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Review Article

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Integrating PLCM strategy in Pharmaceutical Emerging Market

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ABSTRACT

All products and services must denote definite life cycles. The life cycle talks about the period from the product's first launch till it wind-up onto the market. Throughout this age noteworthy modifications are made in a way that the product is manifesting i.e. its mirror image with respect of sales. Ultimately increase of sustainable profit is the aim that every company aspires of the PLCM strategy. The understanding of a product's life cycle, can help a company to understand and realize when it is time to introduce and withdraw a product from a market, its position in the market compared to competitors, and the product's success or failure. This article details regarding Product Lifecycle Management in light of Pharmaceutical environment for the emerging markets (India, China, Russia, Brazil, and South Africa). Also an attempt has been made to compare PLCM of stated emerging countries with- highly regulated market (US).

Keywords: Product Lifecycle Management (PLCM), FDA, ANVISA, eCTD, CTD, ICH, Variation, CDER.

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1. Introduction

One significant and holistic approach to bit today's present-day challenges in the pharmaceutical industry is to emphasize on Product Lifecycle Management (PLCM), which is nothing but business transformation approach to manage products and related information. To adopt PLCM strategy, we need to understand regulatory environment and its implications. In this article we focused for the emerging markets (India, China, Russia, Brazil, and South Africa). Also benchmarking has been done with- highly regulated market (US) (1).

The PLCM must be made an integral part of any drug development. Therefore PLM should be begin as earlier as possible in the process with research into trends and possibilities to increase the drug competitiveness. The regulatory environment PLM strategies vary from country to country

- Regulatory framework affecting PLCM in Regulated Market (US)
- Regulatory framework affecting PLCM in Emerging Market (India , Japan, China Turkey , Mexico, South Africa)

PLM Strategies are divided into two categories

- ✓ Early life cycle management Strategies
- ✓ Late life cycle Management Strategies

In early stage, the regulatory strategies for a molecule focus predominately on receiving the approval as quickly as possible. In Case of NCE, the aim is to have the marketed product protected by a basic patent in force as long as possible and to obtain market exclusivity as long as possible. On the other hand late life cycle management of established product mainly focus on improvement of the product and or increase their differentiation against the first generation product, other competitive product and generics (2).

Life Cycle management for the innovator or Branded drug

During the Development phase, the main objectives are:

- To provide a meaningful improvement in clinical profile
- To increase the patient potential for the brand
- To generate maximum ROI

These objectives can be fulfilled by following Strategies

- Planning for submission
- Approach to early submission
- Prolongation for the period of Exclusivity

1) Planning for Submission: Pursuing approvals in new countries and regimes requires developing a targeted regulatory strategy early in development process. While planning for submission, the innovator or branded drug manufacturer should take the following point into consideration to select the requisite country:

- Time to market
- Fee
- Period of exclusivity
- Handling of regulatory procedure

Handling of regulatory procedure involves how the regulatory agency interacts with the sponsors including the regulatory information available at official website of regulatory agency. It's varies from country to country

US- FDA conducts pre-IND, end of phase 1, end of phase 2, and pre- NDA/pre-BLA meeting or a meeting upon request by sponsor. A comparison for time to market and fee; and period of exclusivity in regulated market (US) and Emerging market namely BRIC countries.

Table 1 Comparison of time to market and fees

Country	Regulatory Authority	Time for regulatory Approval of CTA/IND Application	Time for review of NDA/ NDS/MAA	Required Fee
United States	FDA	30 days	180 days	$194,400
Brazil	Agência National de Vigilância Sanitária (ANVISA)	90 days	180 days	37,000BRL
Russia	Federal Service on Supervision in the Sphere of Public Health Services and Social Development (Roszdravnadzor).	30-40 days	120 days	$50,000 (US)
India	Central Drug Standard Control Organization	30 days	150 days	50,000 INR

Table 2 Comparison of period of exclusivity

Country	Patent Exclusivity		Non Patent Exclusivity		
	Patent Term	Patent term Extension	Data Exclusivity	Orphan drug exclusivity	Pediatric Exclusivity
United States	20	Up to 5 years	5 years for NCE 3 years for non NCE	7 years	6 Months
Brazil	20	NO	No	-	
India	20	NO	NO	NO	NO
Russia	20	NO		-	6
China	20	No	6 years for NCE	-	

2) Approach to Early Submission

Pharmaceutical Companies and regulatory agencies are collaborating for improving drug development process and approval e.g. ICH guidelines for eCTD submission and Qbd which contribute to better first time product quality shortening the review time required by regulatory agency and these guidelines are well accepted by regulated markets. India and China japan still uses the CTD format.

