

Maintenance of Mature and Generic Products

A Pragmatic Approach to Successfully Navigating the Safety and Regulatory Continuum

While development of promising new products is an obvious area of focus for biopharmaceutical companies, maintenance of already established marketed products is a critical activity that cannot be ignored. As products mature, there is high pressure to grow or sustain revenue from established products while keeping maintenance costs low. Ensuring regulatory compliance and reducing product risk while still working within the cost constraints presents unique challenges to companies in managing established products and requires innovative and cost-effective approaches that can help ensure patient safety and compliance while continuing to meet ever-increasing and complex regulatory demands. It is imperative for marketing authorization holders (MAH) to analyze their existing operating models for maintaining mature products and consider how they can benefit from an integrated safety, regulatory and benefit-risk model.

The Importance of Mature Products

Mature pharmaceutical products are those that are long past their marketing exclusivity period but are still sold in substantial volumes because of their well-established effectiveness and safety in certain medical conditions. Mature products have a significant role in the healthcare industry for many patients both in the developed and developing world. The majority of the large pharma companies have a sizeable portfolio of mature products, which are in the final stages of their lifecycle; although they may be marketed or sold for many years to come. These products can still play a crucial role in the company's strategy, more so in emerging markets than in innovation-focused, developed markets.

Large pharmaceutical companies bring value to patients and customers through their high-quality established pharmaceutical products. Their strategy is focused on increasing proximity to patients by building a portfolio of products that best meets each local market's needs. They assign their resources toward increasing access to existing products through geographic expansion, and improving the therapeutic benefits of products by continued innovation in formulation, packaging and new indications. In one recent benchmarking study that examined the relative effectiveness of 20+ strategies for extending the commercial life of mature pharmaceutical products, the new dosage form (e.g., patch, liquid) was the most commonly used strategy. This was followed by the publication strategy demonstrating superior clinical attributes (safety, efficacy, convenience), new indications, expanding into new emerging markets, packaging innovation (e.g., co-packaging with complementary drug), labelling changes, fixed-dose combinations (FDCs) and over-the-counter (OTC) switching strategies for commercial values.

Today, in the face of dwindling drug pipelines, stringent drug regulations and blockbusters crossing their patent exclusivity, mature and established products offer an opportunity for companies to sustain their revenues and bottom lines in the increasingly challenging pharmaceutical market.

Compared to new products, mature products typically consume considerably less energy and resources for their maintenance and promotion. However, due to a changing regulatory landscape, the data and documentation requirements for all products—including those that are well established—have increased significantly.

In such a demanding environment, several companies have either sold or are considering selling off their portfolios of established products to generic manufacturers. Any company that owns mature products, including generic manufacturers, must perform pharmacovigilance (PV) activities, maintain regulatory dossiers and labels and conduct benefit-risk management so as to maintain their licenses. Compliance to these regulatory requirements is mandatory and noncompliance can lead to critical regulatory actions and considerable financial implications for the company. Additionally, decline in revenues and profitability from retiring blockbusters exerts intense cost pressures, necessitating companies to look for ways and means to reduce their maintenance expenses.

A New Paradigm for Managing Mature Products

Rather than handling all products in the same way, organizations have an opportunity to look at managing mature products differently and more efficiently, in order to allow them to focus their resources on new products. As the profile of a mature product is more stable, while many of the regulatory requirements remain the same, the amount of resources spent managing the product can usually be reduced. In some aspects, such as the frequency of PSUR production, the regulations also support a more streamlined approach. Although aspects such as signal detection activities need to be maintained, there are opportunities to take a more pragmatic approach by reducing the frequency of many routine activities.

This white paper discusses various activities required for maintenance of mature pharmaceutical products in the market, advantages of an integrated approach to their lifecycle maintenance and the benefits of working with a partner who can deliver such integration.

Maintenance activities to support mature pharmaceutical products

The activities required for maintaining mature products traverse three main areas that are detailed below. Typically these functional teams are not integrated, yet they are highly dependent on each other along with support functions like legal, finance and CMC.

Safety and risk management support

- Expedited and aggregate safety reporting
- Signal detection and management
- Benefit-risk assessment and risk management (including risk communication and safety label updates, designing and updating Risk Management Plans)

Regulatory support

- License maintenance and variations
- Label maintenance and updates
- Maintaining manufacturing and quality compliance documentation
- Dossiers compilation, submissions and interaction with regulatory authorities for approval in new markets/indications and for new formulations

Post-approval support

- Registration and post-approval studies
- Medical information support for new markets/indications and for new formulations

While each of these activities is required across the product lifecycle, the level of focus on each is typically different for mature products compared with those in the early stages post-approval. The activities are focused on product maintenance and compliance with regulations to keep the product on the market, filing for line extensions or introducing the product to new markets.

