

## Regulatory Practice in Pharmaceutical Industry

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### Introduction

The pharmaceutical sector is a high-technology, knowledge-intensive and heavily regulated industry. All aspects of the life-cycle of new drugs are regulated, from patent application to marketing approval, commercial exploitation, patent expiration and competition with generics. All the important actors in the pharmaceutical industry: the manufacturers, wholesalers, retailers and prescribing physicians are subject to regulatory controls. This helps to ensure the product efficacy and safety which are not immediately observable. This article discusses about the regulatory practice in pharmaceutical industry with respect to various facets of drug development.

### Rising Cost and Role of Regulations

The pharmaceutical industry has two sides of coins. On one side, the larger firms account for the majority of the research and development (R&D) investment in the industry and hold the majority of patents while on other side, a large number of small firms manufacture generic version of off-patent drugs. The larger pharmaceuticals spend heavily on both marketing and R&D. Historically, the research-based industry invests between 15-20 percent of their sales in R&D. The cost of bringing a new compound to market was estimated at 1.3 billion in 2005, an increase from \$138m in the 1970s and \$318m in the 1990s. To a major extent, this high and rising cost of R&D reflects upon the regulations that exist in these countries, requiring that new compounds meet standards of safety, efficacy and quality. Most countries also require pre-approval evidence of efficacy, monitor manufacturing quality throughout the product life and regulate promotion and advertising to physicians and consumers.

### Protection of Intellectual Property Rights

Pharmaceutical companies are heavily reliant on intellectual property right protection (and in particular, patents) to preserve the income flows necessary to finance research and development. Research and development involves huge investments and is a risky business. Of 10,000 products patented, only 100 reach human trials; out of which, only ten are marketed. Research has found that 75 percent of drug company profits come from just ten percent of all drugs. For some major firms, their two-three products account for 70-80% of the total pharmaceutical sales. There are a number of countries who are signatories to the TRIPs agreement which provides for a standard patent life of 20 years, from filing. However, the process for obtaining marketing approval is slow, costly and takes a number of years, thereby reducing revenue. This in turn, reduces the effective or commercial life of a patent. Most OECD countries therefore allow for an extension of up to five years to the patent life for pharmaceutical products (New Zealand and Hungary are exceptions to this rule, allowing no extension; Italy allows a longer extension for a short period). This is often coupled with provisions which enhance and encourage the entry of generic products upon expiration of the patent.

Many countries have adopted a mutual recognition procedure under which drugs approved in another jurisdiction receive expedited (or automatic) approval domestically. The EU also has a centralized procedure which, for successful applicants, grants marketing approval for the whole of the EU. The time required to obtain marketing approval seems to vary widely. While marketing approval can take years in the

US, the time limits are 300 days in the case of New Zealand (for high risk medicines), 95 days in the case of Korea and 90 days in Mexico (60 days for drugs which have been patented in other countries).

### Pharmaceutical Pricing Controls

Control on pricing of a drug is different for different countries depending on pricing policies. These prices are set in different ways. Where the products in a therapeutic class are close substitutes, the prices of the drugs in that class are often set equal to the lowest price in that class. Where a drug has few close substitutes price-setting is more difficult. It is common to set prices based on international price comparisons of equivalent drugs. If almost all countries set prices on the basis of international comparisons, the importance of the price-setting policies in those countries which do not use international comparisons is magnified. A few countries fix prices on the basis of costs (also known as profit controls). These policies are also occasionally complemented with other industry-wide controls such as a limit on annual rate of increase, a broad freeze on prices or an enforcement across-the-board price reduction.

Many countries also regulate the prices and services of pharmaceutical wholesalers. The reason for this remains unclear. Many countries noted that the pharmaceutical wholesaling sector was relatively concentrated. Some countries grant pharmacies a monopoly on the sale of nonprescription pharmaceuticals or require that a pharmacy be owned by a pharmacist, or limit the formation of chains of pharmacies. These restrictions also appear unnecessary. Differences in price control policies encourage traders to purchase pharmaceuticals in low-price countries and sell them in high-price countries. This limits the ability of countries to pursue independent pharmaceutical price-fixing policies. This would likely result in higher prices in poor countries.

### Controls on Prescribing Physicians and Pharmacists

Most insurers control the prescribing practices of individual physicians, to ensure the most cost-effective treatment of patients. These controls typically take the form of prescribing guidelines or controls on who may prescribe certain medications. Some countries also impose nominal or explicit "budgets" on prescribing physicians or give a financial incentive to doctors who achieve a certain level of generic prescribing (e.g., Spain). In a few cases, the payment to the health care provider is fixed, giving strong incentives to economies on pharmaceutical use along with all other health inputs. The clearest example of this is the UK "GP Fundholder" programme under which

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the local doctor is given responsibility for purchasing health care services on behalf of a group of patients in return for a fixed per-capita payment. Such schemes rely on competition between doctors to ensure incentives to maintain quality are retained. Many insurers also control the activities of pharmacists. Since pharmacists are typically compensated on the basis of a percentage margin on the products they sell, in the absence of explicit controls they have an incentive to increase rather than reduce the price of the medications they sell. Many countries allow, encourage or require substitution of cheaper bio-equivalent products. In some cases, pharmacists are allowed to keep some of the cost savings from substituting cheaper equivalent products. Only in Japan and Korea, the doctors are allowed to both prescribe and dispense medications. There is currently a proposal in Korea to separate these two professions to reduce the financial incentive to over prescribe.

