White Paper

Emerging Market Expansion Strategies

ANKIT TYAGI, M.S., MBA., Director, Regulatory Affairs and Drug Development Solutions, IQVIA
AMAR TANDON, MBA., Director, Regulatory Affairs and Drug Development Solutions, IQVIA
GAURAV AHUJA, M.PHARM., Senior Manager, Regulatory Affairs and Drug Development Solutions, IQVIA

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Introduction

A regulatory strategy is not only about selecting the right pathway, such as BLA, NDA, or MAA, for drug approval. It also requires a comprehensive understanding of the drug development process, constant adaptation to the dynamic regulatory environment, knowledge about the local market, and the ability to leverage regulatory requirements in a way that can provide a competitive advantage.

Emerging markets represent a significant opportunity for pharmaceutical companies, accounting for 85% of the world's population[1]. The use of medicines in Latin America and Asia will grow faster than other regions over the next five years[2]. However, navigating the regulatory landscape in these markets presents unique challenges. Health Authorities in emerging markets are implementing stricter regulations and frequently amending requirements, making it essential for companies to develop robust strategies for regulatory approval and lifecycle management.

This white paper explores the critical aspects of expanding operations into emerging markets, focusing on clinical trials, regulatory operations, quality assurance, supply chain coordination, commercial considerations, and lifecycle maintenance. By understanding and addressing these key areas, pharmaceutical companies can successfully navigate the complexities of emerging markets and capitalize on the opportunities they offer.

Figure 1: Critical aspects of emerging market considerations

Commercial considerations

Commercial considerations are vital for the successful launch and sustainability of pharmaceutical products. These involve a comprehensive evaluation of various factors to ensure the product aligns with market needs and regulatory requirements. Key aspects to consider include:

Epidemiological insights and disease landscape

Understanding epidemiological data and the disease landscape is crucial for assessing commercial sustainability. This involves evaluating unmet medical needs within a region and determining if a drug qualifies for orphan drug designation. Health Authorities (HAs) can approve compassionate and emergency use applications based on these unmet needs, as demonstrated by Remdesivir in India and COVID-19 vaccines globally.

Patent and Intellectual Property (IP) considerations

Assessing patent laws, the duration of patent protection, and a country's adherence to international IP treaties is essential. For example, compulsory licensing allows local manufacturers to produce a drug for critical unmet needs while the innovator's patent is still valid, thereby enhancing affordability.

Regulatory pathways

Choosing the appropriate regulatory pathway is crucial, depending on existing approvals, unmet medical needs, or mutual recognition agreements. This decision significantly affects the time to market and the overall success of the product launch.

The formation of new consortiums and partnerships between developed and emerging markets creates significant opportunities. For example, Project Orbis is a global initiative led by the U.S. FDA, with participating agencies including the TGA (Australia), Health Canada, Swissmedic, the UK MHRA, Singapore HSA, and Brazil's ANVISA. This consortium aims to expedite patients' access to innovative cancer treatments worldwide.

ACCESS Consortium is another example, comprising regulatory authorities from Australia, Canada, Singapore, Switzerland, and the UK. This group collaborates to streamline regulatory processes, reduce duplication, and ensure timely access to safe and effective therapeutic products.

In the APAC region, the ASEAN Joint Assessment Coordinating Group (JACG) serves a similar purpose, facilitating cooperation among regulatory bodies to enhance the approval process for new therapies.