3) Prolongation of the Period of Exclusivity

New aspects of the drug formulation (e.g., new synthetic procedures for the drug itself, new scale up strategies, new protocol for treatment, change in dose, mode of administration, modification of the drug formulation, potential use of the NCE with other drug products, and even design protection for package and dosage forms, etc.) should be considered for patent protection. Many of these aspects can be developed throughout the life of product not just during the regulatory approval stage (example new polymorphs, active metabolites, stereoisomers, new crystalline structures).These aspects help the manufacturer to prolong the life of their product. PTEs can also be sought before patent expiration. Pharmaceuticals brands also granted an additional six month marketing exclusivity period in exchange for detailed

pediatric data. The prolonged exclusivity period designates the brand manufacturer as the sole supplier and prevents any generic competitor from reaching the market.

Late life cycle Management (3, 4)

During the commercial phase, the objectives are changed as the following

- To drive wide spread patient access to the brand
- To defend market access and formulary position
- To optimize brand franchise

These goals are fulfilled by considering the following strategies:

- Bringing out post approval changes for improvement
- Introduction of new indication
- Introduction of second generation products
- Investment in generics
- Pricing strategies
- PTEs & Patent litigation

Bringing out post approval changes for improvement

Many minor and moderate changes that enhance the comfort or convenience, improved safety are included in post approval changes

US: According to 21 CFR 314, 70(c) , the FDA may after a review of supplemental information, decided that changes are approvable . The scale up and post approval changes (SUPAC) task force which was established by the center for drug evaluation and research (CDER) chemistry, manufacturing, and controls coordinating committee developed guidance on scale up and other post approval changes.

Level of changes (5)

Level 1 changes are those that are unlikely to have any detectable impact on formulation, quality, and performance and should be reported in Annual Report

Level 2 changes are those that could have a significant impact on formulation quality and performance and should be reported as prior approval supplement(can labeled as changes being affected in 30 days , CBE 30 or changes being affected, CBE 0)

Level 3 changes are likely to have a significant impact on formulation quality and performance and should be reported as prior approval supplement (CBE30).

Table 3 Documentation required for different levels of post approval changes in US

Changes	Reporting Category	Documentation required
Level 1	**Annual Report** Accompanied by a complete transmittal form FDA 2252	A list of all changes contained in the annual report Full description of the manufacturing and controls changes not requiring a supplemental application A summary of any changes in labeling that have been made since the last report A statement by the holder of the approved application that the effect of the changes have been accessed; The date each change was implemented Data from studies and test performed Revised promotional labeling and drug advertising.
Level 2	Supplement changes being affected(CBE0) Supplement changes being affected in 30 days (CBE 30 days)	A list of all changes contained in supplement provided in the cover letter A detailed description of the proposed change The drug product involved The manufacturing site or area affected A description of the methods used and studies performed to access the effect of changes The data derived from each studies Revised promotional labeling and drug advertising
Level 3	Prior approval supplement	

2. Post approval changes in Brazil (6, 7)

On March 22, 2016, the Brazilian Health Authority (ANVISA) approved the amendments of Regulation RDC 48/2009, which refers to the post-approval changes of drug products. The amendments establish a new regulatory framework for post-approval changes through the incorporation of different risk analysis depending on the complexity and the health risk of the modified drugs. The purpose of this regulation is to classify the post-registration modifications of medications and to establish the documentation and tests required by ANVISA. For the purpose of this Technical Regulation, the following definitions shall be adopted:

- Product Change History (HMP): A form in which the post-registration changes/alterations or inclusions of medications shall be registered. Some changes considered as having a smaller impact, as defined in this standard, shall only be registered in this history and shall be exempt from an individual protocol process.
- Stability study protocol: A document by which the stability study plan is defined, including the acceptance criteria and proof, schedule, characteristics of the batch to be submitted to the study, number of samples, study conditions, analytical methods and conditioning material.
- Multiple concomitant changes: These are changes arising from a main request in accordance with the scope of this regulation. Whenever allowed according to this standard, they can be done together with the main change without the need of creating additional protocol processes.
- Multiple parallel changes: Joint protocol processes of two or more change requests directly related and occurring simultaneously.

3. Post approval Changes in Russia (8)

Even after the registration process is complete and the applicant has received a Certificate of Product Registration, state approval may be needed for any changes to these documents.

