A PRAGMATIC WAY TO SUSTAIN IN GENERIC PHARMA ENVIRONMENT: PLCM THROUGH REGULATORY STRATEGIES

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REVIEW ARTICLE

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ABSTRACT

Most thoughtful way to sustain in this competitive highly regulated Pharma generic industry environment is depended on understanding the concept of the product life cycle management (PLCM). Fact is a very less number of Pharma professionals have been familiarized them with this fascinating strategic concept. So, it's the time now to convey that what does this PLCM means and how to put it into work. The objective of this article is to convey the use of PLCM as a strategic concept for enhancing drug's sustainability in market for a long time, making better business decisions, enhancing profitability and finally delivering affordable, quality embedded generic drugs to customers. Also, in this manuscript an attempt has been made to compare corresponding regulatory agencies (US, EU, Canada and India) insights and view on preference of PLCM application. By careful analysis, it's revealed that US provides most favourable environment to employ various PLCM strategies, wherein EU is equally good, nonetheless national polices could be a barrier, Canada is difficult to comprehend due to stringent laws and limited exclusivity and as of now India has least scope for PLCM application.

Keywords: Product Life Cycle Management (PLCM); Regulatory strategies; Pharma generic industry.

INTRODUCTION

Recent trend shows the pharmaceutical industry has faced numerous challenges such as dried R&D product pipeline, changing regulatory landscape and cut through competition, resulting question marking growth and profit margins. However to bit these challenge, PLCM is a meaningful and holistic approach and it has become a necessity to the continued success of pharmaceutical companies. Companies that have instituted a comprehensive life-cycle management strategy and a detailed plan to guide their progress toward their goal are reaping on time regulatory approval, financial and clinical rewards. For the purpose of pharmaceuticals, PLCM does not mean just a way to protect innovation through different patents or obtaining patent term extensions to take the benefit of all available protection but also means to coordinate worldwide intellectual property litigation strategies to achieve the desired result at a global level. The arena of PLCM is so wide that it provides benefits to both large and small industries whether innovator or generic through profit enhancement and revenue acceleration. Although PLCM benefits every person related to it whether Big Pharma or consumers, still it has some lacunae.

Nonetheless, Innovator companies always put across strategies such as legal maneuvers, co-marketing and OTC switching to delay the entry of generic drugs to market. And it leads to drug price increase as well as monopoly in the market. So, there lies the space in Pharma business environment for generic companies to implement PLCM strategies. On the whole, PLCM is a concept to manage a generic company's product-related intellectual capital

starting from its initial conception to retirement and a boom for generic industry for early and healthy entry. Thus, the present manuscript highlights how the tailor made PLCM strategies for generic Pharma industries would be beneficial for both the company and the consumer.

BACKGROUND AND RATIONALE

Lifecycle Management for Generic Drug

Since, the pharmaceutical regulatory process surrounding drug development is fragmented due to differences in approaches of the innovator or branded manufacturers and the generic drug manufacturers, their PLCM strategies are different too. In case of a generic moiety, the target should be defined early in development with an aim to access market before other generics based on the properties of the drug substance, characterization of the Reference Listed Drug (RLD) product and consideration of the RLD label and intended patient population. Throughout the product lifecycle, the manufacturing process performance should be monitored to ensure that it is working as anticipated to deliver the desired product quality attributes. Process stability and process capability should be measured and evaluated. In case, if any undesired process variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control. The additional knowledge gained during routine manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product and should be notified as a commitment to the regulatory agency. (1, 2)

EARLY STAGE LIFECYCLE MANAGE-MENT

During development of a generic drug following objectives should be taken into consideration:

- To define commercial manufacturing process based on knowledge gained through development and scale up activities and to develop a strategy for process control
- To evaluate if the process is capable of reproducible commercial manufacturing and to make continual assurance that the process remains in a state of control (the validated state) during commercial manufacture
- To get the newly developed product to the market place on time (2)