Today's Regulatory Landscape Demands New Expertise

Regulations for the healthcare industry have grown increasingly stringent and undergone significant change over the last few years. Data and documentation requirements have increased considerably even for mature products and in emerging markets. With the evolution of new Good Pharmacovigilance Practices (GVP) Guidelines in Europe many other regions now follow new and more rigorous PV standards. These standards require electronic reporting of individual and aggregate safety reports, maintaining pharmacovigilance system master files (PSMF) and multiple safety data exchange agreements (SDEA), having a well-documented signal detection and management process, and conducting continuous benefit-risk assessment of products with systematic risk management and mitigation measures—the effectiveness of which need to be evaluated from time to time. Similarly, in addition to the initial marketing approval of healthcare products, organizations need to maintain and renew their licenses by generating efficacy, safety, quality and manufacturing data, which needs be reported to regulators wherever the product is marketed. Variations need to be filed and regulatory approvals obtained for significant changes to formulations, manufacturing processes/sites or label contents.

All this requires a large skilled workforce with knowledge of relevant regulations in different regions. Similarly, launching new products or formulations in new markets requires scientific support in terms of designing and conducting registration and post-approval studies, providing medical information support for appropriate promotion of products and responding to product-related queries from healthcare professionals and sales personnel for ensuring effective and safe use of the product. This requires medically trained resources with adequate product knowledge. Such multifunctional requirements for knowledge, skills and a great deal of coordination make maintenance of healthcare products a complex and challenging task.

Organizations that implement a disintegrated approach to maintenance risk having disparate functions and teams looking after individual activities in different markets in a disjointed manner. This may lead to the generation of a significant amount of fragmented data and documentation at different locations, at different time points. Moreover, it requires a large team with different skillsets spread across geographies, large budgets and a significant amount of management time and energies in oversight and coordination of various activities.

There is tremendous benefit in having an overarching strategy to product maintenance that looks at groups of activities as a continuum, deploying efficiently structured teams to carry out these activities in a coordinated fashion, leading to increased efficiencies, cost savings and reduced management time and energies in oversight. Let us look at how this can be done in a pragmatic manner, taking into consideration the different nature and requirements for these activities.