Reimbursement strategies

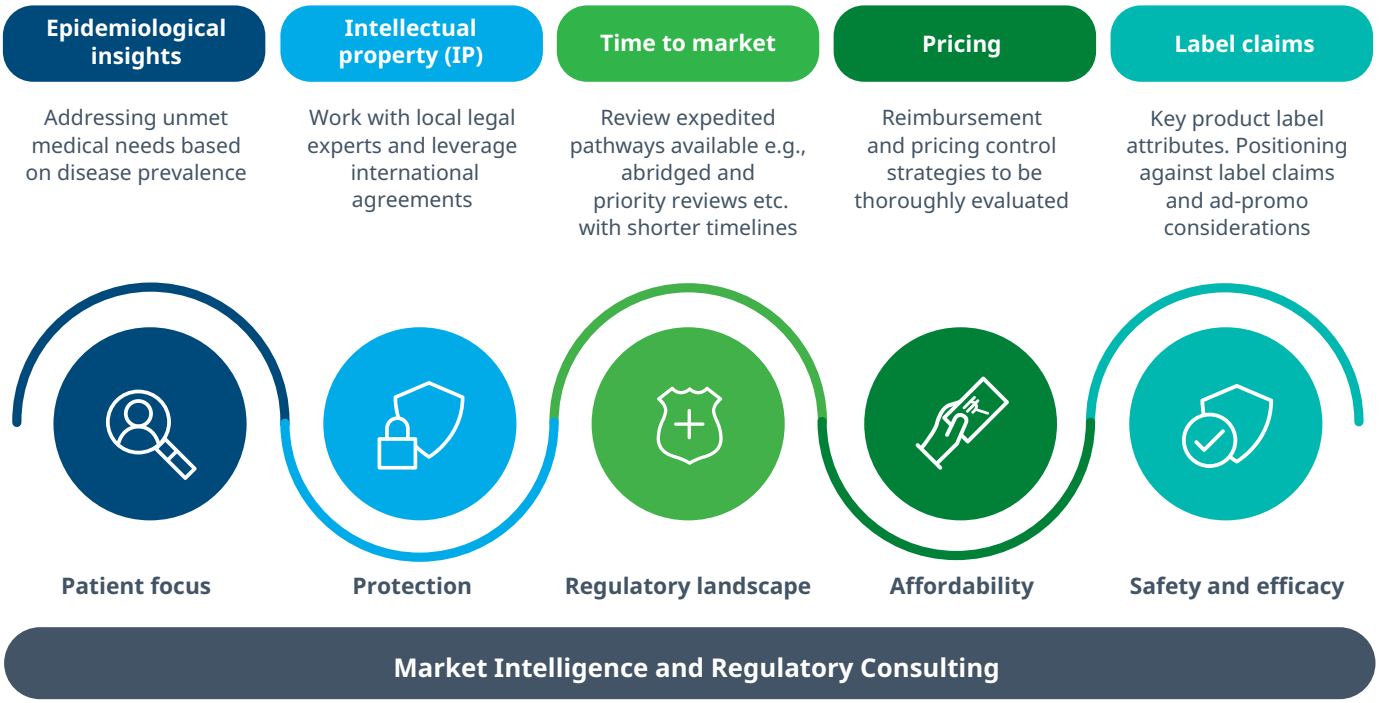
Reimbursement strategies must be meticulously planned. In some emerging markets, local manufacturing is a prerequisite for public reimbursement, as seen in Turkey, Russia, Indonesia, and Algeria. Ensuring eligibility for public reimbursement can influence market access and affordability.

Strategic use of disease prevalence data

Strategically using disease prevalence data helps determine which indications to register in emerging markets. In certain markets, fewer indications may be registered compared to the reference market, guided by market intelligence and disease prevalence.

This approach addresses specific market needs and reduces pharmacovigilance burdens. For instance, a pediatric indication might be omitted in an emerging market if there is insufficient pediatric disease data. Conversely, some emerging markets require the same indications as the reference agency, necessitating case-by-case strategic planning.

Figure 2: Key commercial considerations



Local clinical trial considerations

A critical aspect for emerging markets is the requirement for local clinical trials. The acceptance of foreign clinical trial data varies significantly across countries, impacting strategic planning for drug development. This variation can lead to additional costs and extended timelines for market entry if local clinical trials are mandated.

In some regions, local clinical data is essential to meet regulatory standards, while others may accept foreign data with certain conditions. This necessitates a tailored approach to regulatory strategy, ensuring compliance and optimizing resource allocation.

Understanding these diverse requirements is crucial for pharmaceutical companies aiming to navigate the complexities of global drug development and market entry.

Acceptance of foreign data

Singapore, Malaysia, and Hong Kong accept clinical trial data from reference agencies such as the EU and US, without requiring local trials or bridging studies.

For China, Taiwan, and LatAm, if an innovator product has sufficient foreign clinical study data demonstrating safety and efficacy, and shows no ethnic sensitivity, additional clinical trials may not be required. However, if the drug lacks ethnic sensitivity data or existing data suggests ethnic sensitivity, relevant bridging clinical trials would be necessary.

