White paper

QuintilesIMS™

Complex Generics:
Charting a new path

Complex generics offer a lucrative market for drug manufacturers, but only if they can adapt to a more complicated and challenging development process.

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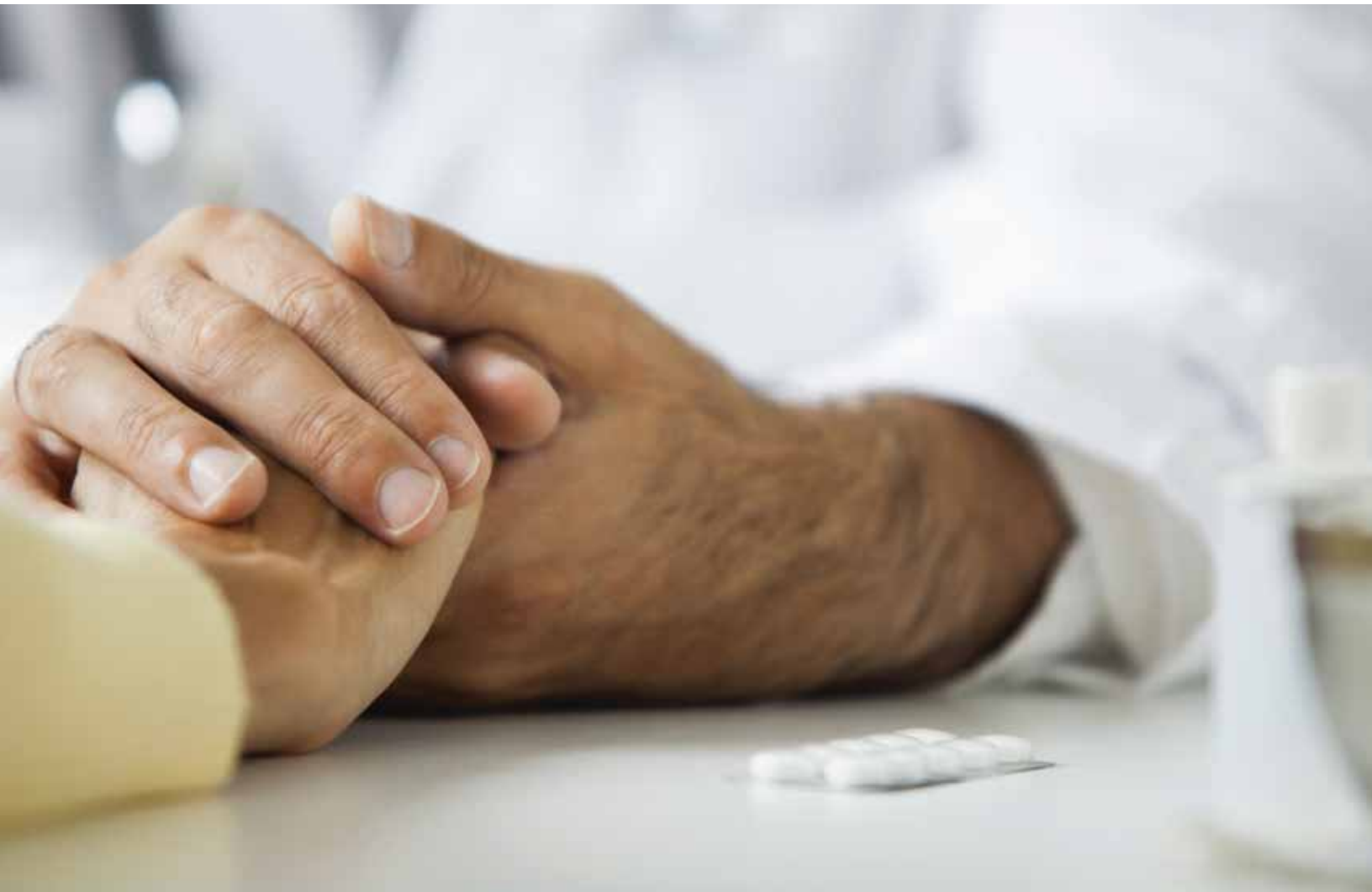

TABLE OF CONTENTS

Executive summary

Generics have been an attractive, lucrative development path for more than three decades. As the market has become saturated with simple generic products, biopharma companies are turning their focus to complex generic drugs, which deliver more value to patients by addressing additional unmet needs and which enable them to achieve market differentiation and opportunities for higher margins.

Developing complex generics in an era of rising costs and increased scrutiny over international development and manufacturing operations requires a higher level of expertise than is required for simple generics development. It demands a more sophisticated planning and development process, and a deep understanding of the regulatory, quality and health technology assessment (HTA, pricing/reimbursement) environment to bring these drugs to market.