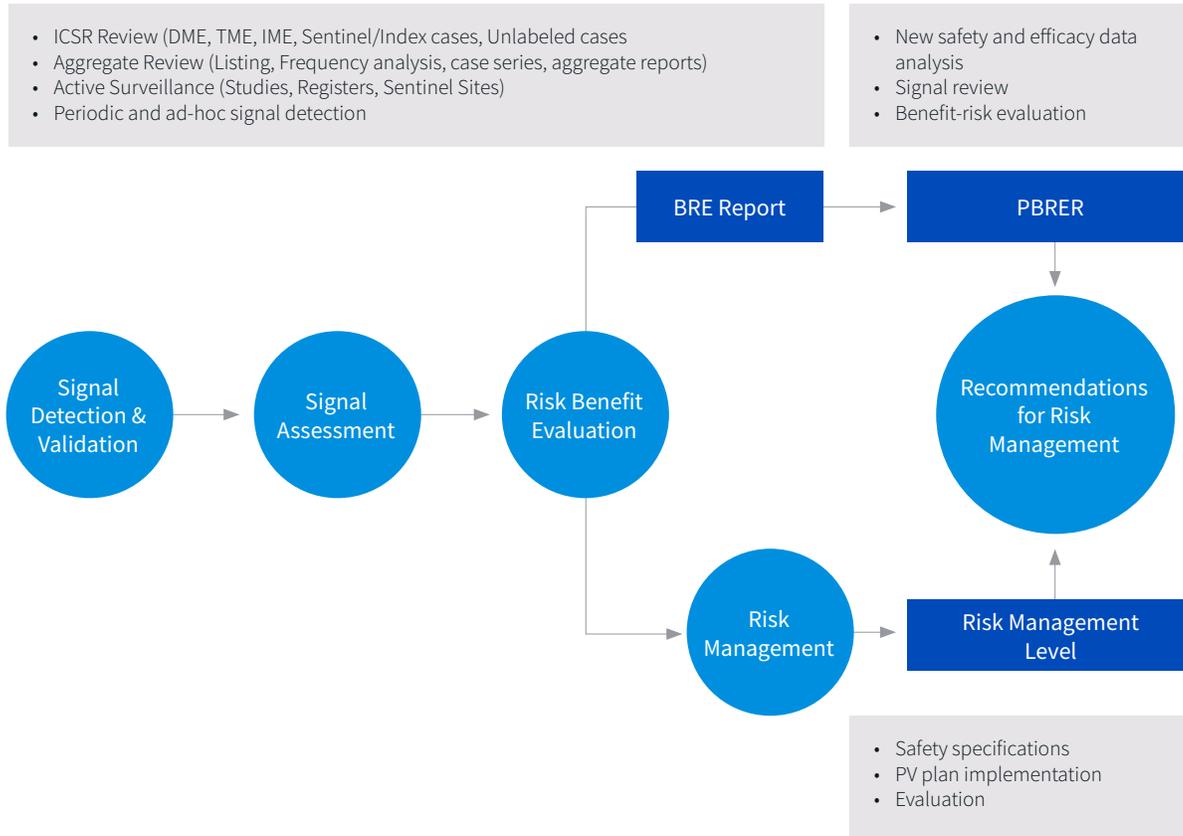
The Safety Continuum

Lifecycle management (LCM) is a set of activities performed by many groups within a company to ensure that the product remains safe and effective for patients and healthcare practitioners (HCPs). PV is one of the central functions supporting LCM and is responsible for continually monitoring the safety profile of the drug to ensure the benefits of the product outweigh the risks in the population using the drug.

While a product's safety profile is more stable in the post-approval stage, it often goes through many changes due to increasing exposure, differences in physician practices, new or untested drug interactions and pharmacogenetic variations. As a result, continual close monitoring of the drug's benefit-risk profile is required and carried out through a variety of PV activities that include collection and assessment of reports of adverse drug reactions from all sources, periodic and ad hoc review of aggregate safety data and signal detection activities in order to identify new safety issues or new aspects of those already labeled. The ongoing benefit-risk evaluation of healthcare products is carried out at different time points to decide if the product is suitable to remain on the market. However, for mature products the safety profile is usually much more stable and well defined; therefore, although PV activities are still necessary, the degree of scrutiny required is generally less.

In addition to designing and updating Risk Management Plans, risk management for healthcare products may require risk-mitigation activities appropriate for the specific risks the product entails, beyond routine PV. Such activities may include risk communication to various stakeholders (regulators, healthcare professionals, patients and the general public), educational and other risk-mitigation activities for patients and HCPs to ensure appropriate use of the product and sometimes designing special strategies and distribution channels for restricting access. All of these activities—from single-case, adverse-event processing to signal identification and risk management—are linked to one another and form the safety continuum.

Figure 1: The Safety Continuum



Signal Management

Signal management—defined as the set of activities performed to identify new risks or changes in character or severity of a known risk—remains an essential component in assuring the safe use of a drug throughout its lifecycle. Ongoing signal management provides a continual risk assessment of the product through many coordinated activities completed both within and external to the PV team. The analysis/assessment and related actions following the validation of a signal are optimally managed in a multifunctional team, e.g., a safety review committee, with actions performed by many functional groups. Validated signals or identified risks must be managed and mitigated, requiring actions such as communication, education and at times changes in manufacturing.

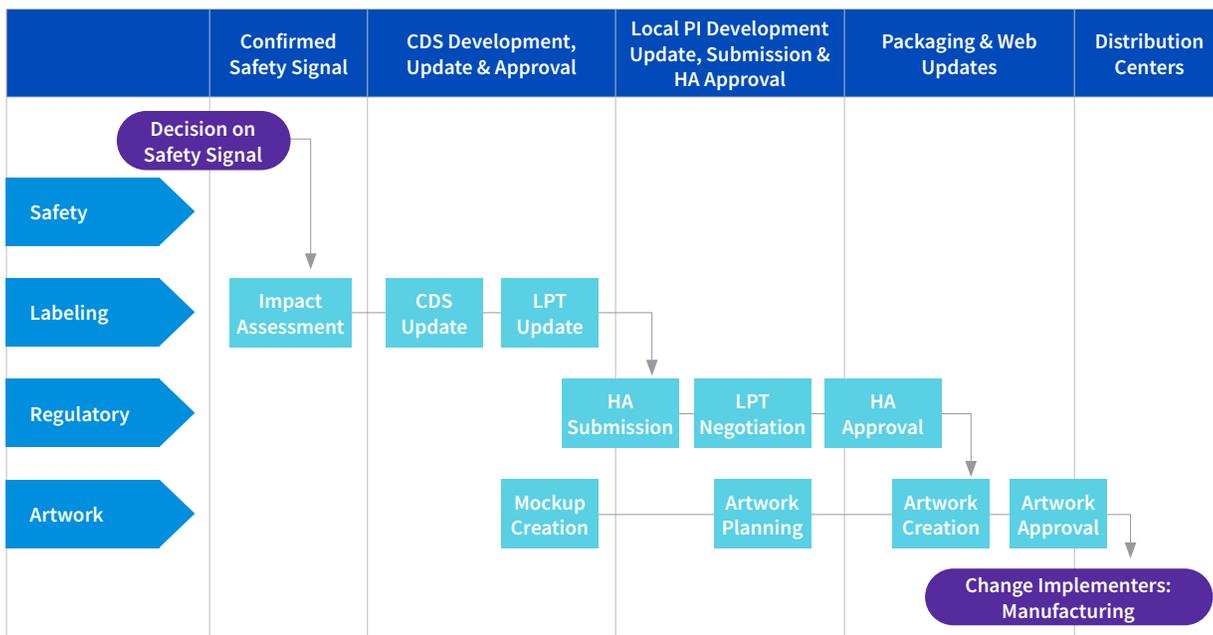
Management of new risks or a change in character of a known risk can often be mitigated by alerting patients and HCPs to the identification of the risk and potential methods to avoid or minimize the risk. This usually requires discussions with regulators, possible changes in the label with new educational activities, and at times direct communications. If the situation becomes urgent, then in addition to regulatory communication, rapid communication such as a press release, website postings and e-mails must be initiated, as well as subsequent educational activities undertaken. Groups such as Regulatory Affairs, Medical Affairs, Marketing, IT, Medical Information and R&D must be involved. In certain cases, safety findings require further evaluation, necessitating studies. Epidemiology, non-interventional and interventional, and thus, additional groups, clinical affairs and clinical operations must collaborate to complete these activities. In summary, signal management remains an indispensable part of LCM and often encompasses multifunctional expertise and activities within a company.

