White paper

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An integrated approach
to biosimilar development & commercialization

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Executive summary

As the market for biosimilar products continues to grow, many biopharmaceutical companies trying to enter the space are struggling to overcome the unique challenges that developing such products presents. From navigating the complex global regulatory landscapes to ensuring optimal access, the development road for biosimilars is riddled with questions:

- How do we ensure speed-to-market while maintaining a high quality of clinical evidence?
- How do we maximize uptake of our biosimilar products to realize a return on our investment?
- How do we ensure physicians and patients are comfortable with using our biosimilar products?

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Introduction

The potential demand for biosimilars certainly creates an enormous opportunity for biopharmaceutical companies. But unlike the development of originator biologics – or generic versions of chemical-based medications – biosimilar development and commercialization is a uniquely difficult endeavor requiring precise, stepwise planning to ensure timely regulatory approval and optimal market access.

Even those companies looking to protect the market share of a branded biologic product are struggling to adapt to the increased competition from biosimilars. In all cases, the uniqueness of biosimilars necessitates that an integrated, strategic development plan – which includes expert analysis and input on the key regulatory, commercial and clinical considerations – must be put in place in the very early stages of any biosimilar development program.

This paper explores further the following key messages:

- The biosimilar market is projected to be a multi-billion dollar industry in the next few years
- Regulatory and market access considerations must fuel biosimilar clinical development
- Biosimilar development strategies must adapt to evolving regulatory requirements
- Clinical development strategies must focus on patient selection and appropriate clinical endpoints
- Commercial strategies must optimize market uptake of biosimilars

The biosimilars playing field

Over the next 5 to 10 years, the biologics market is expected to grow rapidly and continue to gain share relative to small molecules, while simultaneously, the biosimilars industry is expected to explode, as the patents on branded biologics begin to expire.

Forces driving the rapid expansion of the biosimilars industry are an ever-increasing pressure to reduce healthcare costs, expectations for booming market growth due to patent expiry of high-value innovator biologics, and better-defined regulatory pathways.

Many companies have announced plans to develop biosimilar products, and most others have considered it as a possibility. Large multinational companies including Novartis/Sandoz, Amgen, Merck, Pfizer, and others have invested heavily in this space. Additionally, many local and regional companies around the world have established biosimilar portfolios and are seeking to reach additional markets.

Regulatory and market access considerations must fuel biosimilar clinical development

Companies seeking entry into – or a sustained position within – the biosimilar marketplace must first identify the regulatory requirements for every intended market. As guidelines and pathways around the world continue to mature, the complexity of this exercise cannot be understated. This process needs to follow a logical step wise progression to ensure that a global development plan can be leveraged to satisfy regulators in each potential market (See Figure 1). Should a single development plan not appear feasible, a decision must be made whether to undertake a "bridging program" (or separate program) for the market concerned; or, alternatively, improve the product and develop it as a biobetter.

Segmenting Manufacturers of Biologic Products

In general, biopharma companies can be categorized into four segments based on their biologic product strategy:

1. Companies that develop innovative biologics or next-generation biologics (also known as 'bio-betters') only (i.e., Roche/Genentech).

2. Companies that are developing biosimilar compounds while maintaining a portfolio of innovative biologics (i.e., Novartis, Merck, Pfizer).

3. Companies that are established leaders in generics and now leveraging their expertise to develop and market biosimilars (i.e., Teva, Hospira).

