

# Biosimilars – Emergence of a third market dynamic between original products and generics

Current situation, strategic options and recommendations

  
**accenture**

*High performance. Delivered.*

• Consulting • Technology • Outsourcing



# 1. Current situation and market

Biotechnologically produced drugs, so called biologics, are a major growth driver for the global pharmaceutical market. In 2007 the biologics market grew noticeably faster than the overall market; with a double-digit growth of 20% they generated \$95 bn of sales amounting to approximately 15% of global Pharma revenues<sup>1</sup>. Many approved biologics have become enormous blockbusters like Enbrel (Amgen/Wyeth), Remicade (Centcor/J&J) and Rituxan (Biogen Idec/Genentech/Roche).

This bright outlook for biologics is likely to continue. Accenture research shows that the pipelines of the pharmaceutical industry are filled with more than 500 biologics in various stages of development and that their proportion among the number of newly approved drugs is constantly growing. By 2010 approximately 1/3 of all newly approved drugs will be biologics. For instance, one reason for Pfizer taking over Wyeth is the access to a promising biologics pipeline and capability. In-line with this development, the market for generic versions of biologics is becoming more and more interesting as the patents of first generation products like EPO, G-CSF, human growth hormone, insulin and interferon are already expiring. This patent expiration offers companies the opportunity to enter a new, attractive market with the production of replica of biologics – so-called biosimilars. Today, total sales of off-patent biologics amount to approximately \$20 bn, and this number will considerably increase over the next years. Sales volumes of

Fig. 1: Definitions of generics, biologics and biosimilars (Source: Accenture Research)

Generic	A drug with the same active ingredients and equivalence as the original small-molecule pharmaceutical produced by using chemical synthesis
Biologic	A complex biopharmaceutical, produced using biotechnology (i.e. rDNA, controlled gene expression or antibody technologies)
Biosimilar (EMEA); Follow-on biologics (FDA)	An approved drug, produced by using biotechnology, referencing an originator biologic

biosimilars for these drugs are still low, but are expected to grow very rapidly with the entry of more products and new players.

The challenge for the development of biosimilars arises from the fact that biologics are more complex than small-molecule and chemically synthesised drugs; therefore their replica are – in contrast to 'traditional' small-molecule generics – "similar" but not identical to the original drug. The EMEA and FDA have recognized this fact and established the official terms 'biosimilars' (EMEA) and 'follow-on biologics' (FDA), respectively (Fig.1).

The characteristics of biologics are for a large part determined by their manufacturing process. Minor differences in cloning, fermentation or purification can lead to variation of tertiary and quaternary structures and post-translational modification patterns of proteins. These variations can significantly modify the activity, stability, specificity and immunogenicity, which can thus differ significantly from the originator product. Consequently, the registration of biosimilars requires more data than for generics, and manufacturers have to demonstrate efficacy and safety in pre-clinical and clinical studies. This makes the registration of biosimilars a

<sup>1</sup> Accenture research

Fig. 2: High-level Overview – comparison of generics, biosimilars and biologics  
(Source: Accenture Research, Accenture Project experience)

	Generic	Biosimilar	Biologic
<b>Manufacturing</b>	<ul style="list-style-type: none"> <li>• Mostly smaller chemical molecules – less sensitive to production process changes</li> <li>• Produced by using chemical synthesis</li> <li>• Reproducibility easy to establish</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitive to production process changes – expensive and specialized production facilities handling living cells (mammalian, yeast, bacteria)</li> <li>• Highly sensitive to manufacturing changes</li> <li>• Reproducibility difficult to establish</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitive to production process changes – expensive and specialized production facilities handling living cells (mammalian, yeast, bacteria)</li> <li>• Highly sensitive to manufacturing changes</li> <li>• Reproducibility difficult to establish</li> </ul>
<b>Clinical Development</b>	<ul style="list-style-type: none"> <li>• Limited clinical activities, often only Phase I studies</li> <li>• Short timeline for approval</li> <li>• Development costs up to 5 m\$</li> <li>• Enrolment of around 20 – 100 subjects</li> </ul>	<ul style="list-style-type: none"> <li>• Extensive clinical trial activities, including Phase I and III studies</li> <li>• Pharmacovigilance and periodic safety updates after launch needed</li> <li>• Development costs around 80-120 m \$</li> <li>• Timeline of 6 – 10 years</li> <li>• Enrolment of around 100 – 1500 patients/ subjects</li> </ul>	<ul style="list-style-type: none"> <li>• Extensive clinical trial activities, including Phase I – III studies</li> <li>• Pharmacovigilance and periodic safety updates after launch needed</li> <li>• Development costs around 350 – 800 m \$</li> <li>• Timeline of 6 – 15 years</li> <li>• Enrolment of &gt; 1.000 patients/ subjects</li> </ul>
<b>Regulation</b>	<ul style="list-style-type: none"> <li>• Needs to show bioequivalence</li> <li>• Abbreviated registration procedures in Europe and US</li> <li>• Automatic substitution allowed</li> </ul>	<ul style="list-style-type: none"> <li>• Regulatory pathway defined for Europe (EMA); not yet in US (BLA)</li> <li>• Needs to demonstrate "comparability"; currently no automatic substitution intended</li> </ul>	<ul style="list-style-type: none"> <li>• Highly regulated like all innovator drugs</li> </ul>