Signal Detection to Implementation of the Label

A label change is an example of a truly collaborative and cross-functional process that has a high degree of operational complexity and is often an outcome from signal management, subsequent to the validation or confirmation of a safety signal. The label change communicates formally important and, at times, essential information to regulators, patients and HCPs regarding the safe use of a product. In order to complete a safety-driven label change, an organization must have written practices in place to organize the different functional groups with the required expertise.

The precursor to the label is the company core data sheet (CCDS), which includes the minimum safety relevant information that needs to be present in product labels and any local labelling information for different geographies can be derived from this. For a mature product, there is a significant volume of data relating to safety and efficacy to be managed. Regulations require the MAH to promptly and frequently update the CCDS to reflect any new safety signals, efficacy data supporting new indications, warnings, etc. Further, these updates in the CCDS need to reflect accurately in the product's label within pre-defined timelines so as to meet the global and local compliance requirements. Any update to the CCDS triggers the need to update the local labeling documents of each country. Complexity increases when these local labelling documents are in a different language, with differing content. Additionally, for companies with multiple products approved in multiple countries, the management of structured product labeling (SPL) both global and local is an enormous task. It includes maintaining and updating the CCDS for all products, evaluating the need for changes to the CCDS and local labels, comparing local labels with the CCDS to ensure consistency and documenting the rationale for labeling decisions.

Figure 2: Signal Detection to Label Implementation



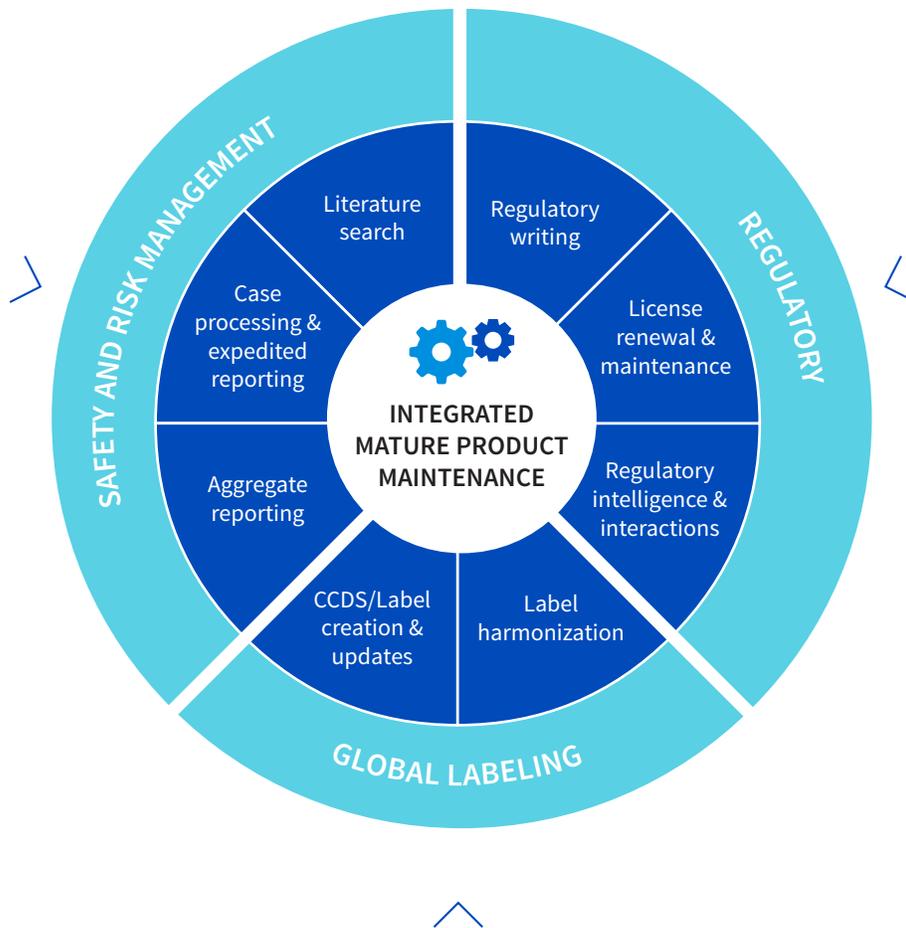
It is evident that LCM and monitoring of a product's benefit-risk profile is a complex process, yet companies can optimize their oversight of these activities and implement processes that mitigate risk and facilitate effective collaboration. For mature products with an established safety profile, most of the label changes are not driven through changes to the core product safety profile, rather meeting the differences in local requirements as the product is introduced to new markets. Therefore, companies have an opportunity to apply a different focus on what is required to manage mature products compared to those with a more dynamic safety profile.