Certain post registration variations, such as changing the manufacturer's name or packaging design do not require additional quality, efficacy or safety expertise. However, if the variation is more significant, such as changing the manufacturing site, the quality or quantity composition of the product or the instructions for administering the product, quality, efficacy or safety expertise will be required. The minor variations can take two to three months to receive approval from the state regulatory authority, whereas the latter types of changes can take anywhere from six months to a year to be approved.

Table 4 Variation Types

Type	Classification	Example
Variation type 1	Don't need Quality, Efficacy or Safety expertise	Don't need Quality, Efficacy or Safety expertise
Variation type II	Need Quality, Efficacy or Safety expertise	Change of manufacturing site; change of quality or quantity composition; change of instruction for administration

4. Post Approval Changes in India (9)

Level I - Supplements (Major Quality Changes)

Supplements (Major Quality Changes) are changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a biological product as these factors may relate to the safety or effectiveness of the product. The changes included in this reporting category shall be filed, along with the recommended supporting data, to DCGI. The appropriate fee must also be paid, in accordance with the prevailing rules at the time of submission of the notification. If, within 30 days of the date of the acknowledgement of receipt of a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

Level II - Notifiable Changes (Moderate Quality Changes)

Notifiable Changes (Moderate Quality Changes) are changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product. The changes included in this reporting category should be filed, along with the recommended supporting data, to DCGI as a Notifiable Change (NC). If, within 15 days of the date of the acknowledgement of receipt of a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

Level III - Annual Notification (Minor Quality Changes)

Annual Notification (Minor Quality Changes) are changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product. The changes included in this reporting category may be implemented by the sponsor without the prior review by DCGI of the data supporting such a change. Supporting data for the Level III changes recommended in this guidance documents should be submitted on annual basis; however, the data on such changes should be available to DCGI within fifteen (15) calendar days, if requested at any time.

In Case of non-biologics there are no separate guidelines ("Guidance for Industry: Post approval changes in biologics Product")

5. Post approval changes in South Africa (4, 10)

A change to a registration dossier in South Africa is more properly known as an "amendment". Amendments are classified in one of the three categories: Type A, Type B, Type C.

Table 5 Regulatory Requirement for post approval changes in South Africa

Type C	Type B	Type A
• Require prior approval before implementation. • Should be reflected under "Amendment History" in the MRF1 1Ac) / Module 1.2.1 f)	• Require notification • Should be recorded and made available for inspection. • Should be reflected under "Amendment History" in the MRF 1Ac) / Module 1.2.1 f).	• Do not require prior approval before implementation. • Do not require prior notification
Guidance of MCC for the Changes		
Addition or removal or increasing or decreasing any release controlling ingredient.	Film coating change from organic solution to aqueous solution	Deletion of colour/flavour/fragrance
Manufacturing Site Changes		
Changes in location, involving or affecting environmentally controlled manufacturing or related support areas.	Changes in responsible individuals specified in approved dossier	Modification of approved production facility or room(s) that will not have an adverse effect on safety, sterility, purity or potency of product.
Batch Size Changes		
Change in batch size of More than 10- fold compared to the original batch size approved at the time of registration	Change in batch size of Up to 10-fold compared to the original batch size approved at the time of registration of the product	Not Mentioned
Manufacturing Process Changes		
Change in type of process used in the manufacturing of the product outside validation.	Change in Equipment or process machinery but with same processing principles.	Change in process timing and/or operating speeds (if validated), but same final product specifications and content uniformity
Container/ Closure System Changes		
Changes in composition of the immediate container affecting stability.	Changes in composition of the immediate container.	Update of approved Storage Instructions to align with currently accepted wording and directive
Filling Type		
Prior written approval	Notification required 30 days prior to intended implementation date	Prior notification not required
Approval Time		
Approximately 30 years	30	00

Introduction to new indication/population

When drug's usage is extended beyond its routine intended use, a whole new and exclusive market is created by the virtue of indicated expansion. Developing a product for new indication allows for a secondary patent, which extends the period of exclusivity for the product and delays generic competition. Indication expansion is usually tried and tested where diagnostic precularities can be blurred. A successful indication expansion requires both the tactical focus on the product as well as strong research and development capabilities. The submission of new indication is different for each country.

US (11)

Any new indication can be filled with FDA through 505(b) (1) or 505(b) (2) application or as supplement to the new drug application. The Procedure for the review will be same as for the new drug as explained earlier.

The application 505(b)(1) required extensive clinical and non-clinical studies to demonstrate the safety and efficacy of a given drug for the target indication and application 505(b) (2) requires only additional clinical and non-clinical studies other than BA/BE to demonstrate the safety and efficacy of previously approved drug. Supplements submitted by the original sponsor for approval of an indication are called supplemental new drug application. After review and approval by FDA, the new indication is added to the approved labeling and can be promoted by the drug manufacturer.