costly and time-consuming process. For example, it took Ratiopharm several years of development, requiring more than 800 patients, before their first biosimilar "Ratiograstim" (based on the agent Filgrastim) was approved in 2008.<sup>2</sup> Furthermore, the EMA requires post-marketing studies to observe immunogenicity and to establish rigorous pharmacovigilance programs. Therefore, major up-front investments are required which will not in all cases then lead to a successful approval of the drug. Marvel Lifesciences for example, part of the MJ Group, recently withdrew Marketing Authorisation application for three biosimilar insulin products, as they could not show comparability with the reference drug<sup>3</sup>. These challenges are very similar to those of producers of originator drugs, who face high investments and uncertainties for their R&D activities. Comparing characteristics of 'classic' generics, biosimilars and biologics it can be seen that overall biosimilars show a greater similarity to biologics than to generics (see also Fig. 2).

Nonetheless, first players, for the most part big generics firms like Teva, Sandoz or Stada, have entered the biosimilars market with different strategies such as; cooperation with biotech companies (e.g. Teva and Lonza), establishment of own biotech affiliates (e.g. Sandoz and Biopharmaceuticals GmbH) and Venture Capital funded biotech firms (e.g. STADA and Bioceuticals AG)<sup>4</sup>.

The regulatory frameworks for biosimilars in Europe and US are in different stages. A robust legislative framework enabled the EMA to develop a series of guidelines for biosimilar approval, and in 2006 the first biosimilars were authorized (i.e. Sandoz Omnitrope and BioPartner Valtropin). Since then, additional approvals have included Sandoz's Binocrit (EPO), Hexal Biotech's Epoetin alfa, Bioceuticals/ Stada's Epoetin zeta and Ratiopharm's copy of Filgrastim (G-CSF; Ratiograstim)<sup>5</sup>. These products are all based on protein-classes that were originally launched in the early to mid-1980s and with recent patent expiries.

The situation in the US is more complicated: biologics are controlled under the Public Health Service (PHS) Act, which does not contain an abbreviated pathway as for 'normal' generics. Therefore, the FDA expressed a demand for new legislation to handle biosimilar/follow-on biologics<sup>6</sup>. A final decision can be expected under the new Obama administration and the first biosimilars will likely enter the US market in 2009.

<sup>2</sup> Ratiopharm press release, 1.10.2008

<sup>3</sup> EMA press release, 24.1.2008

<sup>4</sup> Accenture research

<sup>5</sup> Accenture research

<sup>6</sup> Sandoz Omnitrope was approved 2006 in the US; yet not as a follow-on biologic/ biosimilar but as follow-on protein product

## 2. Trends and hypotheses

Analyzing the current situation, Accenture has identified several trends how the market for biosimilars will likely develop. In general, biosimilars with higher barriers-to-entry than compared to 'classic' generics, competition will be less intensive, leading to a comparably lower margin pressure and a more interesting profitability structure; key differentiators will be technologies and capabilities and only to a lesser extend low prices and market share:

### 1. Increase in biosimilar approvals and market growth both in Europe and the US

– The EMEA expects further approval applications in 2009 and the coming years; also in the US, with a new legislation in place, first biosimilars will likely enter the market. In 2010 the biosimilars market is expected to grow to approximately \$5 bn. Further patent expiries of biologics will likely increase the number of approved biosimilars and players in the market.