The Regulatory Continuum

To meet regulatory obligations and manage most of the critical processes such as license and product lifecycle maintenance, most pharma companies have developed detailed SOPs for every step in the process and implemented comprehensive monitoring and governance plans. Despite these stringent measures, meeting the timelines while ensuring accuracy of information for health authority submissions poses a challenge because of the involvement of multiple teams and stakeholders from different geographies. In many cases, highly trained resources spend time in relatively simple and routine logistical activities such as cross-functional coordination and project tracking just to ensure adherence to submission deadlines. With the increasing challenges of cost pressure, headcount freezes and frequently changing regulatory requirements, pharmaceutical companies are adopting a variety of operating models to remain competitive and meet their tactical requirements for individual processes.

Adopting an integrated regulatory service-providing model that has a flexible matrix structure can promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain requirements. This model provides an opportunity to better integrate the different activities of regulatory, safety and risk management and labeling to lower the maintenance costs and maximize product value.

Figure 3: Integrated Mature Product Maintenance



Below are some of the strategies or requirements that are generally employed for maintenance or to increase commercial value of mature products and examples of an efficient operating system where an integrated team model composed of regulatory, safety and labeling experts can expedite and benefit how organizations maintain mature products.

Dossier Repurposing

With the slowing growth in developed markets, biopharmaceutical companies have made substantial investments in expanding into emerging markets. Aligning regulatory strategy across countries saves time and cost, and results in quicker access to patients. Hence, it is a logical approach to reuse and reformat the core dossier submitted in developed and highly regulated countries to meet region- or country-specific registration requirements. Development of, and regulatory approval for, 'new uses' of already-approved drugs is an important source of innovation for most mature products. This provides an opportunity to reuse the sections or data from the already-submitted dossiers to support the new application with its specific requirements. For appropriate mature products with well-established safety and efficacy, many companies will consider switching their status from prescription to OTC. Agencies like the U.S. FDA, UK MHRA and TGA Australia have defined guidelines and procedures to change the status of a product from prescription to OTC by submitting an application containing proper justification.

License Maintenance and Renewals

Marketing Authorization Holders (MAH) of pharmaceutical products are responsible for validating the effects of any manufacturing or product-quality (generally CMC) related changes to the identity, strength, quality, purity and potency of the drug as these factors can affect the safety or efficacy of the drug. CMC changes are a significant source of license maintenance activity and are inevitable due to many reasons, including continuous process improvement in manufacturing and quality of the product, changing business needs or implementation of regulatory authority suggestions. Pharmaceutical companies are required to notify the regulatory agencies of a change to the conditions established in an approved application or process in accordance with the region-specific regulatory requirements. In the U.S., post-approval CMC changes to established conditions need prior approval: a PAS application for substantial changes, a CBE-30 supplement for moderate changes or an annual report for minimal changes. In the EU, variation applications need to be filed based on the extent of changes (Type II, IB or IA variations). Similarly, for an extension of the validity of an initial marketing authorization, which can be for a fixed or indefinite period of time, renewal applications need to be submitted in eCTD format with a certain set of documents including product label, package leaflet, RMP, addendum to quality overall summary and clinical overview.

All regulatory agencies ensure the quality of drugs by carefully monitoring drug manufacturers' compliance with their cGMP regulations in terms of the methods, facilities and controls used in manufacturing, processing and packing of a drug product. Deviations or violations from cGMP requirements can lead to numerous regulatory actions, including warning letters and import alerts. To manufacture and supply the drug products, pharma companies are periodically required to obtain site registration renewals. This means that for continuous drug supply, companies need to initiate activities ahead of expiration of the country product licenses and site registrations. License maintenance and renewal activities are critical, and need coordination of GMP and quality-related documentation from several stakeholders located across multiple sites, including manufacturing, QA/QC, product development, safety, regulatory, commercial and strategy teams.