To achieve these goals following strategies should be considered:

- Approach to early submission
- Approach to quality submission
- Patent litigation

Approach to early submission: Most generic companies work to similar development timelines as originators—typically around 8–10 years. They start with a product targeting process i.e. actively examining drugs for future development as soon as they've been approved or launched or sometimes even while they're in phase III clinical development. It all depends on the anticipated commercial potential of the compound, the readiness of a reliable source of the generic API, patent protection and exclusivities. At last, 2 years before patent expiry, most generic companies are ready to begin production and distribution the moment the originator's time is up. (3) Thus, use of IT based tools and eCTD (electronic common technical document) would be a helpful hand to them to shorten the drug development and approval time. ICH guidelines for eCTD submissions are well accepted by US, EU and Canada. (4, 5)

Approach to quality submission: A QbD approach is extremely helpful to achieve pharmaceutical quality. In this context, pharmaceutical quality means that consumers will receive a product free from contamination that will reproducibly deliver the therapeutic benefit promised in the label. (6) However, Question based Review (QbR) is more relevant for generic submission than QbD based development as generic submission requires less stability data for submission. QbD is more significant during post approval phase. (7) In

US, the Office of Generic Drugs (OGD) is developing a QbR for its Chemistry, Manufacturing, and Controls (CMC) evaluation of ANDAs (Abbreviated new drug application) that is focused on critical pharmaceutical quality attributes with a goal to ensure that the generic product is appropriately designed (a pharmaceutical equivalent to the RLD) and that sponsors have methods and controls in place for the manufacture, processing, and packaging of a drug that are adequate for assuring and preserving the identity, strength, quality, and purity of the proposed drug product. (2, 6)

Patent litigation: Now-a-days, the validity of patents is being challenged frequently to allow launch of generic molecules before patent expiration. In case of innovators, the patent litigation comes under late lifecycle management approaches. On other hand, the generic drug manufacturers use it as early lifecycle management strategy as the generic drug approval is unresolved until the settlement of litigation. Thus, litigation has become an accepted and necessary part of business models for R&D based pharmaceutical companies. (8) Patent infringement actions often end up in settlements. Patent litigation settlements are extremely rewarding as they may result in a complete foreclosure of the market for generics manufacturers. (9)

By using patent strategy, how generic drug manufacturers are taking privilege with respect to USA, Canada, EU and India pharmaceutical competitive environment has been discussed below:

US: As per the Hatch-Waxman Act, the ANDA filer should give one of the following patent certifications: Paragraph I Certification, where the generic applicant certifies that there are no patents listed in the Orange Book; Paragraph II Certification, that any listed patents have previously expired and it may enter the marketplace immediately upon FDA approval; Paragraph III Certification, where the applicant certifies that any listed patent has not yet expired but will expire on a particular date, the FDA may approve the ANDA and make it effective as of the patent expiration date and Paragraph IV Certification, where the applicant for generic approval intends to market the drug prior to expiration of any patent(s) listed in the Orange Book, it makes a certification that, in its opinion, the patent(s) are not infringed or are invalid, and it notifies the NDA holder and patent owner accordingly. The Para IV filing of Hatch-Waxman Act provides a unique approach for filing an ANDA in order to enter the market before the expiry of innovator patent. This Para IV filing allows the applicant to file an ANDA and to notify the original patent holder that all the applicable patents are invalid or not infringed. On action brought by innovator, FDA approval is suspended until the date of court's decision or up to 30 months. If the decision is in favour of patent owner, the approval is suspended until the expiry of patent. (9, 10) In US, most patent litigation settlements contain exclusionary payment features by which the innovator offers payment to the generics manufacturer in exchange for the generic not entering the market, if it obtains marketing authorization so that the 180-day period (uniquely provided in US) does not begin to run. (11)