Generics developers who can adapt their clinical development to address these added challenges while still achieving speed to market can benefit from exclusivity and considerable return on investment. While cheaper than branded options, complex generics offer biopharma companies the opportunity to capture additional value commensurate with the associated additional risk and patient benefit.

“Complex Generics: Charting a New Path” is a Quintiles thought leadership report exploring the complex generics landscape and the challenges developers face bringing these drugs to market, and offers best practice advice for overcoming obstacles in order to benefit from this profitable shift in the marketplace.

What are complex generics?

The U.S. Food and Drug Administration (FDA) defines a generic drug as one that is identical – or bioequivalent – to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

- **A simple generic** is a copy of a small molecule reference drug and is chemically identical to its branded counterpart.
- **A complex generic** is a generic that could have a complex active ingredient, complex formulation, complex route of delivery, or complex drug device combinations.

Source: U.S. FDA

The European Medicines Agency (EMA) defines a generic drug as a medicine that is developed to be the same as a medicine that has already been authorised. It contains the same active substances and is used at the same doses to treat the same diseases as the reference drug.

EMA refers to complex generics as **"hybrid medicines,"** whose "authorisation depends partly on the results of tests on the reference medicine and partly on new data from clinical trials."

Source: EMA

It is challenging, time-consuming and expensive to develop complex generics and demonstrate the equivalence, safety and efficacy of the therapy.

Challenges in developing a complex generic

As opportunities to develop simple generics are less attractive, many companies are setting their sights on complex generic drug development. The challenges in bringing complex generics to market include:

- The need to identify new commercial and regulatory strategies, and identify targeted markets and indications to address unmet patient need
- A lack of guidance which makes it incumbent to develop effective strategies to gain regulatory approval
- Competition for patients in key markets.
- Increased scrutiny from regulatory agencies for quality systems and data integrity
- The need to bring these products to market rapidly and effectively to gain limited exclusivity

These challenges add time, cost and risk to the project. Biopharma companies that choose the right partners to help with their product development and regulatory strategies can profit significantly from this next big phase in the generics marketplace.

KEY CONSIDERATIONS FOR PURSUING COMPLEX GENERICS

- Assess regulatory requirements for complex generics development including predicate products
- Conduct a detailed gap analysis of the necessary skill set to identify areas of risk
- Access guidance and relevant available data to inform the development roadmap
- Develop a robust clinical strategy
- Acquire scientific advice via regulatory meetings

Part 1: Understanding regulatory requirements and the target market

Simple generics generally have a clear development roadmap which usually includes guidance from the FDA Office of Generic Drugs (OGD) describing endpoints and data required for U.S. approval. With complex generics, developers are less likely to find regulatory guidance, which adds uncertainty and risk to the planning and design process.

Having a clear regulatory strategy that leads to product approval is crucial for these projects. To ensure they are on the right path, developers should meet with regulators early on to present their development strategy and review their study design and comparability studies before they move forward. This enables developers to optimize their program, streamline filings, and avoid surprises during the marketing application assessment process.

KEY CONSIDERATIONS FOR NAVIGATING THE REGULATORY ENVIRONMENT

- **Research similar approvals and predicate products.** In the absence of guidance from regulatory authorities, biopharma companies should review the strategy of the originator and research summaries from similar drugs to inform their development plan.
- **Be clear which regulations you need to follow and what that entails.** It is important for biopharma companies to understand these regulatory requirements from the outset and to incorporate them into the overall development plan. Most complex generics will utilize the 505(b)(2) procedure for approval in the U.S. with specific criteria for the size and scope of trials.
- **Apply Good Regulatory Practice in interactions with agencies and precedents.** Regulators won't answer open-ended questions, but they will offer targeted feedback regarding existing plans, and answer scientific questions to further hone the details.

Part 2: Planning and study design

In most cases with complex generics, the plan will require clinical studies beyond what is typical of a simple generic product, and that should be taken into account from the outset. When planning these trials, the time, location and cost of recruiting in a particular region, especially if there is competition for patients and/or site resources, should be taken into account.