India (9)

A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration, NDAs allow the applicant and regulatory authority to rely at least in part, on the safety and or efficacy data of a previously approved drug. Such types of new drug applications differ from the new drug application in that they allow the applicant and regulatory authority to rely at least in part, on the safety and/or efficacy data of a previously approved drug. However, additional nonclinical and/or clinical data is necessary to substantiate the new claims of he approved drug. The

additional data needed for establishing the safety and efficacy of such new drugs will usually be determined on case-by-case basis depending on the type of new claims being made. Requirements of Animal Pharmacological, Animal Toxicological & clinical data may be abbreviated / relaxed / omitted if all the below mentioned conditions are satisfied:

- If the drug is already approved by various agencies and is being marketed in major countries for the proposed new claim (s).
- There are evidences of no difference in metabolism of drug due to ethnic differences.
- Availability of adequate clinical data supporting the benefit-risk ratio in favor of the drug in the proposed new claim (s).
- The package insert from marketed countries shows that there is no added safety concern if the drug is allowed to be given to Indian patients for the new claim (s). Requirements of Animal Toxicological & clinical data may be abbreviated / relaxed / omitted if the proposed new claim is for serious life threatening disease or disease of special relevance to Indian health scenario. CDSCO will examine the adequacy of such applications for the purpose of granting approval for manufacture/import of such new drugs. Wherever required the matter may also be examined in consultation with experts/expert committees.

Application for an already approved drug which is proposed to be marketed with a new indication the documents required to be submitted are as follows:

- Form 44
- Treasury Challan of INR 50,000 / 15,000 as the case may be.
- Source of bulk drugs /raw materials: For those raw materials, which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, a copy of the same needs to be submitted. Otherwise, provide the consent letter from the approved source regarding supply of raw material
- Chemical and pharmaceutical information
- Animal Pharmacology Data (as per Schedule-Y)
- Animal Toxicology Data (as per Schedule-Y)
- Human / Clinical pharmacology (Phase I) Data
- Therapeutic exploratory trials (Phase II)
- Therapeutic confirmatory trials (Phase III)
- Special Studies
- Regulatory status in other countries for proposed indication
- Prescribing information and draft specimen of label
- Copy of License in Form-29 (Guidance on approval of Clinical Trials & New Drugs,2011)

Introduction of second generation Products

Redesigning of product result in second generation product and include product reformulation, new patient friendly packaging that enhances comfort or convenience, or improved safety system. The second generation product includes:

- Reformulation of molecular entity that includes changing of molecular structure of a drug such that new molecular form is able to qualify for a patent, yet it functions in the body sufficiently like the previous structure to constitute the same drug under the guidelines for the bioequivalence.
- Reformulation by the new delivery that combines a patentable delivery system and in case, a pharmaceutical company may switch to a new delivery system by terminating the market of previous one.
- New combination of two or more drugs in the same dosage form is challenging strategic option. If the Product is launched in new indication and the combination is not deemed obvious, fixed dose combination therapy can be treated as new agent.

US

Reformulation of molecular entity requires a 505(b) (1) or 505 (b) (2) application as or as supplement to new drug application and may involve additional clinical studies. If the new formulation is to be used similarly to previous formulations, the need for further non-clinical data generally will be small and can be submitted as supplement. However if the alternative formulation will be used in a substantially different way than the need for additional non-clinical data becomes greater. A combination product is assigned to a center with primary jurisdiction, or a lead center, based on a determination of the primary mode of action (PMOA) of the combination product. PMOA is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination 88 product." Based on its PMOA, a combination product is assigned to one of the Agency's three human medical product Centers: the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), or the Center for Drug Evaluation and Research (CDER). The lead center has oversight responsibility for the review and regulation of the combination product. The lead center often consults or collaborates with other agency components and OCP, as appropriate, to identify and evaluate the information needed for a regulatory submission (e.g., investigational application or marketing authorization (Draft Guidance for Industry and FDA Staff (7, 11).

India (12)

A clear justification with a valid therapeutic rationale of the particular combination of active substances proposed will be the basis of approval. It is not always

necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality. In case of FDC where all the active ingredients are approved individually, if a Clinical Trial (CT) is required, confirmatory studies to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances may be considered. When feasible, a placebo arm may be incorporated. Comparative CTs of the FDC with reference treatment may be necessary, especially when the therapeutic justification talks more on the FDCs superiority over a reference treatment.