EU: Even though the EU regulatory framework does not contain provisions similar to US, innovators file or threaten to file patent infringement claims against their generic competitors to prevent or delay generic entry. Between 2000 and 2007, originator and generic companies engaged, out of court, in at least 1,300 patent-related contacts and disputes concerning the launch of generic products. However, generic companies won the majority of cases in which a final judgment was given (62%). The settlements, including agreements involving reverse payments, increasingly occur in Europe as well. (9, 11, 12)

Canada: The PMNOC (The Patented Medicines Notice of Compliance) Regulations have provisions to the United States Hatch-Waxman regime. The generic must have a pending drug submission before it can serve a notice of allegation on an innovator. Upon receiving a notice of allegation, an innovator may challenge the allegations by commencing

a Court proceeding and automatically impose a statutory stay of up to 24 months. (13)

India: Due to lack of patent linkage (the practice of linking drug marketing approval to the status of the patent of the originator's product and not allowing the grant of marketing approval to any third party prior to the expiration of the patent term, unless consented to by the patent owner), Indian courts never had as much patent litigation as the American and English courts had. (14) Nevertheless, patent litigation in India has grown owing to better laws and improving registration facilities. Indian firms are taking the patent disputes to courts, as was and is very common in the United States. Post-WTO, Indian law has been amended and patent protection has become stronger. The courts play a very important role in resolving the disputes and interpreting the law. There is, however, a need to expedite the process of resolution of such disputes. (15)

LATE STAGE LIFECYCLE MANAGE - MENT

Upon approval, the drug product is validated using the lifecycle approach that employs making validation guidance throughout the drug product lifecycle to demonstrate that utilities and equipment are suitable for their intended use and perform properly.

During the commercial phase, the objectives are altered as follows:

- To monitor the manufacturing process performance based on additional knowledge gained during routine manufacturing
- To optimize the product on risk-based decision by modifying drug substance, manufacturing process etc.

In order to achieve these goals following strategies should be considered:

- Bringing out various post approval changes
- Modification in the drug product
- Collaboration with the branded drug manufacturer

How above listed strategies can be implemented in different countries are described below:

Bringing out various post approval changes: As mentioned earlier that after approval throughout the product lifecycle, the manufacturing process performance should be monitored to ensure that it is working as anticipated to deliver the desired product quality attributes and should be notified as commitment to the regulatory agency. (2, 6)

US: In reference to the Guidance for changes in approved NDA or ANDA, three levels are defined to make post approval changes for the holders of ANDA. Who intend to make post approval changes three levels is defined: Level 1 Level 2 and Level 3. It worth noting that while assessing the change in case of ANDA when bioequivalence is re-documented for certain post approval changes, the FDA recommends the comparator to be the reference listed drug. (16) Another unique aspect in US is revised labelling of generic drugs following RLD labelling changes. During the marketing life of a drug product approved under a new drug application (NDA), the package insert labelling is frequently revised. When an NDA serves as an RLD for an ANDA, approved changes in the RLD labelling generally necessitate changes in the labelling of one or more ANDAs using the RLD. Under the Federal Food, Drug, and Cosmetic Act and Agency regulations, an ANDA product must have the same labelling as the RLD. The sponsor of an ANDA should routinely monitor the Labelling Review Branch Homepage for information on changes in labelling. All ANDA labelling changes needed because of approved changes to the labelling of the RLD may be submitted as a *Special Supplement – Changes Being Effected*. Such supplements should include:

- 12 copies of final printed labelling
- The date the revised labelling will be used (go into effect)
- A side-by-side comparison of the ANDA labelling with the approved labelling of the RLD with all differences annotated and explained (17)

EU: In EU, the post approval changes for a generic drug remain the same as described in variation regulation i.e. type IA (and IA_N), IB and II variations. While for changes to the active substance(s), changes to strength, pharmaceutical form and route of administration, an extension application is required. (18,19)

Canada: Health Canada also specifies same classification for quality related Post-NOC Changes as Level I, II, III and IV changes. (20)

India: The Drugs and Cosmetics Act 1940, does not provide any abbreviated route for registration of drugs except for drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario where the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority. Thus, no case can arise for any post approval change. However, in case of any imported drug, the same criterion is applied as for a new drug, biologic or non biologic as the case may be. (21-23) Table 1 depicts reporting categories of various post approval changes in different countries. (16, 18, 20, 22)

Modification in the drug product: The generic drug product can be modified e.g. different polymorphic form, solvates or hydrates/ different route/ dosage form and thus filing for the same is also important.