4. New entrants into the global pharmaceutical market (i.e., Celltrion, Samsung).

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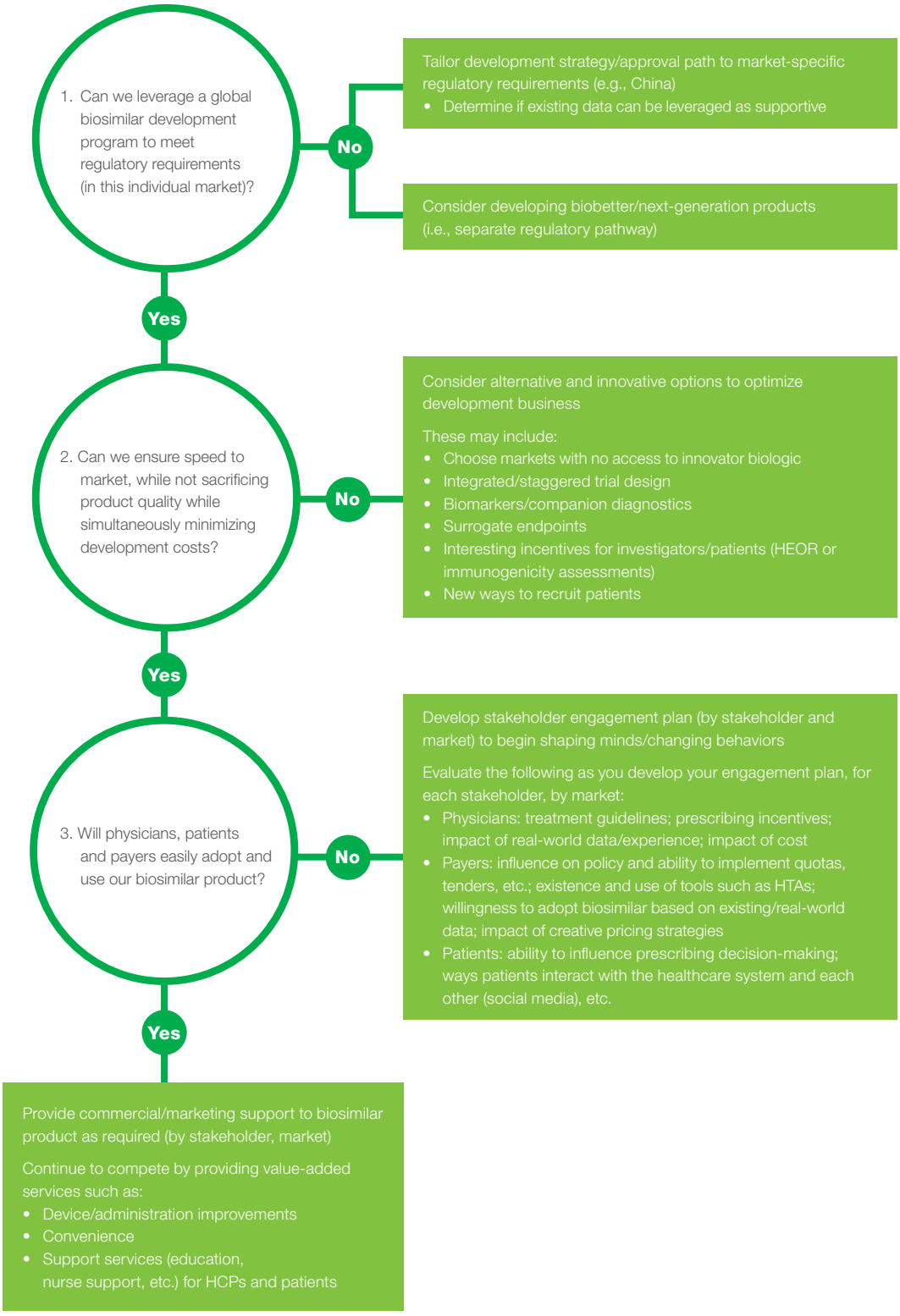
Figure 1 Decision-making framework

An optimal integrated biosimilar strategy consists of three key considerations: regulatory, clinical and commercial.



Segmenting Manufacturers of Biologic Products (continued)

The needs and interests of a biopharma company are generally dependent on which segment it falls into, as outlined above. Companies focused on developing innovator biologic medicines are interested in defending their products against competition from biosimilars; companies developing biosimilars are interested in minimizing the costs and timing of development and maximizing the commercial success of those drugs; and companies that have innovative biologics on the market but are also developing biosimilars will have to maintain a balanced position in terms of how they play in the biosimilar space.