KEY CONSIDERATIONS FOR PLANNING AND STUDY DESIGN

- **Complex generics often lack clear guidance from regulatory agencies.** In this respect these projects are more similar to innovative drug development, and require biopharma companies to think more strategically about the protocol, engagement with regulatory bodies, study design, location(s), trial parameters and data needed to gain approval.
- **Design with the end in mind.** As important as it is to achieve equivalence in the lab, to be successful the study design should have a clear scale up and transition plan to ensure consistent quality in the manufacturing stage.
- **Factor population and access to patients into study plans.** Biopharma companies need to understand exactly what type of patient will be required in their trials to achieve approval in their target markets. They should take into account where those patients can be accessed, and how they will accommodate the risk of attrition and non-compliance among limited patient populations.
- **Look for opportunities to accelerate and mitigate risk.** To reduce risk and speed trial results, biopharma companies may choose an adaptive design approach, in which they begin the trial with limited patient exposure. This cuts time and cost, while enabling them to adapt the protocol based on early results.

Part 3: Site selection: Right sites, right start

Biopharma companies interested in pursuing complex generics should choose partners who can navigate the unique challenges in finding trial sites that have the expertise, interest, and access to targeted patient populations. In many cases, the sites most capable of delivering these projects may not be interested in participating in a generics trial, while those that are interested may lack the experience to manage the additional investigational requirements that complex generics trials require.

To minimize the risk, biopharma companies should look for partners who have extensive site networks, and the ability and willingness to educate novice site leaders who are interested in expanding their offerings and taking on more complex projects. Because these support strategies require additional education, tools and oversight to these sites, biopharma companies should begin working with their partners on site outreach strategies early on in the research process.

KEY CONSIDERATIONS FOR SITE SELECTION

- **Choose a partner who has a demonstrated ability to locate disease specialists.** Because complex generics are relatively new, there could be skepticism among sites to participate in a complex generics trial. Many investigators may not be interested in generic drug trials due to lack of scientific or medical interest in non-novel drug trials or because they anticipate that patients themselves may be less enthusiastic about participating in a complex generics trial. Therefore, biopharma companies need a partner who understands how to identify sites with an adequate patient pool and interested in accessing generic options through trial participation.
- **Invest in sites.** An effective site strategy for complex generics includes willingness to provide additional support in cases where a site has the appropriate populations of patients and specialists but limited or no research experience. This support strategy could include providing staff, education, and/or oversight to help them ramp up their trial capabilities. This increases the likelihood that the biopharma company will have access to the necessary patients and be able to expand their site network for ongoing trials.
- **Talk-up the value proposition.** A good site selection team will encourage research naïve sites to participate in a generic trial by offering additional education and training, and communicating the value of participating in a successful complex generics trials.
- **Start early.** Biopharma companies should begin working with their partners on site outreach as early as possible to minimize lag time in recruiting, and provide enough time to train staff and upgrade site infrastructure, tools and templates prior to the first patient enrolled.

Part 4: Compliance as a competitive advantage

Biopharma companies need to carefully evaluate whether they have the equipment, training, knowledge, leadership and commitment to follow compliance rules especially in the face of pressure to cut time and cost from the project.

Along with managing the rapid timelines and complex development process, biopharma companies must be rigorous in their adherence to good manufacturing and compliance planning to avoid regulatory issues that could delay regulatory approval. Often, the development phase is rushed to expedite regulatory submission, and manufacturing and QC managers bemoan the fact that R&D staff did not take adequate care in creating, transferring and validating analytical methods and manufacturing processes.

All of these compromise increase compliance risks for any development project, but with complex generics projects compliance concerns get more complicated – especially when working with novice sites and manufacturers, or those that have only worked on simple generics projects. Complex generics development plans generally require more nuanced methods and rigorous testing to meet all efficacy, safety and equivalence goals. They also face increased compliance risks in the transition process from pilot project to manufacturing where processing issues can impact identity, quality, purity, potency and consistency from batch to batch.

KEY CONSIDERATIONS FOR GENERICS PROJECTS

- **Make a compliance plan.** Every complex generics project plan should include a compliance component that lays out what each partner needs to do to achieve compliance, and how the biopharma company will oversee and audit that compliance.
- **Have a dedicated compliance expert on the internal team.** This drives a focus on compliance throughout the lifecycle of the project, and demonstrates to regulators that project leadership has the expertise to avoid most problems, and to solve any issues that do arise.
- **Balance the need for speed with compliance.** There is enormous pressure in the generics space to be first to market, but if a drug can't win approval, or gets to market on the basis of faulty data, biopharma companies risk more than poor profits. It can devastate their brand, and present serious patient safety implications, especially when these drugs are designed to treat chronic and deadly diseases.

Conclusion

Complex generic drug development is the current wave, and companies that can adapt to a more complicated development process are positioned to profit greatly in the years to come. Biopharma companies should adopt Good Regulatory Practices in defining where, what, when, and how to achieve crucial “time-to-market” strategic and operational goals. To avoid pitfalls in the transition to complex generics, biopharma companies should choose industry partners with clinical experience and global regulatory know-how, along with site networks and quality/compliance expertise to rapidly deliver validated results. Such collaborations enable developers to optimize their study design, simplify project scope, and speed patient recruiting so they can meet the needs of regulators in shorter time lines and at lower costs, while helping to ensure the long term supply of quality product.