Bridging studies

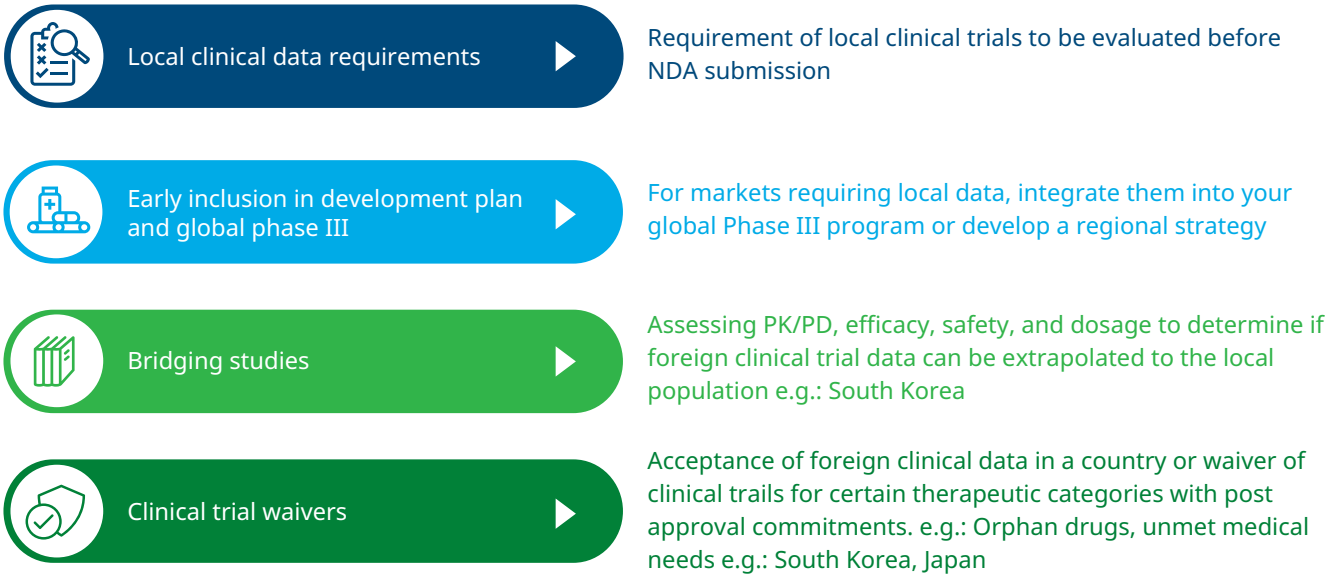
Bridging studies are clinical studies conducted in a new region or country to provide pharmacokinetic, safety, efficacy, or ethnic sensitivity data to extrapolate foreign clinical data to the local population. They play a crucial role in drug development and approval within global drug development programs.

Clinical trial waiver conditions

In some markets, clinical trial waivers based on foreign clinical data are acceptable for certain therapeutic categories, such as orphan drugs and those addressing unmet medical needs with a commitment of post marketing trials.

In India, a waiver for local clinical trials can be granted under specific conditions, inclusion of India in global Phase II and III trials, no ethnic sensitivity, a written commitment to conduct Phase IV trials, or the drug's approval in countries specified by the Central Licensing Authority, provided no major unexpected adverse events have been reported.

Figure 3: Local clinical trials considerations



Importance of alternative regulatory pathways in medicinal product registration

Patient demand for faster access to new medicines, particularly in areas with high unmet medical needs, is increasing. Regulatory approvals play a critical role in this path towards access, and thus, regulators are crucial in meeting these patients' needs by establishing appropriate registration pathways.

Many regulatory agencies have already begun to address patient needs by creating new or alternative registration pathways. These pathways aim to expedite the development, submission, or review of marketing authorizations for specific types of products.

Reliance pathways to facilitate regulatory decisions

In a verification procedure, the aim is to reduce duplication of review efforts by health authorities by allowing products authorized by Stringent Regulatory Authorities (SRAs) to be marketed locally in the importing country. The National Regulatory Authority (NRA) in the importing country verifies that the product's local registration matches the SRA authorization and ensures the product use, dosage, precautions conform to the reference authorization. Additionally, the product must be equal or similar to that approved by the reference agency and should be approved within a specified time period.

The abridged review procedure relies on assessments of scientific data reviewed and accepted by SRAs but includes an independent review of certain parts of the registration dossier relevant to local conditions. This could include a review of CMC data in relation to climatic conditions, zone specific stability data and a benefit-risk assessment in relation to use in the local ethnic population, culture, and patterns of disease. The product must be equal or similar to that approved by the reference agency.

