PANEL MEMBER
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Licensing of Generic: Needs and Expectations of Industry

Introduction

The generics face multiple challenges: ever increasing scrutiny by the regulators across the world; growing barriers of protection by innovators; and the government pressures for price reduction. All these tend to push up the costs of generics or make the business unviable. This is unlikely to change. If at all, it may become worse. The clamour for product quality; the impact of longer periods of exclusivity; push for liberal patentability standards; and need to contain health care expenditure in the major markets will continue to exert pressures on the cost and price of the generics. The product and process innovations that have helped generics in the past may no longer be enough for the future. The generics will have to look for something more to remain relevant and protect their growth. They need to work with the drug regulators to eliminate or reduce inefi ciencies in the system. This article makes an attempt to identify and list potential areas that can be explored by the generics to remain viable and emerge stronger.

1. Cost Containment

The foremost among them is cost containment through regulatory approval process. It is difi cult, but is doable. The five key areas are:

a. A Single Reference Product:

Regulators in several markets approve a new product based on a global multi-country clinical trial. The innovators use one product in all countries for its trials and subsequent registration. However, on expiry of patents and other exclusivity periods, when an approval is sought for generic version, many countries insist that the applicant must use a "local" product as reference product. This results in testing of multiple reference products for a company seeking regulatory approvals in more than one market.

Is it possible to convince the drug regulators to accept one "reference" product as was accepted by them during the global clinical trial? As the safety and efi cacy of the product is already established by the innovator, irrespective of geography, a generic manufacturer operating in many countries should not be required to

prove equivalence multiple times with reference to a product in each country. It should sufi ce to establish equivalence with a product from the country of origin. This would save considerable costs in product registrations. This is particularly important for the follow on biologics or biosimilars.

b. Uniform Product Standards:

Some product monographs vary according to the pharmacopeia; e.g. USP, BP, JP, etc. All of these variations are not necessarily based on science alone. The variations reflect mindsets of different markets. The monographs usually incorporate the originator's standards.

If only the regulators were to agree to a common standard for a product, instead of multiple pharmacopeias, the convergence of standards will not only reduce variability but will also help cost containment, as a manufacturer of a generic does not have to produce a product with multiple standards.

c. Common Packaging Specifications:

Like product standards, the packaging specifications vary according to markets. The variations in different jurisdictions are mostly linked to the regulatory and/ or marketing needs. However, if only common specifications were laid down for each type of container, say, bottle, foil, blister, etc., and a manufacturer had freedom to choose its own packaging, the resultant synergy could help reduce cost. It is recognized that a generic producer would like to match his product with the originator in each market for better acceptance. At the same time, common standards could help reduce variability and cost.

d. Timely Product Approvals:

Currently, the time taken for approval of generics varies from 4 months to 36 months in various jurisdictions. If this time was compressed and the waiting period was reduced to max 12 months, not only the manufacturers could commence production earlier, but will also benefit patients by early on-set of competition.

e. Establishment Inspection & Report (EIR):

The time taken by the regulators for inspection of new manufacturing facilities and re-inspection of old facilities under warning letters/import alerts is a major cost. The waiting period for establishment inspection and, after the inspection, time taken for releasing the report is crucial for business. The regulators have their own constrains. In addition, their annual travel schedules, finalized well in advance do not allow flexibility. Nonetheless, it must be recognized as a major element of cost for generics and the generic manufacturers and the regulators need to find a solution to this vexed problem.

Thus, a coordinated approach to regulatory convergence could help cost containment for generics.

2. Compliance

After cost, the next important issue is compliance. The manufacturers have increasingly realized that the cost of non-compliance is far greater than the cost of compliance. However, to improve compliance, it is important to also address the role of regulators. How can they help? What should they do?

It needs to be recognized that the regulators' role does not end with laying technical guidance and checking their compliance. They should also assume responsibility for dissemination, understanding and absorption of the guidance. The compliance can be better achieved by explaining the scientific rationale behind the guidance, not just by diktats. Secondly, they should ensure that these rules and guidance are science driven, simple and practical. Thirdly, they must avoid creating a perception of frequently shifting goal posts. Fourthly, they need to ensure that their inspectors have understood the guidance and are adequately trained for their uniform implementation. These expectations change the role of regulators form merely being an auditor to that of being a facilitator. As the compliance is a major cost-saver, the generic manufacturers need to find ways of working with the regulators for ensuring product quality and patient safety.