New entrants into the healthcare and biopharmaceutical space will need to develop manufacturing capabilities in addition to the clinical, regulatory and commercial expertise required to develop and commercialize biosimilars successfully.

A concurrent work stream should also be undertaken to assess physician and payer willingness to prescribe and pay for the potential biosimilar. For cases in which reimbursement or adoption appear unlikely or challenging, biosimilar developers should design the development program to provide as much outcomes data as possible. This could include comparative effectiveness data, health technology assessments or even the potential effect on public health.

As with the regulatory assessment, detailed market access analysis will drive the subsequent clinical development strategy. This approach does not minimize the importance of a proper clinical development plan – specifics of which are discussed later in this paper – but regulatory and commercial considerations are the primary drivers for successful biosimilar development.

As regulatory guidelines evolve, biosimilars development strategies must adapt accordingly

Although biosimilar regulations differ around the globe – and are still evolving – companies can and are still devising strategic development plans based on existing regulations and biologics/biosimilar products guidance documents. Ideally, regulatory strategies should address analytical, non-clinical and clinical considerations, desired indication of choice and market specific requirements.

Companies should prioritize markets based on a combination of regulatory approvability and commercial potential; they need to engage with regulators in those markets early on in the development process to capture their interest and to ensure the country/region specific requirements for marketing approval are being addressed. Companies should therefore initiate conversations with national regulatory authorities in the markets in which they are interested as soon as they begin to contemplate developing biosimilars for those markets.

It is important to remember that each country is on its own maturity curve in terms of the biosimilar regulatory approval process. For countries with still-evolving regulatory pathways and guidelines, companies need to be aware of where they currently are in the cycle, and then anticipate likely future scenarios based on the existing regulations and their experience.

The EMA was the first agency to establish a regulatory pathway for biosimilar marketing approval and to issue regulatory guidelines for biosimilar development requirements, setting precedent standards that are used as a model by many other national and global regulatory authorities, including the World Health Organization (WHO). Beginning in 2005, the EMA issued overall guidelines for biosimilars, including clinical, non-clinical, and quality considerations to show comparability to the originator biologic. Recently, the EMA has begun to revise its original biosimilar guidance documents, based on the practical experience provided by approved biosimilars to date.

The FDA also issued draft biosimilar guidance documents in 2012. These consisted of quality and scientific considerations as well as two Q&A documents. Advising a "totality of evidence" approach, FDA makes it clear that the agency has the authority and the flexibility to determine animal and/or clinical testing requirements on a per-product basis upon assessment of the comparative analytical data. FDA is also encouraging early dialogue and is more than willing to provide guidance throughout the development of the biosimilar product.

To streamline the development of biosimilar products, FDA is highly recommending the stepwise approach – consisting of analytical testing (including fingerprint-like analysis for the quantification of similarities and differences between the proposed biosimilar and the U.S.-licensed reference product), followed by *in-vitro* functional testing, *in-vivo* animal toxicity studies, and clinical studies (PK, PD, efficacy, safety including immunogenicity). Overall, the required amount of nonclinical and clinical safety data is assessed on a case-by-case basis and is dependent on the results of the comparative analytical testing.[1]

The Importance of Pharmacovigilance

Biologic products, like all medicines, are authorized on the basis that at the time of approval, the benefit-risk is judged positive for the target patient population of a specific indication. However, not all actual or potential risks or adverse events will have been identified then, and will only become clear through ongoing pharmacovigilance efforts.

The potential for different immunogenic reactions in patients due to biologic therapies can cause serious adverse events. Some biologics have shown "rare, but potentially serious" safety concerns post-approval. As a result, ongoing post-marketing surveillance is especially important for biologics.

For biosimilars, pharmacovigilance becomes even more important as they are approved based on abbreviated clinical studies, and any potential differences or any long-term safety issues will not be fully known until greater experience in their use is established.