US: The 505(b) (2) application is intended to encourage sponsors to develop improved generics, i.e., drugs similar to an approved product with some significant changes that are not permitted under Abbreviated New Drug Application (ANDA) rules. The sponsor of a 505(b) (2) product is not required to obtain a right of reference from the innovator product manufacturer. However, the sponsor needs to include data from bridging studies to support changes from the reference drug. Perhaps the biggest incentive to develop 505(b) (2) products is the three to five years of market exclusivity in the US, depending upon the extent of changes to the previously approved drug and the amount of data submitted to FDA. (24) A 505(b) (2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference
- Identification of any and all listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number, if the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drug
- Information with respect to any patents that claim the drug or the use of the drug for which approval is sought
- Information required under 314.50(j) if the applicant believes it is entitled to marketing exclusivity
- A patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted
- Patent certifications for the patents listed for the pharmaceutically equivalent drug specifying the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired, if there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application
- A certification stating for approval of a new indication, and not for the indications approved for the listed drug, in case of a new indication
- A statement as to whether the listed drug(s) identified above have received a period of marketing exclusivity. If a listed drug is protected by exclusivity, filing or approval of the 505(b)(2) application may be delayed
- A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any)
- Studies necessary to support the change or modification from the listed drug or drugs (if any)

- Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). (25)

EU: In case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product, hybrid applications which rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data can be submitted. However, results of appropriate pre-clinical tests and clinical trials will be necessary. (26) Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:

- where the strict definition of a 'generic medicinal product' is not met;
- where the bioavailability studies cannot be used to demonstrate bioequivalence;
- Where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data. The summary of such application should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned. Some guidance on the appropriate additional studies required is depicted in Table 2. (27)

Canada: A modification in molecular entity requires a supplemental new drug submission in Canada. (20) However, in the current framework, there is no provision for any hybrid application or 505 (b) (2) submissions. However, a regulatory framework is under development for subsequent-entry biologics (SEBs) in which an analogue of the USFDA 505(b) (2) process may be considered. (28)

India: There is no abbreviated route for registration of drugs, and as a result there is no existence of generic drugs. However in case of an imported drug which is proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration, new drug applications allow the applicant and regulatory authority to rely at least in part, on the safety and/or efficacy data of a previously approved drug. (29, 30)

Collaboration with the branded drug manufacturer: There is a dramatic amplification in the frequency of firms participating in inter-firm collaborations over the last twenty years. Firms may also ally with competitors to set standards in an industry or to meet difficult time goals for development of new technologies. The licensing agreements that give the pharmaceutical company rights to use the technology combined with discovery research and/or product development activities in which each party has a continuing role are one of the common forms of such collaborations. (31) A research-driven pharmaceutical company facing patent expiration can introduce their own generic drug, or alternatively, license the drug to a generic company before the expiration of the patent in exchange for royalties. Today many branded pharmaceutical companies have either divested their generic subsidiaries, or run them as an entirely separate business. For example, the pharmaceutical companies Novartis and Pfizer have taken this approach with Sandoz Inc. and Greenstone Ltd. respectively. (32) A licensed generic company enjoys additional advantage of preferential access to raw materials and manufacturing know-how, ahead of their competition. In addition, there is 180 days market exclusivity in the US, for the first generic applicant challenging a patent. This

exclusivity may delay or deter other generic manufacturers from entering the market. (33) However, the settlement agreements arrived during patent litigation, between the pioneer drug manufacturer and the generic drug manufacturer may allegedly delay the market entry of the generic product. (10)

The overall environment for PLCM strategies in different countries for generics is depicted in Table 3.