3. Inspection & Inspectors

The resource constrains have forced regulators to develop quality metrics to move to risk based inspections. It is a welcome step. However, a lot more requires to be done to develop the metrics and the standards of measurement. The generic industry can help in these efforts. Concurrently, the regulators need to explore possibility of evolving a common check-list to avoid multiple inspections of a site.

Likewise, and as noted above, the need of training and retraining of inspectors cannot be overemphasized. It is very essential to avoid subjectivity of inspectors and variability in the implementation. The effective management of the inspection and the inspectors require that the regulators continuously monitor and measure performance of their inspectors. These actions would inspire greater confidence in inspectors and promote better compliance.

4. Quicker Resolution of Remedial Actions

The warning letters and import alerts suspend supplies from many manufacturers for prolonged periods. The timely resolution of remedial actions and a system of providing an opportunity to manufacturers to discuss remedial actions could go a long way in resolving the quality issues and early resumption of supplies from the affected sites. This would not only help reduce cost of generics, but also prevent shortages of medicines and avoid unwarranted price increases.

5. Capability Building

Many regulators have demonstrated that they are willing to help industry in the capability building, if only the manufacturers were willing to take responsibility for quality of their products and ensure patient safety. It is important that the senior management of companies also demonstrate their commitment. This could pave the way for capability enhancing workshops. These workshops can promote two-way learning for the industry and the regulators. The discussion of scientific rationale by the regulators would help better absorption of guidance. Likewise presentation of practical problems of the industry in implementation would help regulators to improve the guidance. This dialogue can provide a lasting solution to the problems of compliance and quality.

The generic industry should therefore explore possibilities of working with the regulators in their own country and across the world. It may help improving affordability and availability of medicines, which is what the most governments are looking for.

Q&A

Q) Do you have any perspectives on GDUFA ii – do you think it's a good idea, too expensive etc? (will it speed up regulatory approvals)?

The GDUFA II will further reduce the number of applications and discourage marginal players who do not have deep pockets. On the other hand, there is commitment by the FDA to clear the backlog. Thus, fewer applications and extra efforts by the regulator may result in improving the disposal time.

Q) How can we achieve the goal of having one reference product for generics – does this need some kind of harmonisation across countries, how long do you think that this will take? (who might be a leader(s) in this regard?

This needs convergence of standards, not harmonization. International Generic Drug Regulators Programme (IGDRP) is already working for convergence by the regulators. If not all, at least a few major markets aided by the WHO can initiate this process. It is not necessary that all should do it at the same time. A beginning can be made by a few and others may follow.

Q) How can generic approval be kept down to under 1-year?

At one time, the USFDA had achieved 17 months. Some jurisdictions have made it possible. The cost of creating an appropriate organization is insignificant compared to the potential savings from early approval of generics.

Q) Do you think any regulators are yet acting as facilitators rather than simple auditors – I know many people are encouraging the FDA be part of a two way dialogue with industry. How long before this shift occurs, do you think it will occur. Are certain regulators better than others at acting in this more two-way educating role?

Not yet, but how many industry associations have even asked for it? The IPA is actively pursuing this goal. We believe that the regulators can achieve better results and ensure greater patient safety by helping manufacturers to do the things in the right way. Inspection is a snapshot, whereas training is long lasting. Some regulators seem to understand the importance of capability building as an option and are supporting these efforts.

Q) Do you think the industry and regulators are likely to engage more now, or do you fear the generics model will come under increasing pricing pressure – what will be the end result of this?

The engagement between the industry and the regulators is growing rapidly. However, this engagement and the pricing pressure are two independent phenomena. They are not interlinked. The engagement with the regulators could help save costs to cope up with the pricing pressures.

Q) Can you make any prediction(s) about the outcome for the generics market in 3-years time – do you think any of the above will be achieved or to the solutions found?

We will see pockets of success in the next three years. The industry and the regulators will be working jointly for capability building. We may not achieve everything, but we will see a beginning.

Q) Lastly, and most importantly, what sort of cost savings or magnitudes do you think can be achieved by these types of changes? (how long will it take to implement this properly)

Consider only the cost of procuring originator's biotech products at the current prices for 100 subjects each from five different countries for BA/BE studies. The cost and time involved of doing this study on 100 patients for each market is extra. Add the cost of delay in launching the product.... it is significant. The generics need to rely on "science" to convince the regulators that "one reference product" will not compromise patient safety.