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FDA encourages biosimilar manufacturers to evaluate multiple lots of the U.S. reference product throughout its shelf life, as well as the biosimilar product, for establishing meaningful acceptance criteria. To avoid conducting further bridging studies late in development, the biosimilar product tested in clinical studies should be the same as one planned for commercialization.

The FDA also indicated that data extrapolation to additional indications (of the reference product) may be possible if the mechanism of action is the same and with proper scientific justification. Further, the agency specified that any biosimilar manufacturers interested in obtaining the interchangeability designation will have to conduct additional, specific Phase 3 switching studies to show that safety and efficacy risks are not greater than using the reference product without switching. FDA concurrence on the interchangeability study design is highly recommended prior to initiation of any such studies.

Lastly, biosimilar sponsors should assess if a pediatric study is necessary for their biosimilar products, as the Pediatric Research Equity Act (PREA) guidelines apply to biosimilars that have not been found interchangeable with the U.S.-licensed reference product.

Clinical development strategies must focus on patient selection and appropriate clinical endpoints

In order to minimize the need for extensive clinical evidence of similarity, analytical and non-clinical functional similarity to the innovator biologic must be established in a stepwise process during development. Key challenges relevant to the clinical development of biosimilars – discussed below – include maximizing patient recruitment and choosing the most sensitive patient population that is most likely to respond to therapy, while expediting clinical trials and minimizing sponsor costs.

- **Patient recruitment** can be accelerated by choosing the countries/markets in which to conduct the clinical studies with the greatest unmet need for the biosimilar (i.e., those that do not have access to the innovator biologic). On the other hand, companies can accelerate speed to market by selecting markets where regulatory agencies are willing to work with companies to bring biosimilars into market earlier (i.e., markets where governments are incentivized to reduce healthcare costs). Additionally, investing in education of both investigators and their patients on the potential benefit of participating in a biosimilar trial (e.g., better standard of care for patients with no access to the drug otherwise) can facilitate patient recruitment in all markets.
- Selecting an appropriate **patient population and sample size** for the primary indication with which to demonstrate clinical similarity is critically important to obtain regulatory authority buy-in upfront as to what will be required to secure extrapolation to other indications for which the reference product is approved. Benefits of earlier commercialization may be realized if participation in clinical trials in such countries is a regulatory prerequisite.
- **Incorporating the right clinical endpoints** for clinical trials, including biomarkers or other surrogates predictive of clinical efficacy, may obviate lengthy clinical trials. They should also invest in establishing physicochemical, functional and nonclinical *in vivo* comparability to decrease the amount of clinical data required.

It should be noted that incorporating all these requirements into a global clinical development plan is challenging for integrated biosimilar development.

The Importance of Pharmacovigilance (continued)

Therefore, regulators are encouraging biosimilar manufacturers to consider any particular safety or efficacy concerns associated with the use of the reference product and its class, in addition to what is learned about the proposed biosimilar product during clinical development. Additionally, biosimilar pharmacovigilance must also make sure to identify any potential adverse events that were not previously associated with the reference product.

Stringent pharmacovigilance and ongoing surveillance will help ensure that biosimilar products will continue to meet efficacy and safety standards.

Clinical trial design

Factors that influence the design of clinical trials to evaluate proposed biosimilars include: immunogenicity concerns; existence of reliable/validated biomarkers of efficacy; molecular structure of the biosimilar; extent of characterization of the mechanism of action and targets of the innovator compound; indication and patient population; safety experience of the innovator product; biological class of the proposed biosimilar; and the complexity of clinical endpoints that may be acceptable to regulatory authorities globally.

The acceptability of clinical endpoints for biosimilar clinical trials should be agreed with the regulatory authorities early in the development process for the proposed biosimilars. Such trials require a patient population sufficient to establish equivalence with the innovator drug. Clinical trials may be shortened by the use of surrogate biomarkers providing certain criteria are met, (e.g., CD19 in rituximab, pharmacodynamic data), and moving forward, investigators may be encouraged to participate in studies incorporating the continued exploration of the use of such surrogate biomarkers and endpoints in the development of biosimilars.