Mature Product Lifecycle Management – A Case Study

A meaningful way to address the challenges in today's complex regulatory environment is to focus on an integrated team approach for product LCM to manage products and related knowledge in a transparent and seamless manner, as well as improve regulatory compliance. Most pharmaceutical companies suffer from virtual walls between the functional silos, with product and process data being separated, thus making it difficult for cross-functional information to flow quickly and securely.

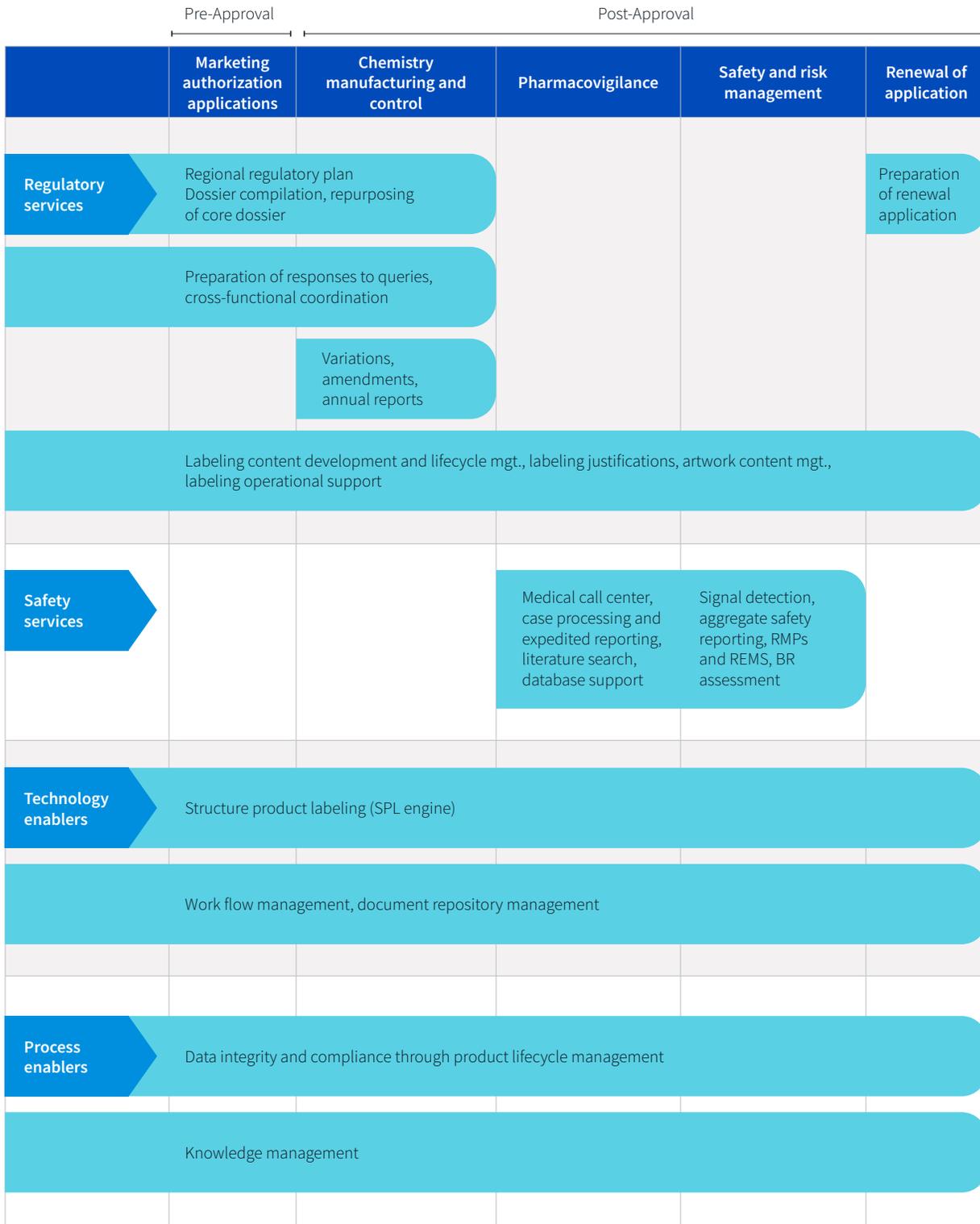
Labcorp Drug Development has successfully delivered comprehensive product LCM support to a large generics client by integrating regulatory, safety, risk management and product labeling operations. With the client's products being manufactured at various locations worldwide, and teams located in different geographies, the main challenge was to manage the data generated across the different locations and regulatory submissions. A dedicated cross-functional team at Labcorp Drug Development invested in acquiring in-depth knowledge of the product portfolio, various regulatory information management systems and publishing tools. The knowledge base provided a useful repository and allowed us to identify potential risks early, consistently meet high quality standards, quickly address emerging problems, improve efficiency and finally reduce the need for regulatory oversight from the client. Labcorp Drug Development now provides end-to-end PV support (ICSR processing, aggregate safety reporting, signal detection to labeling updates) for 350+ products of this client across various therapeutic areas. Any newly identified risk from routine individual and aggregate review of cases is communicated to the client. A core group—including safety and risk management staff, the QPPV office and key client stakeholders—meets every quarter to discuss the cumulative safety data for the marketed products. During these meetings, the important identified and potential risks for products are presented to the client and a final decision is taken on the inclusion of these risks in the safety monitoring plan of these products in the next review period. Based on the level of risk, Labcorp Drug Development helps to proactively manage the risks by generating risk-management plans (RMPs) and risk-mitigation strategies. Additionally, while authoring aggregate safety reports, the writing team collaborates with the case processing team for generating case line listings, making causality assessment and verifying the data. This reduces the dependency on the client by bridging the gap between case processing and aggregate reporting, and ensures data consistency, quality and regulatory compliance. The product labeling team in conjunction with the safety and regulatory teams maintains labels to keep the product safety up-to-date and meet regulatory compliance. Labcorp Drug Development leverages its regulatory intelligence to proactively track the updates to the reference label, or any health authority warnings or precautions and apply the same to the client's generic product labels in a predefined timeframe to avoid non-compliance. Labcorp Drug Development updates approximately 200 labels (including artwork) annually for this client.