An application for a marketing authorization may comprise:

- Entirely original data.
- Entirely data from the literature.
- Both original data and data from the literature ("hybrid").

For FDCs, it is likely that hybrid submissions will be the most common type. Chemical and pharmaceutical data should be always totally original, unless there is sufficient justification with literature when partial data can be in-original. Treasury Challan: of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is unapproved or approved for less than one year. However, a Challan of only INR 15,000 is required, in case the applicant has already submitted an application along with a Challan of INR 50,000 towards any of the single active ingredient approval, which is less than 1 year old. Any test batch/trial batch of new drugs for test and analysis purpose should be manufactured after obtaining License in Form 29 from the concerned State Licensing Authority and copy of the license should be submitted along with the application for seeking permission to manufacture and market the new drug.

Data required for approval for marketing FDCs

- FDC - Not marketed anywhere but individual components used concomitantly
- FDC - Not marketed and individual components are not used concomitantly

FDC - Not marketed anywhere but individual components used concomitantly, for approval of such FDCs, following documents have to be submitted.

- Form 44
- Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
- Complete chemical and pharmaceutical data
- Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.
- Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.
- Summary of available pharmacological, toxicological and clinical data on the individual ingredients
- Clinical data showing safety and efficacy of the FDC / Concomitant use of the ingredients, in the same strength, including published data.
- In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.
- Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.
- Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamics and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

FDC not marketed anywhere but individual components used concomitantly requires a summary of all individual Active ingredients.

For obtaining permission to carry out bioavailability/ Bioequivalence Studies

- BA/BE study protocol (when applicable), and Clinical study protocol as per Appendix X of Schedule Y
- Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V of Schedule Y.
- Copy of 'Ethics Committee' approval letters (if available)
- Case Record Form (CRF)
- Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV N. Certificate of analysis of study drug(s)
- Summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted along with any published data.

After the successful completion of clinical trial(s) following documents have to be submitted to complete the marketing application:

- Complete chemical and pharmaceutical data
- Source of bulk drugs /raw materials (for those ingredients which are considered new drugs)

- BA/BE study report and Clinical Study Report conducted in Indian population as per Appendix II of Schedule Y. The study report should be certified by each of the participating investigator(s) in the study and the certification should acknowledge the contents of the report, the accurate presentation of the study as-undertaken, and express agreement with the conclusions. Each page should be numbered.
- Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamics and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.(" Guidance on Industry for Fixed Dose Combination")

OTC Switching (10)

Rx to OTC Switches are being actively persued by pharmaceutical companies to fuel new growth, extend product life cycle, diversify product portfolios and stabilize revenue streams. This strategy can be applied for conditions that are non-serious and easy to self-diagnose, with drugs that are non-addictive, have a wide safety margin, and are easy to administer. Prescription to OTC switch, helps R&D based pharmaceuticals companies to extend their brands and reduce market loss to generic companies upon patent expiration because the launch process of generic companies is delayed as they need to revise labels and packages.

US (13)

After a sufficient amount of time has passed when the manufacturer is able to gather appropriate scientific information on the product, he may elect to submit NDA to FDA so that it may be considered for OTC status. FDA experts review the application and determine if that product has a high enough safety profile and if labeling can be developed so that the medicine can be marketed safely and effectively as an OTC medicine. The US regulations establish a two-part process. First, to determine whether a drug product is eligible to be considered for inclusion in the OTC drug monograph system, certain information must be submitted in a time and extent application (TEA) to show that a drug product can meet the statutory standard of marketing to a material extent and for a material time

Second, if the drug product is found eligible to be considered for inclusion in the OTC drug monograph system, we will publish a notice of eligibility in the Federal Register that requests that interested persons submit data to demonstrate the safety and effectiveness of the drug product for its OTC use(s). An applicant can submit an application under section 505 of the FD&C Act for a new OTC drug condition. An applicant can also submit an application under section 505 to request approval of an OTC drug product that deviates in any respect from a monograph that has become final (21 CFR 330.11). An application under section 505 of the FD&C Act seeks approval of a specific product that is formulated and labeled as it is to be marketed. Benefits of this approach may include the following, Confidentiality during the approval process, a period of marketing exclusivity, for certain applications, upon approval if certain conditions are met historically less time for review of the application from submission to a final decision, compared to other routes to market drugs (i.e., citizen petitions and TEAs). However, an application includes the following, Approval only for a specific drug product, reporting requirements subsequent to approval, in addition to adverse event reporting, prior approval requirements for certain subsequent labeling and formulation changes to the drug product & also subject to required fees. A citizen petition may be used to request the amendment or repeal of conditions covered by proposed or final OTC drug monographs The citizen petition process should not be used to make an initial request to include in the OTC drug monograph system conditions marketed in the United States after the beginning of the OTC drug review in 1972 or those without any U.S. marketing experience; these must first be determined to be eligible for potential inclusion through submission of a TEA.