Integrated protocol designs, which allow data from multiple trial phases comparing the biosimilar to the innovator product to be merged into one protocol, should be considered for markets where medical practices and agency evaluators are sufficiently experienced and accepting of this methodology. Such a design does not necessarily reduce the cost of or the number of patients needed for the trials, but it can save some time, which is important in biosimilar development as more and more players enter the marketplace. However, in certain markets where medical practices and Agency evaluators are less sophisticated, an integrated protocol design may not be accepted.

Staggered Phase I and Phase III clinical studies is another approach to saving time in clinical development. In this scenario, interim safety data is gathered from Phase I PK study. Commencement of Phase III study in parallel is proposed to follow the review of an interim safety report for the Phase I study. The interim report captures adverse events (AE), serious adverse events (SAE), vital signs, and clinical laboratory results for a specified period of time.

Commercial strategies must optimize market uptake of biosimilars by prioritizing the development pipeline, engaging stakeholders and minimizing barriers for use

Companies need to prioritize their biosimilar development pipeline to maximize the commercial potential of their products, and engage stakeholders such as patients, physicians and payers/insurers to improve market uptake. To optimize commercial potential, they should consider market size, product price, reimbursement policies, healthcare policies, competing products and barriers.

Biosimilars are not expected to have the same uptake as small-molecule generics, and in fact, uptake of marketed biosimilar products to-date has varied per particular molecule, product class and regional market dynamics. Because of this difference, it is important to consider commercialization strategy early in the development process, which can help companies identify and prioritize, which molecules to develop, which markets to prioritize and what the expected revenues and return on investment can be.

Because biosimilars differ from small-molecule generics by not having identical active ingredients to the reference product, and the price differential is generally smaller (~20-50 percent)[2,3] effective commercial strategies for biosimilars tend to be more similar to the strategies employed for a branded biologic versus those of generic products. These strategies may include effective market and KOL development, device improvements, and patient support programs. Additionally, the role of real-world patient data (e.g., post-marketing observational studies) becomes more important, as potential risks inherent to biologic products, such as immunogenicity, are not always immediately evident.

Innovator Biologic Brands Can Protect Against Biosimilar Competition

Although many branded biologics face patent expiry in the next few years, thus leading to a growth of the biosimilar industry, branded biologics are still expected to maintain the majority of the market share in major developed markets, including the U.S., E.U., and Japan.

Companies manufacturing originator biologics have a vested interest in protecting their branded biologics versus biosimilar competition. In order to protect their brands, companies have used a variety of strategies to-date, including:

Working with regulatory and health authorities in markets around to world to ensure that they develop strict guidelines for the approval of biosimilar products, such as by referencing the EMA or WHO standards.

Working with global and regional thought leaders to inform and educate all stakeholders (including regulators, prescribing physicians, payers, patients, and medical or patient organizations) on the complexity of biologics and why biosimilars are not easily interchangeable with branded biologics (in the same way small-molecule generics are).

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The fact that lower prices for biosimilars simply isn't enough is supported by the lesson Sandoz learned through marketing its first biosimilars in the U.S. and Europe. In a 2010 *Pink Sheet* article, Ameet Malik, Global Head Sandoz Biosimilars, conceded that "healthcare stakeholders [doctors, payers, and patients] care about cost when other things are equivalent."[4]

Appropriate identification of successful commercial strategies requires involvement by commercial and brand teams prior to and throughout the clinical development process; and successful implementation requires a cross-functional approach, including continued input from medical teams (e.g., CME activities), manufacturing experts (e.g., for device improvements) and market access strategists (e.g., outcomes data). Collaboration between these cross-functional experts throughout the development process is critical for commercial success.