The regulatory affairs team manages the CMC-related changes in terms of compiling and submitting annual reports, supplements, variation and site renewal application. A specific example of efficiency gain, compliance and reduction in regulatory oversight is Labcorp Drug Development's contribution in harmonization of the client's annual report submissions across different sites. Annual reports need to be submitted by the applicant within 60 days of the anniversary date of the U.S. approval of the application. Prior to using this outsourcing model, the client's regulatory compliance was at a record low of 50%. With the issuance of the Draft Guidance for CMC Post-approval Manufacturing Changes Reportable in Annual Reports in 2010, the scope of information that needed to be reported in the annual report had increased. Labcorp Drug Development helped the client comply with the draft guidance before the final guidance came into effect, update its SOPs and establish a proactive working environment. Labcorp Drug Development continues to play a key role in helping them with the entire U.S. product portfolio of 270+ products to achieve 100% compliance for the annual reports submitted to U.S. FDA.

The team at Labcorp Drug Development also tracks and manages the regulatory submission calendar for different submissions such as U.S. annual reports and aggregate safety reports, and different dates such as license expiration dates and renewal dates. For products whose licenses need to be renewed, the cross-functional team collaborates to trigger actions, support the renewal application by authoring and providing the required documentation such as product label, package leaflet, RMP, quality overall summary and clinical overview. We help the client author nonclinical and clinical overviews to support their marketing authorization application by providing the expert reports signed by globally recognized experts.

This entire integrated process enhances communication and knowledge management by leveraging subject matter expertise across the organization. It also brings parity to the regulatory oversight of marketed products, leading to enhanced LCM. Thus, leveraging the integrated regulatory and safety service model leads to better management of post-approval changes by both pharmaceutical companies and regulators.

Figure 4: Mature Products – Lifecycle Management



Post-Approval Support

Expanding the use of mature products in new, especially emerging, markets and extending product use through the approval of new indications and innovative formulations requires undertaking local registration studies. These studies, though not as intense as Phase I to III developmental clinical trials for new drugs, still need scientific rigor and adequate resource. Designing and undertaking such studies is often done either by the local affiliate of the company or outsourced since regulatory interaction, local knowledge and availability of clinical research and monitoring support is an advantage. Even after the product is registered and marketed there are commercial benefits in undertaking post-approval studies (interventional or observational) for comparative effectiveness and outcomes research. Companies benefit by collaborating with a partner with local knowledge and skilled resources. Products on the market require medical information support. This entails responding to physician queries on the appropriate use of the product, its safety and benefits to their patients as well as supporting field personnel for scientifically promoting the products with relevant and most recent published information. Generation of standard and customized responses to medical queries and developing an easy-to-retrieve database of frequently asked queries is a necessity. A well-trained team of medical information personnel can provide these services under the guidance and supervision of product specialist physicians.

An Analysis of Operating Models to Support Mature Products

Assuming a company has decided to retain its portfolio of mature products, most organizations typically apply one of three operating models.