In Singapore, drugs approved by two reference agencies undergo a verification process with a 60-day review timeline, compared to the standard 270 days. If only one agency approves, the abridged pathway is taken, with a 180-day review timeline.

Expedited regulatory pathways for medicines targeting unmet medical needs

EXPEDITED REVIEW

Expedited review speeds up the review process for certain products, enabling faster approval. The review time is substantially shorter than that of a standard review, based on the product's importance to public health e.g., Brazil, China, Egypt, Saudi Arabia, Singapore, Indonesia, South Korea, and Israel.

EXPEDITED SUBMISSION (ROLLING SUBMISSIONS)

Expedited submissions or rolling submissions allow information, data packages or CTD sections to be submitted and reviewed by regulatory agencies as they become available, even before the official submission date. This enables regulatory agencies to review data sets as soon as they are available, potentially shortening regulatory procedure review timeline e.g., South Korea.

EXPEDITED DEVELOPMENT

The objective of this approach is to expedite development which involves greater collaboration with regulatory agencies to identify options for speeding up the process or ensuring the most efficient development strategy. One such approach is, expedited approval based on less complete data (e.g., surrogate endpoints, Phase 2 data only) has been seen in Brazil, South Korea, and Taiwan.

Quality, GMP, supply chain and other considerations

Quality

When crafting a strategy for emerging markets, it's important to consider CMC (quality) aspects, given that quality is a key component of a CTD dossier. For certain emerging markets, we redact information from US and EU CTDs, as the same level of information might not be needed in these markets. It's essential to have this level of awareness when dealing with emerging markets. Some of these markets request more raw data and stability chromatograms, for instance, LATAM markets, and countries like Peru have specific stability data templates.

The strategy should consider the correct climatic zone, relevant stability data, and the minimum number of batches. Special considerations like alcohol-free and porcine-free declarations are needed for the Middle East, and there should be careful evaluation of potentially banned excipients or those known to have specific effects.

GMP

Good Manufacturing Practices (GMP) clearance or GMP confirmation for product (DP) sites, drug substance (DS) sites, packaging sites, and batch release sites submissions might be required for certain markets before submitting the MAA application dossier to Health Authorities (HA), for e.g., Australia, Taiwan, South Korea, and Turkey. In Turkey, the process could take between 6 to 9 months. Depending on the market, the inspection could either be onsite or a virtual desktop review, and these timelines should also be factored in when deciding on the overall timeline.

There are established mutual recognition agreements such as the Pharmaceutical Inspection Cooperation Scheme (PIC/S), the US and EU MRA GMP agreements, and the EAEU GMP for CIS countries.

These arrangements allow countries to accept GMP certificates from reference agencies or other countries, based on pre-agreed mutual recognition.

Country specific setup and supply chain considerations

Some of the countries necessitate establishing a local manufacturing plant, partnering with a local manufacturer, or transferring technology locally.

In some markets, such as Algeria and Vietnam, it is mandatory to have a local manufacturing plant or to partner with a local manufacturer. This requirement ensures the local economy's participation and growth but can pose significant operational and financial challenges for companies entering these markets.

Further, certain countries demand local technology transfer, ensuring that the local workforce is equipped with the necessary skills and knowledge. Countries like Argentina, Mexico, and Brazil also require QC testing for every incoming batch. These countries also necessitate transport validation, ensuring that the transportation process doesn't compromise the product's quality and safety.

Moreover, some markets like Hong Kong, Thailand, Vietnam, Cambodia, and the Philippines have stringent regulations about manufacturing and supply chain sites. These markets only allow one manufacturing or supply chain site per license. If a company wishes to establish additional manufacturing sites, they will need to acquire additional licenses.

When expanding into new markets, understanding the legal requirements for filing a MAA is crucial. These requirements vary by country. For instance, in Argentina, only a locally authorized lab with a licensed pharmacist can file a MAA. In Brazil, a locally authorized commercial importer, distributor, or manufacturer (with local QC facility) is eligible. In some countries, a native expert with a valid Power of Attorney suffices. Partnering with local distributors or labs is an option. However, due diligence and clear agreements are necessary before MAA submission.

Potential complications can arise if, per local requirements, the partner becomes the drug MAA owner and later resists transferring the MAA. Therefore, detailed contractual agreements are critical.