Summary

The successful development and commercialization of a biosimilar product requires a business strategy that integrates a regulatory strategic roadmap, appropriate clinical strategy and trial design, regulatory compliance with scientific advice received, as well as commercial and market access considerations. Companies looking to develop biosimilars aim to ensure speed-to-market and minimize development costs, without sacrificing product quality, while ensuring broad clinical labels and commercial viability. They must also address the unique challenges involved in developing and commercializing biosimilars, such as navigating an inconsistent global regulatory environment and identifying willing investigators and eligible patients for the required clinical trials. To ensure commercial success and maximize uptake of its biosimilar products, a company should ensure that physicians and patients are comfortable with the comparative efficacy and safety and with using its biosimilar products while optimizing access among payers.

To expedite commercialization and optimize market access, a business plan should, via a comprehensive market assessment, anticipate competitive scenarios; spell out an effective market entry strategy; provide a value dossier and value-based pricing; and set forth goals and objectives for interactions with all stakeholders, including healthcare providers, payers and patients. The goal of such comprehensive strategies is to ensure competitiveness and optimize return on investment in the fast-growing biosimilars space.

Finally, it's important to note that because biosimilar development is so complex, the timeline and sequence of processes must be compressed. Successful biosimilar companies will be those who collapse their clinical, commercial and regulatory thinking into a streamlined cohesive function and embrace the organizational change that such a framework necessitates.

Innovator Biologic Brands Can Protect Against Biosimilar Competition (continued)

Forming partnerships with governments and/or local manufacturers in return for exclusivity agreements (particularly relevant in emerging markets such as China and Brazil).

Differentiating their brands through commercial strategies such as developing next-generation products (i.e., reformulation, improved devices, etc.); highlighting their manufacturing/process quality and capabilities; and using their long-term patient data to demonstrate efficacy and safety.

In general, some of these strategies are more long-term strategies (i.e., influencing health and regulatory authorities), and can begin several years prior to establishment of any biosimilar guidelines or the entry of any biosimilar competitive products. Obviously, differentiation becomes much more important as the number of competitors increases.

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Deepa Dahal's background lies in commercial strategy, market development, brand planning, product launch, life cycle management, and pricing and reimbursement. At Quintiles, she has focused on developing commercial strategies for multiple clients in the biologics and biosimilar space, including innovator biologics as well as biosimilars in development. She has also played a leading role in defining Quintiles' own global biosimilar strategy.

Prior to joining Quintiles, Ms. Dahal was a Senior Consultant at both Campbell Alliance and IMS Health. At Campbell, she focused on Marketing and Brand Management strategy among pharmaceutical and biotech companies. At IMS, she worked on Managed Care Contracting and Compliance with pharmaceutical clients. Ms. Dahal has a bachelor's degree in Business from the University of Idaho and an MBA from the University of New Hampshire.

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Dr. Chance has over 25 years of work experience in the healthcare industry, including the last 15 years in regulatory affairs at pharmaceutical and biotechnology industries. She advises pharmaceutical and biotechnology companies in the development of region specific and/or global regulatory strategy for the development of biosimilars. She is passionate about biosimilar products and to that end she has obtained extensive training on EU and US biosimilars product development as well as authored and/or co-authored number of articles on the subject matter.

Her overall regulatory experience encompasses strategic regulatory planning, preparation of briefing documents, meetings with FDA, IND/CTA submissions, Marketing Applications (NDAs, BLAs, ANDAs) in the CTD format as well amendments to drug applications and post approval supplements. Dr. Chance has considerable experience directly interacting with numerous FDA divisions at CDER and CBER. Her therapeutic expertise includes: CNS, Reproductive and Urologic Products, Metabolism and Endocrinology, and Oncology products. She is also serving as a regulatory strategist in the development of global regulatory strategies with number of biosimilar products in early development. Dr. Chance received her PhD in Nutrition/Nutritional Biochemistry from the University of North Carolina in Greensboro and her MPH from the University of North Carolina in Chapel Hill. She obtained Regulatory Affairs Certification from Regulatory Affairs Professional Society in 2003. Dr. Chance is a member of Quintiles Biosimilars Advisory Board.

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