Brazil (7)

ANVISA issued Rule #98 of 2016, containing the administration's new guidelines for a drug to obtain the OTC status, which allows it to be sold without a medical prescription. Rule #98 requires the drug to comply with seven criteria:

- A minimum time of commercialization of the drug's active pharmaceutical ingredient: ten years, five of which being sold in Brazil as a prescription drug, or five years being sold as an OTC drug in countries where regulations in this matter are similar to ANVISA's;
- A high level of safety: the causes of the adverse reactions must be well known and easily handled, the drug must have a low level of toxicity and a safe therapeutic window and a low level of drug and food interaction;
- The clinical condition treated by the drug cannot be one that potentially evolves rapidly and its symptoms must be easily identifiable by the consumer;
- The drug must pose low risk when used off label or in overdose scenarios;
- The drug cannot be indicated for continued use, it can only be indicated for a small amount of time or a fixed period, which is pre-determined in the drug's label, except for drugs aiming at prevention.
- The consumer must be capable of using the drug without any physical assistance from healthcare professionals.
- The drug cannot generate chemical dependency on consumers.

A company can request the OTC status at any time, whether simultaneously with the Marketing Approval

Application, or after the drug has been approved. The OTC status request must be supported by the documents listed in Rule #98, proving the compliance with the seven criteria above. The Company must also support its request with a risk reduction plan, informing the ANVISA how it will monitor occasional risks arising from the commercialization of its drug with the new status.

Once the OTC status is approved, the ANVISA will publish its decision in the Official Gazette and include the drug's API in the list of OTC drugs, which will be made available in the administration's website. Although the inclusion in said list does not automatically grant all drugs the same API the OTC status, it holds companies marketing them liable to file, within a 180-day term, a request to have its product sales status changed to OTC, as well as the appropriate amendments to the drug's packaging and label.

Finally, Rule #98 also sets out which products are not entitled to receiving the OTC status:

Drugs with parenteral administration and the commercial packing, which can only be sold with a prescription, as it contains API in a quantity that exceeds the maximum limits fixed by ANVISA for each product.

China (14)

The State Food and Drug Administration ("SFDA") recently announced a set of technical guidelines for switching prescription drugs to over-the-counter drugs ("Rx-OTC Switch Guidelines"). The Rx-OTC Switch Guidelines include the Tentative Evaluation Guidelines for Rx-OTC Switch, the Principles for Defining the Indications of OTC Drugs, the Evaluation Guidelines for Traditional Chinese Medicines ("TCM") with Toxic Ingredients to be switched to OTC Drugs, the Principles for Defining Class B OTC Drugs, the Indications of OTC Drugs (TCM Section), and the Indications of OTC Drugs (Chemical Drugs Section).

- A prescription drug is qualified for OTC evaluation if it meets the following basic requirements: Its formulation or active pharmaceutical ingredient must be approved by SFDA and be widely applied in patients over a long period of time.
- There is sufficient research on its formulation or active pharmaceutical ingredient with precise results and satisfactory safety data.
- There are statutory quality specifications for its formulation or active pharmaceutical ingredient and a proven quality profile there.
- The method of use, dosage and treatment course are precise and the efficacy can be ascertained.
- The indication is listed in SFDA's approved scope of OTC indications, typically common diseases or symptoms, recurring diseases or chronic diseases.
- The instructions for clinical application are clear if intended for pediatric diseases or pregnant women.
- The route of administration, dosage form, dosage, specification, timing of administration, storage, packaging, label and insert sheets are suitable for self-medication.