The first is essentially status quo. The organization uses the same resources and processes to manage mature products, meaning that all safety and regulatory activities are performed in the same way regardless of whether a product has been on the market for one year or 20 years. The advantage with this approach is that it's easier to manage a single set of processes across the organization and apply them to all staff regardless of geography or the products they support. It also typically means that a high degree of rigor is applied to the management of mature products. However, it's usually a more expensive model and though in theory it means that each product is getting the same attention, in reality newer products in late stage development or around the peri-approval period are prioritized. The mature products are de-prioritized, and often neglected, resulting in delayed submissions in emerging markets or even missed deadlines for routine deliverables.

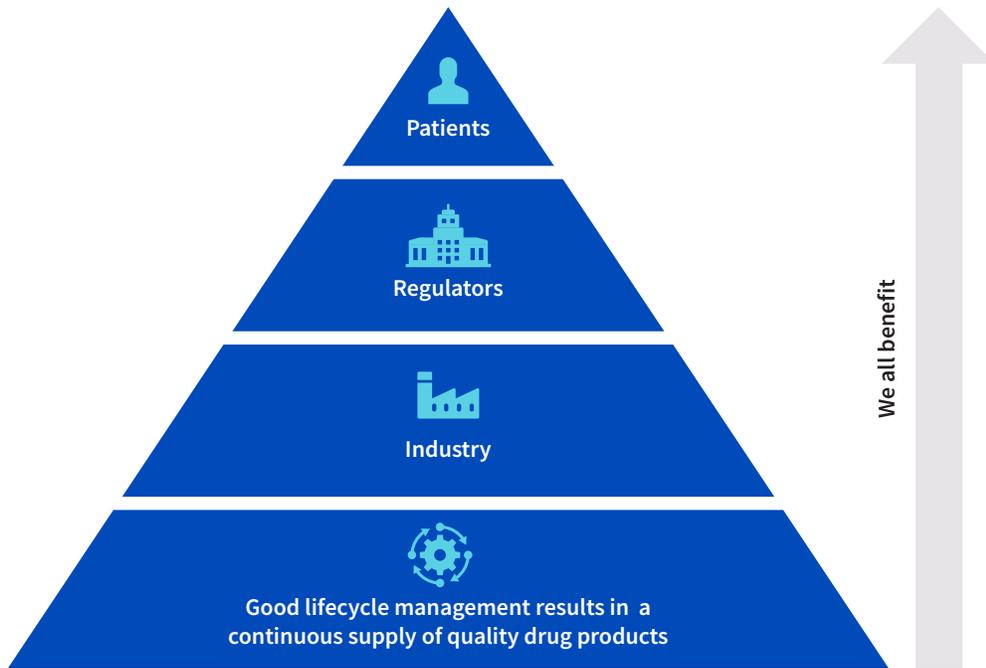
The second approach taken by some companies is to manage the mature products as though they are a separate part of the business, by assigning specific dedicated internal resources and even developing processes unique to the mature products. The objective for this approach is greater efficiency, yet still ensuring that the products receive adequate focus in terms of LCM. Typically the organizational re-alignment will create a simplified structure with less management overhead coupled with a pragmatic approach to processes. From a safety perspective, examples of improving efficiency include reducing the frequency of signal-detection activities to quarterly or semi-annually, and developing new templates and approaches to streamline the content of aggregate reports, while remaining compliant with regulations. By taking a leaner approach to the management of mature products, companies will usually realize cost benefits in terms of resource utilization, while ensuring that the maintenance of the products remains compliant and not de-prioritized at the expense of newer products in the portfolio.

The third approach taken is by outsourcing the maintenance of the mature product portfolio to a service provider. This has the obvious advantage of allowing internal resources to focus on products in late-stage development and those that are new to the market, while providing a model that dedicates resources to focus on managing the mature products.

Ideally the provider should have the ability to manage the end-to-end safety and regulatory deliverables required to support mature products, both in major geographies but also, critically, in emerging markets. From a process perspective, the approach taken may follow either of the principles laid out above. Any supplier should be able to support the portfolio by using the same processes that the client uses for the rest of their products or, if the company wishes to drive cost-savings further, they may ask the provider to use their own leaner processes and technologies to gain further efficiencies. As the relationship develops, the company may then adopt similar practices to drive the same efficiencies across different stages of the product lifecycle. In addition to the budgetary aspects of using a provider, adequate internal resources are still needed to support the supplier and ensure they are given access to necessary data. However, over time the amount of internal resources required will diminish, and the provider will be able to manage the safety and regulatory activities to support the entire mature product portfolio.

In conclusion, whether activities are managed internally or by a service provider, creating an environment where information from all stages of a product's lifecycle is updated and readily available to all stakeholders is critical to success in managing a product across the safety and regulatory continuum.

Figure 5: Industry Value Pyramid



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