Table 1: Reporting categories of various post approval changes in different countries

Quality Attributes		Reporting category in various countries			
		US	EU	Canada	India
Drug Substance					
Description	Changes in particle size, solubility solid state form etc.	Annual Report or Supplement: Changes Being Effected (CBE) or Prior approval supplement (suspension)	Type II variation	Supplement	Annual Report or Application for change (quality issue)
Manufacture (1) Process	Change in the manufacturer of active substance	Supplement: Changes Being Effected (CBE)	Type II variation	Supplement	Annual Report or Application for change (quality issue)
	Minor change in the manufacturing process of active substance	Supplement: CBE	Type IA variation	Supplement	Annual Report or Application for change (quality issue)
	Minor change in the manufacturing process starting material	Annual Report	Type IB variation	Annual Notification	Annual Report
	Substantial change to the manufacturing process	Supplement: CBE	Type II variation	Supplement	Application for change
(2) Batch size	Up to 10-fold increase/ downscaling	Need not be submitted to the Agency	Type IA variation	Annual Notification	Annual Report
	More than 10-fold increase	Need not be submitted to the Agency	Type IB variation	Notifiable Change	Annual Report
(3) In-process test limits	Tightening of in-process limits	Supplement: CBE 30	Type IA variation	Annual Notification	Annual Report
	Addition of a new in-process test and limits or Deletion of a non-	Supplement: CBE 30	Type IA variation	Notifiable Change	Annual Report

	significant in-process test				
	Addition or replacement of an in-process test as a result of a safety or quality issue	Supplement :CBE 30	Type IB variation	Notifiable Change	Application for change
	Deletion of an in-process test which may have significant effect on the overall quality of the active substance	Supplement: CBE 30	Type II variation	Notifiable Change	Application for change
Control of Drug Substance (1) Specification parameters	Tightening of specification limits	Annual Report	Type IA variation	Annual Notification	Annual Report
	Addition of a new specification parameter or Deletion of a non-significant specification parameter	Annual Report	Type IA variation	Notifiable Change	Annual Report
	Deletion of a significant specification parameter	Supplement: CBE	Type II variation	Notifiable Change	Application for change
(2) Test procedures	Minor changes to an approved test procedure	Annual Report or CBE (if change in impurity)	Type IA variation	Annual Notification	Annual Report
	Deletion of a test procedure, if an alternative test procedure is already approved	Annual Report or CBE (if change in impurity)	Type IA variation	Annual Notification	Annual Report
	Other changes to a test procedure	Annual Report or CBE (if change in impurity)	Type IB variation	Notifiable Change	Annual Report
Container closure system	Qualitative and/or quantitative composition	Annual Report (no interaction)	Type IA variation	Annual Notification	Annual Report
	Qualitative and/or quantitative composition for Sterile active substance	Prior approval supplement	Type II variation	Notifiable Change	Annual Report
	Liquid active substances (non sterile)	Annual Report (no interaction)	Type IB variation	Annual Notification	Annual Report
Stability	Reduction in Re-test period/storage period	Annual Report or Supplement: CBE	Type IA variation	Annual Notification	Annual Report
	Extension of the retest	Supplement:	Type II	Notifiable	Application

