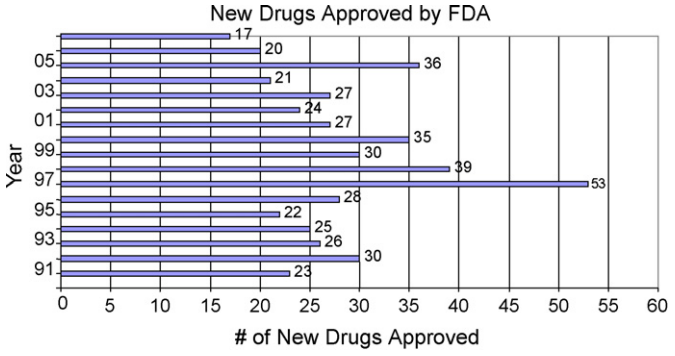

Fig. 2. Number of New drugs approved by FDA from 1990.

biochemical characteristics of an individual who would produce either a positive or negative response to the drug.

We have to reevaluate the current design of pharmaceutical formulations. Most of the current formulations contain one active moiety. It is easier to control the quality of the formulations, which has only one active ingredient. Currently, we think that this is the perfect design of pharmaceutical dosage forms. Recently, there has been renewed interest in natural products, which contain more than one active ingredient. If it is assumed that various ingredients have additive/synergistic effects and that some of the ingredients may neutralize the side effects of the main drug moieties, then our current design of formulations with one drug molecule becomes questionable. Combination drug therapy has been commonly used to treat AIDS and cancer patients. Pfizer's is marketing a drug product (Caduet™), which contains a calcium channel blocker and a Statin. GlaxoSmithKline has developed Mistral™—a combination of an anti-inflammatory and an anti-ulcer medication for arthritis sufferers. Arthritis pain is worse in the morning and the peak drug levels are achieved during that time of the day. Anti-inflammatory drugs in the morning may cause stomach upset and anti-ulcer drug may alleviate symptoms. In combination drug therapy, convenience to the patient is a major aspect. The patient may experience a positive psychological effect by thinking of taking only one pill instead of several. The patient may feel that he/she is taking only one tablet.

Pharmaceutical scientists strive to design a dosage form, from where the drug absorbed at a desired rate and which may deliver the drug to the targeted site *in vivo*. The ultimate goal is to produce an ideal "targeted" drug delivery system, which will carry the drugs only to the needed area(s) and only in sufficient quantity. We have made progress, but are still far away from such a "perfect" design. The list of factors mentioned in Fig. 1 influence the formulation scientist in designing drug delivery systems. Formulation scientists may wish to develop the best formulation design. However, management may ask them to develop, for example, immediate release formulation initially, followed by a novel drug delivery system to extend the intellectual property rights (strategic aspect in the Life Cycle management). An additional factor is the "time of availability" of the formulation to patients. Another factor could be the cost of pharmacokinetic trials to develop a "perfect" formulation—companies may not deem that necessary.

Although Quality Control and Quality Assurance (QC and QA) functions play a major role in every industry, their effects in the pharmaceutical industry are very prominent since drug formulations are used to treat sick patients. Pharmaceutical companies follow current good manufacturing practices in producing drug products. What is a quality drug product? The current model of controlling quality incorporates specifications in drug formulations. The specifications are the limit values or a range for a test performed to determine the quality of drug products. The Food and Drug Administration (FDA) has set standards for setting specifications and companies try to meet with them. Thus, specifications determine the quality, and specifications are based on the set of assumptions. As a result, we are already compromising perfection in drug products.

The FDA has taken steps in the right direction to implement Process Analytical Technology (PAT). One should build quality into the drug product throughout the manufacturing process. Current pharmaceutical manufacturing operations are not very efficient for several reasons. Presently, pharmaceutical manufacturing mostly undertakes the batch process approach thereby increasing the cost. It is impossible to come up with a one-size-fits-all "perfect" design of a manufacturing process. The design of manufacturing processes of the same drug substance or a similar drug product varies from company to company because there are numerous ways to produce each product. The manufacturing design may not be perfect, but it is based upon the needs of the company and resources available.

The pharmaceutical business model is constantly changing. The current top players are facing the dilemma of dry drug pipelines despite spending billions of dollars on drug research. The wave of high through-put screening of drug molecules subsided quickly without producing the desired outcome. Designing drug molecules and formulation development is far from a "printing" job. Individual attention needs to be given to each drug molecule being developed. It is in this area that small players have been shown to be very successful. In a new business paradigm for the pharmaceutical industry, drugs may be designed by small biotech companies. In order to fill their pipelines, major pharmaceutical companies license drugs from small biotech companies at the Phase III stage and then undertake to develop and market them.

3. Conclusions

In the pharmaceutical industry, none of the currently available drugs molecules and drug products is perfect. However, they are serving their purpose of curing diseases and improving the quality of life of patients. The impact of the concept of "imperfect design" should be judged by the pharmaceutical industry and the FDA. The goal should be to produce medicines, which are effective to an individual patient. We should define and refine suitable criteria using a variety of techniques including biochemical analyses, which will identify those patients who would benefit from a drug from those patients who would show severe side effects. Combination drug therapy is already part of our lives and new designs in this area are expected in the coming decades. There may be a hidden "perfection" in natural medicines and we may need to revisit them with a different point of view.

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