Other considerations

Pre-submission meetings are critical in our regulatory strategy, particularly when discussing expedited pathways or clinical trial waivers. Timeframes for these meetings should be factored into our planning.

Certificate of Pharmaceutical Product (CPP) requirements vary between the country-of-origin and the reference country. The process of obtaining these may involve either apostille or embassy legalization, each with differing timelines.

For countries not part of the Hague Apostille Convention, the process becomes more complex, requiring embassy or consular legalization. This process can take up to 2-3 months, a significant factor to consider in our strategic timelines.

Considering local aspects, such as document translation requirements and registration sample needs, is crucial in our emerging market strategy. Acknowledging these unique requirements and their varying timelines ensures a successful and timely market entry.

Post-approval strategies

In emerging markets, having a strong post-approval strategy is essential. Commercially, it's important to minimize the risk of pile-offs and stock-outs in each market. As a regulatory expert, it's crucial to develop these strategies in collaboration with commercial teams, supply and forecast planners. This starts with a thorough change control assessment, evaluating the impacts on the supply chain and global variation strategy.

Planning variation filings is vital, considering grouping variations and choosing between parallel or sequential filings to prevent supply chain disruptions. In countries like Hong Kong, where new variation filings are not permitted until previous ones are approved, understanding stock availability is crucial.

License renewals, required every five years in most markets, should be anticipated with applications submitted 6 to 12 months before license expiry. Determining if a market allows variation submission alongside renewal is a key part of the strategy.

In cases of discontinuation or license withdrawals, it's essential to ensure patient groups have alternatives and that the sponsor complies with regulatory requirements to maintain good standing with authorities and avoid penalties.

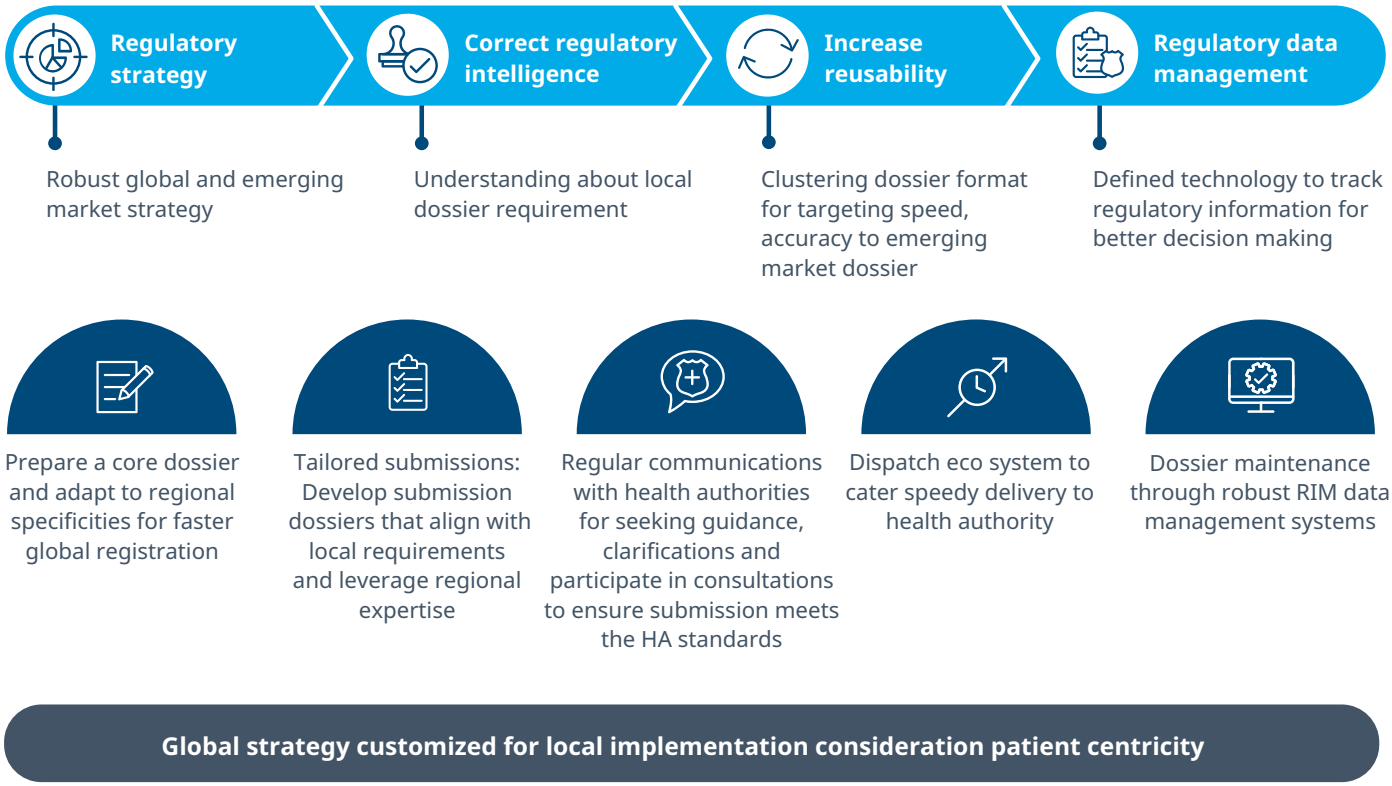
If the withdrawal market is a reference country, advance planning is necessary to ensure dependent countries aren't affected. Consider transferring the dependent market to another country entity within the same company before the reference country withdrawal.