To learn more about how Quintiles’ complex generics offering can help you improve your probability of success, visit quintilesims.com.

About the authors

Ann Duncan

Senior Director, Therapeutic Strategy

Ann Duncan has over 35 years' experience in the pharmaceutical industry, predominantly within the contract research environment, holding global leadership roles developing project specific strategies and driving delivery of large global studies and programs in line with customer goals. Ann holds a senior leadership role for generic strategy development, aligning generic and NCE development knowledge in the evolving sphere of complex generics.

Viswanadh K

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As Director, Business Development, QuintilesIMS India, Viswanadh works closely with global generic and biopharmaceutical innovator companies for new business acquisition and positioning QuintilesIMS as a key strategic partner for clinical and commercial segments. He brings on board close to two decades of global experience in corporate development, sales & marketing, new business development and portfolio management across products and services. He holds a Senior Management Program from the prestigious Indian Institute of Management, Kolkata and a Master's in Veterinary Medicine with a specialization in Cardiovascular Physiology.

Silvina Baudino

Director, Site Managed Networks, Site & Patient Networks

Silvina Baudino has over 19 years of experience in the clinical research industry. She is actively involved in engaging with sites and customers and developing new strategies to improve projects delivery. She was previously Site Management Director, supporting QuintilesIMS's strategy to expand the pool of investigational sites, establishing partnerships and alliances with high quality sites to drive performance and ensuring excellent results and data delivery. She has also held roles with Feasibility, Project Management and Clinical Operations, both as an individual contributor and leading local and regional teams in the Americas.

Ronan Donelan

Senior Director, Regulatory Affairs

Dr. Ronan Donelan is Head of Global Regulatory Affairs Europe. In this role, he and his teams work with global clients to provide strategic and operational support on innovative pipeline, generic and marketed pharmaceutical products. He has deep expertise in the development and registration of medicinal products with successful track record in oncology, CNS, immunology and rare-diseases registration approvals. His expertise also includes strategic and operational support in the management of pharmaceutical mergers, asset acquisitions, asset divestments and asset optimisation gained both during his 20 years with QuintilesIMS and from his roles with pharma prior to joining QuintilesIMS. Dr. Donelan holds a Master's in Pharmaceutical Medicine from Trinity College Dublin and a PhD from the School of Pharmacy, Cardiff.

Peter Lassoff, Pharm.D.

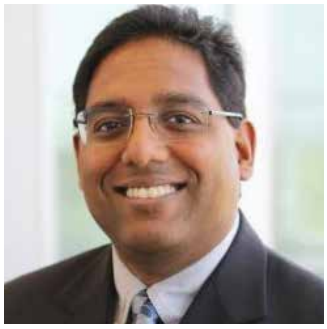
Vice President and Head, Global Regulatory Affairs

Peter has over 30 years' experience within global regulatory affairs and is presently running the Global Regulatory Affairs division of QuintilesIMS based in London. Peter has deep domain expertise in regulatory affairs and drug development, and has established and grown businesses in the regulatory outsourcing sector on a global basis. He is a conference speaker, published author, and on the Board of Supervisors for the International Center for Regulatory Science at the University of Southern California. He has extensive experience in the development and registration of complex generics and has been responsible for the registration of scores of these "hybrid" drugs.

Robert A. Rhoades

Senior Vice President, Quality & Compliance Services

With 37 years of experience, Bob Rhoades has been a preferred advisor to senior pharmaceutical and medical device executives regarding compliance and its impact on corporate direction and strategy. A skilled practitioner of both the Quality System Regulation (QSR) and the pharmaceutical cGMPs, he has designed and implemented compliance improvement initiatives for major manufacturers in the U.S., Europe, China and India. He has also worked in concert with client counsel on a wide variety of legal cases and has designed and executed quality systems programs and remediation efforts for client companies in China, Europe and India. He is frequently an invited speaker at pharmaceutical and medical device conferences in the U.S., Europe and Asia, and has authored several articles on quality-related topics.



Chris Mathura

Senior Director, Clinical Development Services Strategy

Chris Mathura has over 15 years of experience in the healthcare and clinical research industries. He has led numerous multi-disciplinary teams to develop and launch science and technology based service and product offerings that meet critical patient, sponsor, caregiver, and other stakeholder needs across the healthcare continuum. He earned a BSc in Computer Science and Mathematics from Purdue University, and an MBA from Indiana University, USA.

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