### 2. Cost saving potentials by biosimilars

The prices of a biosimilar are currently approximately 20–30% below the original product price. An increase in market competition might lead to further reductions, but due to high necessary up-front investments, biosimilars are unlikely to realize the price reductions of 70–80% typical of 'classic' generics. Nevertheless, payers and health care systems can still achieve significant savings since biologic treatment costs are on average \$50 per day, some 20 times higher than traditional pharmaceuticals. Therefore, this price reduction could also allow a higher number of patients to benefit from innovative and expensive treatments<sup>7</sup>.

### 3. Higher margins and interesting profitability structure

The regulatory authorities have underlined that biosimilars need to be treated differently from generics as they can only establish a similarity to their reference product. Therefore, an automatic substitution in the pharmacy, as seen for 'classic' generics, is currently not intended and unlikely to be implemented. Thus, even if several biosimilars, referencing the same originator drug, compete with each other, an intensified price pressure with rebate contracts and other discounts discussions is less likely to take place than with 'classic' generics. This will make

biosimilars a comparably more profitable and higher margin business than generics, with less price regulation and pressure by payers and governmental bodies.

### 4. Careful selection of protein classes

For the short-term, manufacturers of biosimilars will focus on the five protein classes of EPO, hGH, G-CSF, Insulin and Interferon due to their recent patent expiry. In the long term, more complex proteins (e.g. antibodies) will likely also be 'biosimilarized'. But it can still be expected that individual companies will focus their production and marketing on selected protein classes driven by strategic fit (e.g. company therapeutic area focus) and operational feasibility (e.g. availability of required skills for production).

### 5. Uncertainties and risks for biosimilars manufacturers

Uncertainties and risks for biosimilars manufacturers will continue to be relatively high. The regulatory frameworks in Europe and the US are becoming more robust, but still the guidelines will not allow a standardized approval process but force both agencies to continue with case-to-case decisions. Furthermore, reluctance from physicians and patients to prescribe and use biosimilars due to potential efficacy and safety issues might negatively impact prescription behaviour, making the early adoption of biosimilars difficult. Thus the probability of a successful product launch is lower compared to the generic market.

<sup>7</sup> Accenture research

### 3. Strategic options and implications

As described, biosimilars will evolve to an interesting market in the coming years and with its very specific dynamics, this market will differ significantly from those for originator products and for 'classic' generics. In general, biosimilars will be a higher-risk but also higher-rewarded business than compared to classic generic drugs.

The dynamic developments will put pressure both on originator companies and generics firms to meet these challenges and to develop a position in this new environment. Based on the analyzed trends, Accenture sees the following likely strategic options:

#### Option 1: Generics firms enter successfully into the biosimilars market

The development of biosimilars represents a significant opportunity for generic firms interested in entering the marketplaces for biotechnologically produced drugs. Without the necessity of undertaking costly full-scale R&D activities, they can master the manufacturing and marketing of recombinant proteins. In the long run it is possible they themselves gain the expertise and resources needed to modify and improve biopharmaceuticals and bring innovative biologics to the market, as the core competencies for production, development and approval needed for both biologic or biosimilar are largely the same. This trend can already be observed

for companies like Teva, which has built-up required capabilities and successfully launched innovative biologics.<sup>8</sup> However, success in the biosimilars industry will require significant capital investment and in-house experience. In particular, biosimilars manufacturers have to face higher costs for manufacturing, clinical development, registration and product marketing compared to classic generics as described in Fig 2. The development costs of a classic generic product are between \$0.5 m and \$5.0 m, whereas for a biosimilar product they can go up to more than \$100 m<sup>9</sup>. Therefore, market entry barriers are especially high for smaller generics firms, as these obligations require a significant upfront as well as long term investment. Intense competition and financial pressure in the generics market might make it difficult for these players to deal with the financial risk and to undertake the required investments.

In general, companies must be aware of the long-term commitment they are

required to make when developing and marketing biosimilars and the risk of failure they must be willing to take. In addition, they need to understand the market dynamics and pipeline developments, so that sales of newly launched biosimilars are not lost to improved second and third generation biologics of pharma companies.

Necessary actions for generic companies therefore include:

- Development of a long-term biosimilar strategy, taking into account the implications from high initial investments and potential regulatory and approval risks.
- Establishment of competitive intelligence for the biologics and biosimilar market.
- Evaluation of options to build up required capabilities and competences for manufacturing, clinical development, pharmacovigilance and marketing of biosimilars. Generic companies have the possibility to develop new in-house competencies or

to outsource large-parts of those activities to CROs and to build up new partnerships.

- Directing of sales force detailing activities both at generalist and specialist doctors to support uptake and prescription of biosimilars. Biosimilar producers will still need to have a substantially sized sales force to have medical discussions with physicians and to promote uptake of biosimilars.