	period	CBE	variation	Change	for change
	Change to more restrictive storage conditions of the active substance	Annual Report	Type IA variation	Annual Notification	Annual Report
	Change in storage conditions of the active substance	Supplement: CBE	Type IB variation	Annual Notification	Annual Report
Drug Product					
Description	Changes in imprints, bossing or other markings	Annual Report	Type IA_N variation	Annual Notification	Annual Report
	Changes in scoring/break lines	Supplement CBE or Prior approval supplement	Type IB variation	Notifiable Change (addition) Annual Notification (deletion)	Annual Report
	Change in the shape or dimensions of IR tablets, capsules, suppositories and pessaries	Prior approval supplement	Type IA_N variation	Notifiable Change	Annual Report
	Change in the shape or dimensions of modified or prolonged release forms and scored tablets	Prior approval supplement	Type IB variation	Notifiable Change	Application for change
Composition	Addition , deletion or replacement in the flavouring or colouring system	Annual Report	Type IA_N variation	Annual Notification or Notifiable Change (if involves stability)	Annual Report
	Any minor adjustment of the quantitative composition	Annual Report	Type IA variation	Annual Notification or Notifiable Change	Annual Report
	Significant Qualitative or quantitative changes in one or more Excipients	Prior approval supplement	Type II variation	Supplement	Application for change
	Change in coating weight of oral dosage forms or change in weight of capsule shells	Supplement: CBE or Prior approval supplement (modified release)	Type IA variation or Type II variation (modified	Notifiable Change or Supplement (modified release)	Annual Report

			release)		
	Deletion of the solvent / diluent container from the pack	Annual Report	Type IB variation	Annual Notification	Annual Report
Manufacture (1) Site	Changes in Packaging site	Annual Report or CBE (depending upon location)	Type IA_N variation	Annual Notification	Annual Report
	Changes in site for batch control/ release	Annual Report or CBE (depending upon location)	Type II variation	Notifiable Change	Annual Report
	Changes in site other than batch control/ release	Annual Report or CBE (depending upon location)	Type IB variation	Notifiable Change or Supplement (modified release)	Annual Report
(2) Process	Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	Annual Report	Type IA variation	Annual Notification	Annual Report
	Significant changes in the manufacturing process	Prior approval supplement	Type II variation	Notifiable Change or Supplement(if require in vivo data)	Application for change
	Minor change in the manufacturing process of an aqueous oral suspension	Annual Report	Type IB variation	Annual Notification	Annual Report
(3) Batch size	Up to 10-fold increase/ downscaling	Annual Report	Type IA variation	Annual Notification	Annual Report
	More than 10-fold increase	Supplement: CBE	Type IB variation	Notifiable Change	Annual Report
(4) In-process test limits	Tightening of in-process limits	Annual Report	Type IA variation	Annual Notification	Annual Report
	Addition of a new in-process test and limits or Deletion of a non-significant in-process test	Supplement: CBE	Type IA variation	Annual Notification	Annual Report
	Addition or replacement of an in-process test as a result of a safety or quality issue	Supplement: CBE 30	Type IB variation	Annual Notification	Application for change
	Deletion of an in-	Prior approval	Type II	Notifiable	Application

	process test which may have significant effect on the overall quality of the active substance	supplement	variation	Change	for change
Control of Excipients (1) Specification parameters	Tightening of specification limits	Annual Report	Type IA variation	Annual Notification	Annual Report
	Addition of a new specification or Deletion of a non-significant parameter	Supplement: CBE	Type IA variation	Annual Notification	Annual Report
	Deletion of a significant specification parameter	Supplement: CBE 30	Type II variation	Notifiable Change	Application for change
	Addition or replacement of a specification parameter as a result of a safety or quality issue	Prior approval supplement	Type IB variation	Annual Notification	Application for change
(2) Test procedures	Minor changes to approved test procedure	Supplement: CBE 30	Type IA variation	Annual Notification	Annual Report
	Deletion of a test procedure if an alternative test procedure is already approved	Prior approval supplement	Type IA variation	Annual Notification	Annual Report
Control of Drug Product (1) Specification parameters	Tightening of specification limits	Annual Report	Type IA variation	Annual Notification	Annual Report
	Addition of a new specification or Deletion of a non-significant parameter	Supplement: CBE	Type IA variation	Annual Notification	Annual Report
	Deletion of a significant specification parameter	Supplement: CBE 30	Type II variation	Notifiable Change	Application for change
	Addition or replacement of a specification parameter as a result of a safety or quality issue	Prior approval supplement	Type IB variation	Notifiable Change	Application for change
(2) Test procedures	Minor changes to approved test procedure	Supplement: CBE 30	Type IA variation	Annual Notification	Annual Report
	Deletion of a test procedure if an alternative test procedure is already approved	Prior approval supplement	Type IA variation	Annual Notification	Annual Report