OTC evaluation is comprised of safety evaluation and efficacy evaluation. The safety evaluation focuses on (i) safety of the pharmaceutical product when it is regulated as a prescription drug, e.g., analysis of the pharmacology and toxicology data, adverse drug reactions, likelihood for drug dependence, in-vivo tolerance and interaction with foods, (ii) safety of the pharmaceutical product under the circumstances of self-diagnosis and self-medication, and (iii) safety of the pharmaceutical product in the event of abuse or misuse. The efficacy evaluation focuses on whether a majority of the target patient population would benefit from the pharmaceutical product for cure and symptom relief provided sufficient instructions for use and warning. OTC drugs with higher safety will be classified as Class B OTC drugs and can be purchased by consumers at ordinary retailers, e.g. supermarkets or department stores, without seeking guidance from healthcare professionals for administration, compared to Class A OTC drugs which would require guidance from healthcare professionals for administration and are available only at retail pharmacies. OTC drugs which meet the following criteria will be regulated as Class B OTC drugs those applied to minor ailments/symptoms or used as nutritional supplements, those with higher safety, i.e., marketed in China for over ten years, widely applied in patients, with precise research on safety of its active pharmaceutical ingredients and adverse drug reactions, stable quality, and very unlikely to be abused or misused by consumers.

India (12)

In India OTC has no legal recognition, drugs which are not included in the list of the prescription only drugs are considered to be nonprescription drugs. Hence OTC drugs means drugs legally allowed to be sold over the counter by pharmacist i.e. without the prescription of a registered medical Practitioner or physician.

Pricing Strategies

Pricing is of utmost importance when a drug goes off patent and faces the prospect of the less expensive generics flooding the market. It relies on the pharmaceutical company to decide whether to maintain the price and potentially lower sales volume, reduce the price and meet the competition head on, or even raise price to increase profitability in short term. Price reduction can be effective with a short brand range as one of a number of strategies. Government price controls may prevent the use of price increase in some countries, and where reference pricing for multi-source drug is employed.

US

In Us the Prescriptions drugs are largely unregulated. That differs from most other countries, where drug prices are regulated either directly through price control (e.g. France & Italy), indirectly through limits on reimbursement under social insurance scheme. Thus the Pharmaceutical Company may use Pricing Strategies without any restriction. In US increasing profile will only work while the market has a high proportion of indemnity /full medical coverage plans; this will be less successful if

pharmaceutical cost containment method used in managed care are adopted (7).

Brazil (7)

In Brazil, once market authorization for your pharmaceutical product is granted, you'll need to file for a list pricing registry, a process overseen by Pharmaceutical Market Regulation Council (CMED), which sets prices for the public and private sector. Prices are subject to annual review in March, and more than 60,000 commercial pharmacies in Brazil rely on mark-ups on medicines for their profits, with the prices set by CMED being the maximum price tag a pharmacists can put on a given medicine. The list price is the official, fixed price for a product. It might be adjusted annually according to some criteria depending on which market it's sold into, if it has a generic or not, but once you have a list price, it's a price for a lifetime of the product. Once you have a price you can launch the product in the market, and then think about future public reimbursement.

CMED sets the prices according to criteria contained in six categories a substance can fall under. **Category I** consists of new patent-protected drugs that present better efficacy or safety profile compared to established treatments. The launch price is set by external reference pricing and must not exceed the drug's lowest price in any of the following countries—Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain, the United States, and the country of origin. **Category II** are 'me-too' drugs, where a cost minimization approach is used; **category III** is a new presentation of a drug already marketed by a given company, in the same dosage, where the price is worked out based on the arithmetic mean of the prices of previously launched products. **Category IV** includes new presentations of drugs already marketed by a company, but in a different dosage, and the launch price must not exceed the average price, weighted by sales, of available presentations of the drug that have the same active ingredients, strength, and dosage form. **Category V** consists of new presentations of a drug that is a new dosage form in Brazil or a new combination of active ingredients already available in Brazil. The launch price must not exceed the drug's lowest price in any of the following countries—Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain, the United States, and the country of origin; **category VI** consists of generic drugs that cannot have a launch price that exceeds 65% of the respective reference product's price.

IF CMED finalized the price, it may restrict the Pricing Strategies.

Russia (8)

The Russian Government controls prices of drugs on the Essential Drugs List (EDL). Unfortunately, local and foreign manufacturers are treated differently in that respect, according to Russia's Law on the Circulation of Medicines. Generally speaking, local companies (including those who package their drugs in Russia) are able to adjust prices on an annual basis, while foreign firms are not. Selling prices are subject to state control only if they apply to medicines included on the Essential Drug List (EDL), annually approved by the Russian Government. The Ministry of Health (MoH) approves the maximum drug prices that a foreign supplier (for imported drugs) or domestic manufacturer (for locally produced drugs) may charge. Since July 2015, the FAS have been actively involved in setting of prices for EDL medicines together with the MoH. As a result, the FAS significantly changed previously existing pricing approaches. In October 2016, the FAS announced its plans to change the pricing regulations and associated practice by 2018. In particular, it has been proposed that the maximum sale price will be determined not by the manufacturer, but by the FAS itself. So there is no Provision of Pricing Strategies.