### Option 2: Pharmaceutical companies expand their biologics business and enter biosimilars market opportunistically

For manufacturers of biologics the challenge is to define defence and push-back strategies. On the one hand, this can include the development of improved second generation biologics with better protein stability and efficacy. These biologics can be well positioned on a competitive market including vis-à-vis biosimilars of first generation biologics. Amgen, for example, reported that while the sales of first generation EPO products were hit by biosimilars entry, their second generation product Aranesp increased its market shares in selected Therapeutic Areas and was able to maintain price premium of 15 - 30% over first generation products<sup>10</sup>. On the other hand pricing strategies of biologics can be redefined to better meet increasing competition and to optimally position original products in re-imburement discussions. Part of this strategy can be increased communication activities with regulatory agencies and payers regarding potential safety and efficacy issues. Also scientific communications with physicians focusing on the potential safety and efficacy issues of biosimilars can be enforced and Key Opinion Leader (KOL) management approaches leveraged.

In addition, Pharma companies could develop strategies to complement and expand their therapeutic portfolios by bringing biosimilars of other companies to the market, as they have the required R&D, manufacturing, regulatory and marketing competences and experiences in-house. This would allow them to

expand portfolios faster, with less R&D risk and cost, establishing additional sources of revenue. An interesting example for this strategy is the current announcement of Merck & Co to enter the biosimilar market by establishing the subsidiary Merck BioVentures<sup>11</sup>. Besides, for selected Pharma companies with both pharmaceutical and generics expertise in-house, there is also the possibility for a company internal 'switch', i.e. launching a biosimilar of the company's own biological product. This option might only be taken into account for older first generation biologics, whose second generation biologics is about to be launched. This could be an interesting opportunity for those corporations pursuing both an original product and generics strategy like Sanofi-Aventis, Novartis or Daiichi Sankyo.

This potential market scenario therefore includes the following actions for Pharma companies:

- Revision of R&D strategies promoting the development of improved second-generation biologics with extended half-lives and increased efficacy and safety to position those drugs as superior to launched biosimilars.
- Refinement of marketing and pricing strategies for biologics including a refined approach for reimbursement discussions with payer organizations and how to position biologics vis-à-vis biosimilar competition.
- Adoption of scientific push-back activities against biosimilars by using communication activities with regulatory agencies, opinion leaders and payer organizations.
- Analysis of biosimilar opportunities fitting into the therapeutic area strategy or meeting operational feasibility for expansion of the portfolio.
- Identification of 'switching' potential of own biological product into a biosimilar by evaluating the impact on the overall company group's value; this includes promotion of biosimilars in selected geographies as part of an emerging market strategy.

### Option 3: New types of cooperation between Pharma, Biotech or Generics

As a third option, new forms of cooperation between relevant players, Pharma, Biotech or Generics could evolve. For example, generic companies are already partnering or acquiring biotech firms. In 2009, Teva announced a joint venture with Lonza, based in Basel, Switzerland with the objective to cooperate in development, manufacturing and marketing of biosimilars<sup>12</sup>. Lonza is a manufacturer of active pharmaceutical ingredients both chemically as well as biotechnologically. Another likely scenario is the cooperation and stronger alignment between Pharma companies and generic firms.

This market scenario therefore could include these activities (in addition to those described under scenario 1 and 2):

- Development of novel co-development, cooperation and alliance approaches, as well increased M&A activities between Pharma and generic companies, allowing them to partner on selected products for selected markets. Sandoz recently formed a strategic alliance with Gambro, a distributor for dialysis products, for sales and promotion activities of its EPO biosimilar Binocrit in selected European markets<sup>13</sup>.
- Development of 'early-entry' strategies between Pharma, Biotech and generic firms for the production and marketing of biosimilars. These strategies will include a careful balance and selection of local and regional markets in which to switch from biologic to biosimilar, and where and how to sell or out-licence a certain drug.
- Increase in market consolidation activities, especially as big generic companies will likely continue to acquire competencies they need to successfully bring biosimilars to the market.