### Harmonization of Pharmaceutical Regulations

The global pharmaceutical industry is a powerful player in developing harmonized regulations. Each country has a peculiar regulatory system and hence pharmaceutical companies sometimes may take advantage of the different standards and regulations across different regions to game the system. For example, an impure or under strength product that is forbidden from sale in one country being dumped in another nation with looser laws is sophisticated international laws evasion strategy. To avoid this, harmonization of regulations not only reduces game playing by pharma companies but also opens doors for them to enter into several markets with ease.

### Good Regulatory Practice

Regulatory system is an important backbone for the healthcare division of any county and hence, government must emphasize for development and implementation of good regulatory practice considering the public interest. At the same time, pharmaceutical manufacturing firm/sponsor should also support the formation of such a platform. Consideration of following points is important in establishment of good regulatory practices:

#### Scientific approach

Adequately health care division of any country includes scientific knowledge based structure to support regulations. Regulators and auditors should possess the regulatory knowledge to interpret technical dossiers, manufacturing facility and prepare inspection reports. Dossiers should be in a standardized format and should be compiled in accordance with ICH guidance/ international standards.

#### Communication

Communication is one of the important sources. Government should follow a regular practice of effective communication with sponsor for changing the laws, modification or update of any regulation. Involvement of the pharmaceutical industry during law making discussion can help in formation of efficient regulations. Regulatory agency should also consult third party for understanding the market need. It is the responsibility of the regulator to provide timely feedback in case of any dispute related to rules and regulations with more transparency. On other hand, the pharmaceutical industry should also hear their counterparts which can lead to successful law formation and reduce the time and cost.

#### Consistency

Consistency of regulatory guidelines and laws over the period of time is necessary. If, for example, the government has set some rules for

manufacturing of any drug, then it must not alter. Government should specify all regulations in such a way that, industry must not be able to take undue advantage. While developing any regulations government should consider all possible pros and cons so that they are available without any ambiguity and with clear expectation. Moreover, all the rules and regulations need to be organized properly. Each regulation must have a separate regulatory body, structure, functioning, staff, controls etc. Each regulatory body is designated with a responsibility and authority along with standard operating procedures. Sponsor or pharmaceutical companies should also act consistently. For example, they strive for excellence in producing high quality submission. They ought to exhibit high level of professional and scientific competence while practicing the regulations.

#### Efficiency

The efficient regulatory agencies require aligning with global standards such as ICH which is acceptable international standard, WHO guidelines or other international requirements. This will help in making local regulations to be accepted at an international platform. Similarly, the regulator should avoid duplication of review and streamline administrative process. Contrary, one has to confirm that the sponsor efficiently follows the regulations by adhering to technical and standards, consistent with local requirements and submission of high quality data at all times.

#### Predictability

Result oriented regulations are need of the hour. For example, if any pharma company has submitted clinical trial application to regulatory agency to undertake a clinical trial, then they must define review process for application and timelines/ milestone of events. This will give confidence to sponsor and can help to decide the future path. This way, the sponsor can also give a timely and satisfactory response to queries raised by the regulator and allocate resources as appropriate to address need of timelines/ milestone events.

#### Transparency

Transparency is the key to gain public trust in system and effective implementation of any rule, regulations or law. For example, any changes in regulatory personnel or policy related to manufacturing of HIV drugs should be published. Public must be aware about the review process for draft regulation. Regulatory authority must also produce a report on metrics in public. Table 1 shows the metrics of review time for the new drugs.

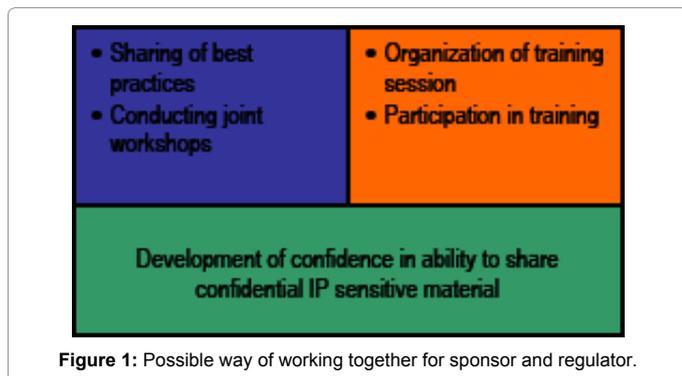
Pharmaceutical organizations will be able to increase sales and will be more profitable if they are transparent. They should timely publish positive and/ or negative results of a study, comments on draft regulations and also timely communicate changes to risk/ benefit profile of a drug.

#### Collaboration

All of the majors for good regulation practice can possibly be carried out only when regulatory agencies and pharmaceutical

Fiscal year	Total review time (months)	Regulatory review time (month)	Applicant's time (month)
FY 2009	19	12	7
FY 2010	16	11	5
FY 2011	12	9	3
FY 2012	12	9	3
FY 2013	12	9	3

Table 1: Review times for new drugs (standard products).



organizations work together on various fronts. Figure 1 highlights the way by which a regulator and sponsor can work together. This will help not only government agencies but also the pharma sponsor to save

time, resources and could eventually lead to the promise of a healthy life (Figure 1).

## Conclusion

Although, there is a large and growing literature on regulation of the pharmaceutical industry that has produced valuable information and useful lessons learned; still large and important issues remain for future research. Models of regulation in other industries are either not relevant or require significant adaptation and extension in order to fit this industry's peculiar characteristics, in particular; high rates of R&D and technical changes, patents, insurance and physicians, consumers, payers and pharmacists as potential customers. This industry remains a liberal ground for future research.