Emerging market dossier management

The format of the dossier and content reusability are key aspects of operational efficiency and lifecycle management in emerging markets. Understanding the specific dossier submission requirements of each market, be it eCTD, NeeS, paper format, or a specific electronic format, is crucial.

Adopting a focus on content reusability in dossier submissions can significantly enhance operational efficiency. By creating adaptable content for reuse across different submissions, companies can expedite their regulatory processes. For instance, the common use of M2, M3, M4, and M5 content across GCC countries, the ECOWAS region-specific CTD format, and the ACTD format for ASEAN countries are examples of regional adoption of a common format.

Figure 4: Key consideration for dossier management



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MARCELA MINO, Senior Director, Regulatory Affairs and Drug Development Solutions

CHIKKAM RAMA MOHAN RAO, Senior Director, Regulatory Affairs and Drug Development Solutions

VERONICA GLIZER, Director, Regulatory Affairs and Drug Development Solutions

RAINA SINGH PAPLIKAR, Associate Director, Communications R&DS APAC

Conclusion

Global market expansion demands more than mere ambition; it necessitates a comprehensive understanding of the drug development process, the ability to adapt to the ever-evolving regulatory landscape, and a deep knowledge of the local market. Collaborating with regulatory team possessing both global and local expertise can ensure compliance, support business objectives, and drive international success.

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About the authors

ANKIT TYAGI, M.S., MBA.
Director Regulatory Affairs,
IQVIA

Ankit Tyagi has over 14 years of experience in regulatory Affairs, specifically in CMC and Lifecycle maintenance across emerging markets. His expertise lies in regulatory strategy, labeling strategy, submission management, and submission readiness management support. Ankit has extensive experience in handling global submissions strategies for Biologics, small molecules, and Biosimilars. He has worked with reputable companies such as Biocon, Fresenius Kabi, and Kinapse (now Syneos).

Ankit is an expert at maintaining strategic labeling and lifecycle maintenance projects, overseeing project delivery including defining project strategy, project governance, defining budget, staffing, quality management, and ensuring client satisfaction.

GAURAV AHUJA, M.PHARM.
Senior Manager, Regulatory Affairs and Drug Development Solutions, IQVIA

Gaurav Ahuja is IQVIA's Senior Manager holds 14+ years of experience and Leading Life Cycle Management (LCM) as well as Chemistry Manufacturing and Control (CMC) for Pharmaceuticals as a Subject Matter Expert. He is also leading medical devices Centre of Excellence (CoE).

AMAR TANDON, MBA.
Director Regulatory Affairs,
IQVIA

Amar has over 15 years' experience in the pharmaceutical industry, with emphasis in establishing regulatory strategy, submission management, clinical submission readiness management support, license maintenance, Regulatory and clinical data management compliance and project management.

Extensive experience establishing and handling global clinical and regulatory operations including full service and major strategic partnership projects for regulatory affairs and clinical operations; maintaining health of projects by overseeing project delivery including defining project strategy, project governance, defining budget, staffing, quality management, CAPA management, forecasting and revenue recognition.

CONTACT US
Anand Rishi
anand.rishi@iqvia.com
iqvia.com