<sup>8</sup> Accenture research

<sup>9</sup> Accenture project experience

<sup>10</sup> Amgen Q2 FY08 Earnings Call, 28.7.2008

<sup>11</sup> Merck & Co press release, 12.2.2009

<sup>12</sup> Lonza press release, 20.1.2009

<sup>13</sup> Sandoz press release, 8.1.2008

## 4. Key Success Factors to enter Biosimilar Market

The development of the biosimilar market will bring a new dynamic into the Pharma world. Despite the described risks and challenges it will open up very interesting opportunities for both Pharma and generic companies. The dynamics in the biosimilar market will be more challenging than in the classic generic market requiring greater investments and risks, forcing the producers to make careful selection on protein classes, building up new competencies and developing new models for cooperation. In general, the main differentiator for players in the biosimilars market will be safety, efficacy and convenience of their products; and to a lesser extent the price of their drugs.

To achieve high performance in such a complex and dynamic market, biosimilars manufacturers need to consider the following key success factors:

1. The decision to enter the market should only be made based on a **clearly defined long-term biosimilar strategy**, which addresses important long term considerations, development and manufacturing capability investments, marketing, pricing and commercial approaches as well as geographic and regional focus.

2. Entrants need to have a **healthy financial structure to perform high up-front investments**. They also need to carefully assess if and how they can make the required investments into facilities and capabilities to successfully bring a biosimilar onto the market. Taking into account regulatory risks and reluctance from physicians and patients to take up biosimilars when projecting future sales.

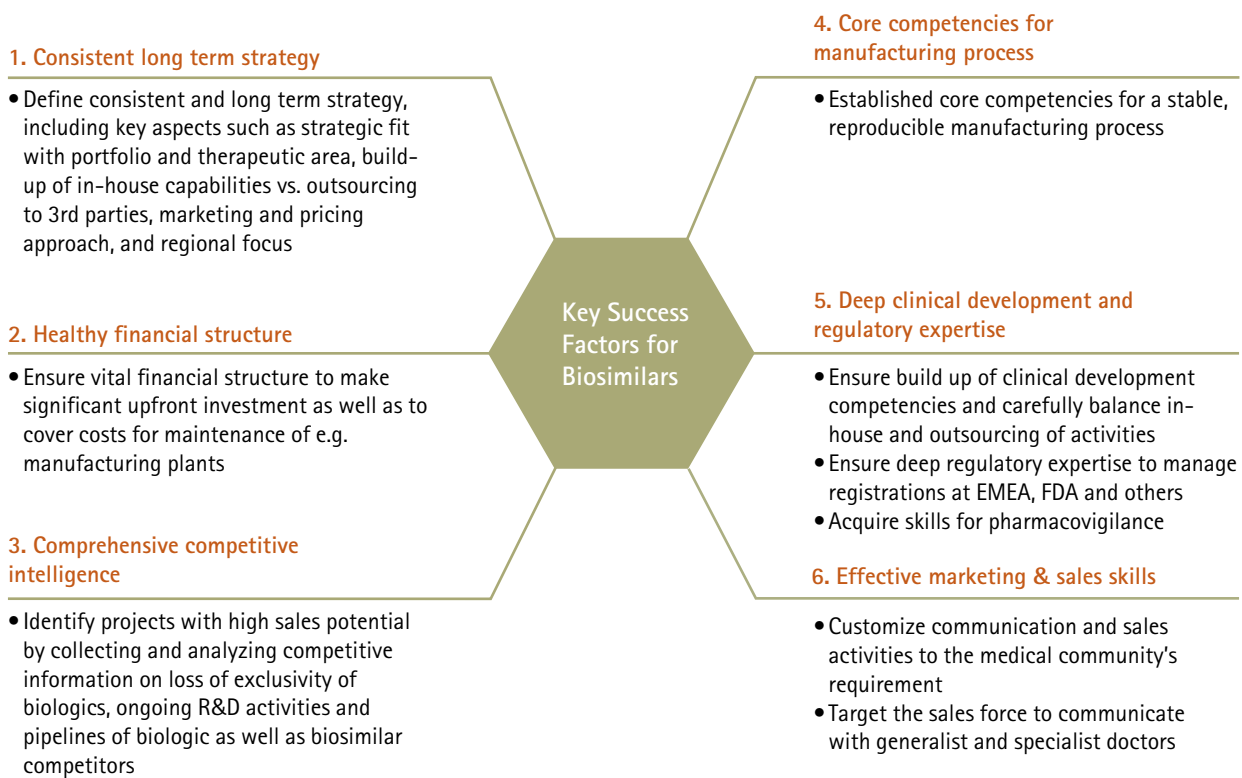
3. Manufacturers of biosimilars will need to build up **comprehensive competitive intelligence on the biologics and biosimilars market** and pipeline and R&D activities of competitors to successfully select target biosimilars with optimal sales potential. As their products will not only compete with originator brands but also other biosimilars entrants, second-generation branded biologics, second-generation biosimilars, and other branded biologics, they need to understand the pipelines of relevant competitors and how they will likely act in the near future, to be able to make strategic and tactical decisions of which biosimilars to select and develop.