	Other changes to a test procedure	Annual Report	Type IB variation	Annual Notification or Supplement (sterility test)	Annual Report
Container closure system (1) Qualitative and quantitative composition	Solid pharmaceutical forms	Annual Report (no interaction)	Type IA variation	Notifiable Change	Annual Report
	Semi-solid and non-sterile liquid pharmaceutical forms	Prior approval supplement	Type IB variation	Notifiable Change	Annual Report
	Sterile medicinal products	Prior approval supplement	Type II variation	Supplement	Application for change
	Changes associated with reduction in shelf life	Prior approval supplement	Type II variation	Supplement	Application for change
(2) Type of container	Solid, semi-solid and non-sterile liquid pharmaceutical forms	Prior approval supplement (in case of no quality change except solid)	Type IB variation	Notifiable Change	Annual Report
	Sterile medicinal products	Prior approval supplement	Type II variation	Notifiable Change	Annual Report
(3) Specification parameters	Tightening of specification limits	Annual Report	Type IA variation	Annual Notification	Annual Report
	Addition of a new specification or Deletion of a non-significant parameter	Supplement: CBE	Type IA variation	Annual Notification	Annual Report
	Addition or replacement of a specification parameter as a result of a safety or quality issue	Supplement: CBE 30	Type IB variation	Notifiable Change	Application for change
(4) Test procedures	Minor changes to approved test procedure	Annual Report	Type IA variation	Annual Notification	Annual Report
	Deletion of a test procedure if an alternative test procedure is already approved	Supplement: CBE 30	Type IA variation	Annual Notification	Annual Report
(5) Change in shape or dimensions	Non-sterile medicinal products	Supplement: CBE or Annual Report (solid dosage form)	Type IA variation	Annual Notification	Annual Report
	Change concerning a significant impact on the delivery, use, safety	Prior approval supplement	Type II variation	Notifiable Change	Application for change

	or stability				
	Sterile medicinal products	Prior approval supplement or CBE 30	Type IB variation	Notifiable Change	Annual Report
(6) Pack size	Change in the number of units	Supplement: CBE 30 (sterile) or Annual Report (non sterile)	Type IA_N variation or Type IB (outside the range)	Notifiable Change	Annual Report or Application for change (outside the range)
	Change in the fill weight/fill volume of sterile product	Supplement: CBE 30	Type II variation	Notifiable Change	Annual Report
	Change in the fill weight/fill volume of non-sterile product	Annual Report	Type IB variation	Annual Notification	Annual Report
(7) Packaging material	Change in any part of the (primary) packaging material not in contact with the finished product that affects the product information	Annual Report	Type IA_N variation	Annual Notification	Annual Report
	Addition, replacement or deletion of a supplier of packaging component or device	Prior approval supplement	Type IA variation	Annual Notification or Notifiable Change	Annual Report
	Any change to suppliers of spacer devices for metered dose inhalers	Prior approval supplement	Type II variation	Notifiable Change	Application for change
Stability	Reduction of the shelf life of the finished product	Annual Report or Supplement: CBE	Type IA_N variation	Annual Notification	Annual Report
	Extension of the shelf life of the finished product	Supplement: CBE	Type IB variation or Type II variation (not in accordance with ICH)	Notifiable Change	Application for change
	Change in storage conditions of the finished product not in accordance with an approved stability protocol	Supplement: CBE	Type II variation	Notifiable Change	Application for change