India (9)

In 1979, 347 bulk drugs were under the price control and with a gradual decrease only 76 drugs were limited by the DPCO of 1995. However the department of Pharmaceuticals had proposed under the National Pharmaceutical Pricing Policy, 2011, to seek Price control on all 348 essential medicines through a market based Pricing mechanism and also decides on the span of control. On the other hand, the MNC led body organization of Pharmaceutical Producers of India has already make its concerns public by intervening in the ongoing drug pricing issue in Supreme Court. The government will finalize the policy after receiving the comments of all stakeholders. If the policy is finalized it may restrict the use of pricing strategies.

China (14)

The powerful former state planning commission, now called the National Development and Reform Commission (NDRC), has issued nine policies on drug pricing since 2000. These new policies set maximum retail prices for medicines included in the essential medicine list of the urban BMI, based on a mark-up above the average production cost declared by manufacturers. All other drug prices are market based when setting drug prices; the government aims to cover manufacturers' production costs as well as profit margins, to help cover the general operational costs of drug distributors and drug dispensers such as hospitals. Firms that market medicines with higher quality and safety or with shorter treatment cycles and lower overall treatment expenses (compared to other medicines with the same chemical composition) can apply for higher regulated prices.

PTEs & Patent Litigation

In order to expand and extend the life cycle of the product, PTE is the foremost approach .Now a day's validity of patents is being challenged frequently to allow the launch of generic molecules before patent expiration. As a result litigation has become an accepted and necessary part of business models for R &D based pharmaceutical companies. Developed countries, on behalf of their pharmaceutical companies, seek a term extension arguing that it is necessary to recoup the research and development (R&D) costs. The proponents also argue that patent-term extension could make up for the loss of effective patent term—time lost in getting regulatory approval or owing to delays at the patent office.

However, these arguments are untenable. Consistently, major pharmaceutical companies report profits that are many times more than the costs involved in R&D. Any further extension in the term of the patent will result in corporate welfare at the cost of social welfare.(FF,D&C Act, 21 USC)

US (7, 11, 15)

In the United States, patent term extension is available under the 1984 Drug Price Competition and Patent Restoration Act, also known as the Hatch-Waxman Act ("The Act"). The Act allows the extension of the term of a patent claiming a product that requires regulatory approval prior to being sold, or a method of using or manufacturing the product. Such products include human and veterinary pharmaceuticals, food additives, color additives and medical devices. The determination as to whether a patent term extension should be granted is made by the U.S. Patent and Trademark Office ('USPTO"), in consultation with the regulatory agency responsible for approval of the product. The term extension aims to restore a portion of the patent term that is lost while the patent holder is awaiting regulatory approval of the safety and efficacy of the product. In US, the Hatch-Waxman Act, a company can seek approval from FDA to market a generic drug before the expiration of a patent relating to the brand name drug upon which the generic is based. The first company to submit an Abbreviated New Drug Application (ANDA) with the FDA has the exclusive right to market the generic drug for 180 days (1).

To begin the FDA approval process, the generic applicant must certify in its ANDA that the patent in question is invalid or is not infringed by the generic product (known as "paragraph IV certification"); and notify the patent holder of the submission of the ANDA. If the patent holder files an infringement suit against the generic applicant within 45 days of the ANDA notification, FDA approval to market the generic drug is automatically postponed for 30 months, unless, before that time, the patent expires or is judged to be invalid or not infringed. This 30-month postponement allows the patent holder time to assert its patent rights in court before a generic competitor is permitted to enter. (FF, D&C Act, CFR 314.94(a)(12)(i)(A)(4))

- Brazil does not provide patent term extensions based upon regulatory delays.
- India There is no PTEs in India yet so far
- China Patent term extensions for regulatory delays are not available in China. (Forrestor, & Morrisson, June 2012).

6. Conclusion

Major emerging national economies are Brazil, Russia, India, China, and South Africa. These counties are evolving as newly industrialized countries, but all are notable by their large, fastest-growing economies and significant influence on regional regulatory guidelines. As of 2015, these five countries represent over 3 billion people or 42% of the world population; all five members are in the top 25 of the world by population, and four are in the top 10. So, with an attempt of integrating PLCM for these countries and comparing with highly regulated market USA is insightful. At all stage of PLC, company should adopt holistic strategy to make company's journey profitable and in return general public will also get quality medicine in affordable price.

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Conflict of interest

The authors declare that there are no conflicts of interest, financial or otherwise.

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