4. **Established core competencies for a stable, reproducible manufacturing process** are the basis for successfully gaining access to the biosimilars market. Key production processes need to be build-up, either in-house or in cooperation with an experienced partner,

and fully established to lead to the desired outcome. Proper supply chain management and further optimizations might allow to improve products and thereby to better position them on the market.

5. Biosimilar producers have to build up **deep clinical development expertise including pharmacovigilance and regulatory capabilities; and appropriate balance between in-house and outsourcing to CROs**. Organization and processes need to be clearly defined and established to allow fast generation of high-quality data and proper management and analysis of a large amount of information. This will support the fast development of a product, minimizing costs and failure risks. In addition, development capabilities need to be tightly integrated with production facilities which represent a major challenge to create biosimilars that are comparable to the original biologics.

Fig. 3: Key Success Factors for Biosimilars (Source: Accenture Research)



6. To commercialize biosimilars, companies need to have **customized marketing and sales activities for the medical community and beyond**. This can include scientific communication activities with regulatory agencies, opinion leaders and physicians as well as sales force detailing activities to have medical discussions with doctors and to promote uptake of products. For a successful commercialization, targeted geographies need to be carefully selected and commercialization approaches tailored to market environment.



## 5. Why Accenture?

To develop a sustainable biosimilar approach, a company needs to understand both the pharmaceutical as well as the generics business, and it needs to develop strategies, tactics, organizational models and the necessary processes to develop and bring biosimilars successfully to the market.

Accenture can offer proven expertise and experience in the ethical pharmaceutical, generics and consumer health industries worldwide. Accenture has helped many clients in defining and implementing corporate and functional strategies, such as in the area of Research & Development, Business Development, Manufacturing and Marketing & Commercial, as well as evaluating market scenarios and building competitive intelligence analytics. Accenture's proven expertise in developing market scenarios using the FutureView methodology and High Performance Business research will support life science companies to define sustainable strategies. Furthermore, by conducting war-gaming workshops Accenture has helped clients to gain a common understanding of current and future market dynamics and competitors' strategies. The valuable insights have served as a basis to define further growth opportunities and make investment decision.

The re-design of the clinical development and pharmacovigilance processes has helped many clients to achieve significant results, both in terms of quality and time. Also, Accenture's Global Marketing & Sales Practice has helped clients to define innovative approaches to increase commercial efficiency and effectiveness. Accenture's structured Key Opinion Leader management approach and detailing programs, like Close Loop Promotion, have supported life science companies to master intensive requirements in the marketing & sales area.

Life science companies can rely on Accenture's Health and Life Sciences professionals and dedicated methodology that support them to define a long-term biosimilars strategy that drives high performance

Copyright © 2009 Accenture  
All rights reserved.

Accenture, its logo, and  
High Performance Delivered  
are trademarks of Accenture.

#### For more information

To learn more about Accenture's  
approach to developing biosimilar  
strategies that help pharmaceutical  
businesses achieve high-performance,  
please contact the authors of this study:

Michael Brückner  
Managing Director,  
Health & Life Sciences  
Phone: +49 6173 94 67245  
[michael.brueckner@accenture.com](mailto:michael.brueckner@accenture.com)

Dr. Alexandra Resch  
Consultant, Health & Life Sciences  
Phone: +49 175 57 63713  
[alexandra.resch@accenture.com](mailto:alexandra.resch@accenture.com)

Thao-Binh Pham-Thi  
Consultant, Health & Life Sciences  
Phone: +49 175 57 68429  
[thao-binh.pham-thi@accenture.com](mailto:thao-binh.pham-thi@accenture.com)

#### About Accenture

Accenture is a global management  
consulting, technology services and  
outsourcing company. Combining  
unparalleled experience, comprehensive  
capabilities across all industries and  
business functions, and extensive  
research on the world's most successful  
companies, Accenture collaborates  
with clients to help them become  
high-performance businesses and  
governments. With more than 186,000  
people serving clients in over 120  
countries, the company generated net  
revenues of US\$23.39 billion for the  
fiscal year ended Aug. 31, 2008.  
Its home page is [www.accenture.com](http://www.accenture.com)