	Change in storage conditions of the finished product or the diluted/reconstituted product	Supplement: CBE	Type IB variation	Notifiable Change	Annual Report
Labelling	Changes in the product label	Prior Approval Supplement (new study data) Supplement: CBE (addition or strengthening of warning, precaution, etc.)	Type IB variation (safety variation)	Notifiable Change (new safety indication)	Application for change
AR: Annual Report; **CBE:** Supplement: Changes Being Effected; **CBE 30:** Supplement: Changes Being Effected in 30 days; **PA:** Prior approval supplement; **NA:** Need not be submitted to the Agency; **IA:** Type IA variation; **IA_N:** Type IA_N variation; **IB:** Type IB variation; **II:** Type II variation; **AN:** Annual Notification; **NC:** Notifiable Change; **S:** Supplement; **AC:** Application for change					

Table 2: Guidance on the appropriate additional studies required (34)

Conditions	Additional data usually required
Different salt/ester complex/derivative (with the same therapeutic moiety)	Evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile(otherwise, to be considered as a new active substance)
Different route/pharmaceutical form (For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes) i) new route of administration ii) new pharmaceutical form (same route) (conventional to modified)	Clinical data (safety/efficacy), pharmacokinetics, pre-clinical (e.g. local toxicology), if justified
Different strength same route/ pharmaceutical form and posology	Bioavailability
Supra Bioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	Bioavailability studies may suffice
Active substances associated in a different proportion/different posology or if one or more is intended for modified release.	Clinical studies comparing existing/new proportion or dosage regimen, including bioavailability studies.

Table 3: Environment for PLCM strategies in different countries for generics

PLCM strategy	US	EU	Canada	India
Early Lifecycle Management				
Approach to early submission	eCTD	eCTD	eCTD	No such provision yet
Approach to quality submission	QbD, QbR	QbD	QbD	No such provision yet
Patent litigation	Due to patent linkage, Para IV filing generally result in infringement suit	Due to Patent linkage, Notification of generic application to patent holder may lead to infringement suit	Due to patent linkage, notice of allegation generally result in infringement suit	No patent linkage; patent disputes are less frequent but slowly increasing based on 'patent policing'
Late Lifecycle Management				
Various post approval changes	Level 1: Annual report Level 2: CBE 30,0 Level 3: Prior approval supplement Labelling changes as per RLD: *Special Supplement – CBE*	Type IA: Variation application Type IB: Variation application Type II: Variation application	*Quality Changes* Level I: SNDS/SANDS Level II: Notifiable change Level III: Annual notification Level IV: Record of changes *Safety and Efficacy changes* Level I: SNDS/SANDS Level II: 90 day risk management change, 120 day change Level III: Annual notification	Not mentioned. For imported - Biological product: Level I: Supplements Level II: Notifiable change Level III: Annual notification Non-biological product: Minor change or modification: notification Major change or modification: Subsequent New Drug
Modification in the drug product	Improved generics, 505 (b)(2) application	Hybrid application	SNDS/SANDS	No description
Collaboration with the branded drug manufacturer	Well accepted	Well accepted	Well accepted	Well accepted

CONCLUSION

There has been a misconception that PLCM is a tool to prevent/delay generic competition and cannot be applied to generics. In fact, PLCM is a tool to manage product related intellectual capital and that 'product' (generic). In US, most of the PLCM strategies are well accepted. The provision of 180-day marketing exclusivity, QbR for generics and submission of improved generics through unique 505 (b) (2) pathway are a few examples to reveal that US is equally concerned for growth of generic drug market. The PLCM strategies can be applied with equal ease in EU as well. However, the national regulations may complicate the circumstances. Canada also provides a good platform for PLCM application over generic drugs. However, India a hub of generic market does not contain the word 'generic' in its legislation. Hence, scope for PLCM application is not very promising. However, the authorized generics market and M&As with foreign pharmaceutical firms and distributers is the other side of coin and possibility for PLCM application is not over here.

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CONFLICT OF INTEREST

Author declares that there are no conflict of interest.

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