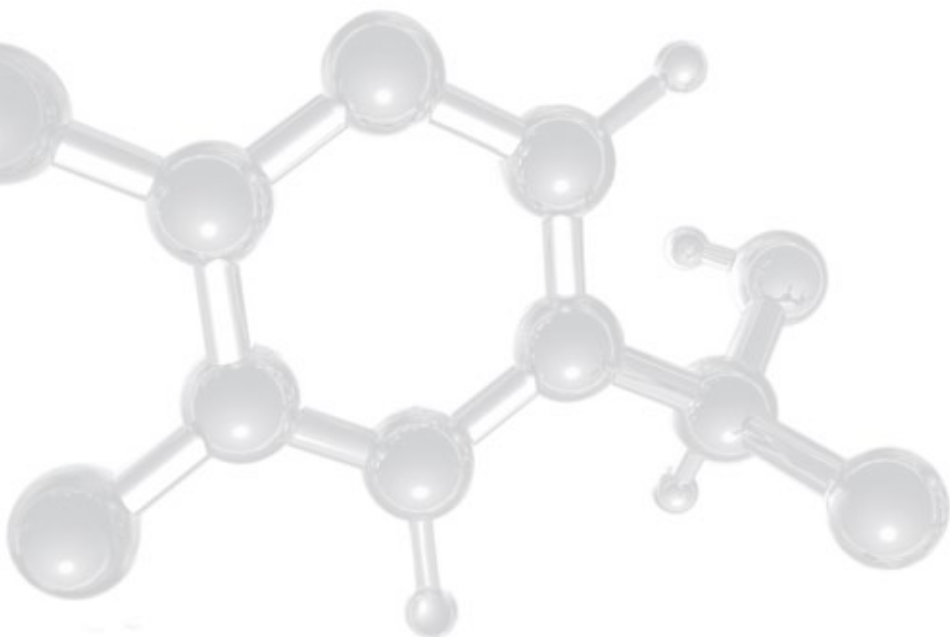


## Custom Manufacturing Driven by Core Competencies

---

By Torsten Woehr, Ph.D.  
*Director, Commercial Development, Americas*  
*Genzyme Pharmaceuticals*

Marc New, Ph.D.  
*Senior Director, Commercial Development, Europe & Asia*  
*Genzyme Pharmaceuticals*



**genzyme**  
Pharmaceuticals

## Market overview and challenges

---

The event catalogue of last year's CPhI exhibition in Frankfurt, Germany, listed well over 1,000 companies involved in the global custom production of fine chemicals such as intermediates, excipients and active pharmaceutical ingredients (APIs) for the pharmaceutical industry. The line between the fine chemical and the speciality chemical producers is not always clearly defined. Historically, most suppliers in the fine chemical business forward-integrated a pre-existing bulk chemical business (fertilizers, dyes, explosives, etc.) along the value chain. Others have been spun out of pharmaceutical companies and only a small number of the players have been incorporated with the intent to produce fine chemicals.

The companies vary in terms of size (revenues), resources and complexity of the chemical technologies. The top 500 companies each report revenues above \$80 million according to a Frost & Sullivan survey. This is generally considered the critical mass for a fine chemical company to compete effectively in the pharmaceuticals arena and manage the inherently high attrition rate in drug research and development. Some of the larger players complement their project based custom manufacturing business with an integrated, less risky product catalogue business. Mid-sized companies frequently mitigate the custom manufacturing business risk with a traditionally lower margin but steady generic API business. The smaller market players develop special technology competencies to compete in niche markets. Interestingly enough, the three tiers of large, mid and small-sized companies split the market in almost equal revenue portions<sup>1</sup>.

On the customer side, earnings reports recently published by drug companies show that the pharmaceutical and biopharmaceutical industries are not exempt from the current economic slowdown. Unfavorable economic factors require drug developers to prioritize and streamline development pipelines. Furthermore, established drug companies are under pressure from fading patent protection and increasing generic competition. The industry's sales growth has slowed to a mere 5% even in the years before the current recession<sup>2</sup> and the FDA's approval rate for new drugs remains low. In 2008, approvals were granted for 21 new molecular entities and 3 biologic license applications<sup>3</sup>. There are no clear signs of rising R&D productivity and higher approval rates for new products. In addition, less venture capital is flowing into the biotech arena today, forcing small companies to postpone development projects and restructure their operations in order to balance ever-dwindling cash reserves.

In light of these unfavorable economic trends one may speculate that global manufacturing overcapacity will intensify competition and lead to further business consolidations on the supplier side. Concerns are justified in particular for fine chemical companies without unique technologies or production capabilities as well as those missing the critical mass to compete in a global market place and overcome temporary project portfolio shortcomings and periods of increased margin pressure. Their businesses are also at risk of being absorbed by more cost competitive Indian and Chinese market players.

## Differentiation strategies and success factors for the future

---

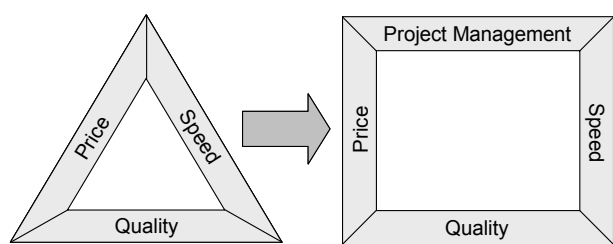
Suppliers with insufficient capability differentiation are exposed to increasing cost pressure and the threat that business will go elsewhere, namely to Asia. A number of Indian companies have progressed to become reputable suppliers of advanced intermediates, generics and in some cases, even of APIs. China emerged in recent years as a rich source for low-cost basic intermediates and building blocks. Shifting production from Europe and the US to Asia is thus an obvious strategy for established companies to stay cost competitive.

Divested Western assets on the other hand became attractive acquisition targets for Indian companies looking for closer access to the largest markets for fine chemicals.

Investments in expensive equipment and capabilities for the manufacture of high-potency compounds, or those requiring hazardous chemistries, offer some competitive protection due to the know-how and top-dollar entry barrier. In-depth knowledge of specialized process technologies such as simulated moving bed technology or super critical fluid technologies can open the door to competitively advantaged niches.

Considering the quest for highly potent, selective and low-dose drug candidates with optimal risk-benefit profiles, paralleled with the emerging trend towards the development of specialized drugs for personalized medicine applications and orphan indications, it is assumed that material requirements for many future APIs will stay below 10 tons per year. Consequently, the target markets of custom manufacturers with large operations overlap more and more with those of niche players. The ability to leverage economy-of-scale effects, in other words, lost some importance as a differentiating factor over the last few years.

Similarly, more and more companies are mastering the standard set of chemical reaction technologies. With increasingly overlapping technical capabilities, market players today are trying to differentiate on the basis of the breadth and quality of their service offerings. Small and eventually mid-sized companies have an advantage in terms of responsiveness and flexibility. Traditionally, the paradigm in the industry has been illustrated by the triangle “Speed – Quality – Price” with the understanding that customers had to accept trade-offs between three somehow conflicting interests.



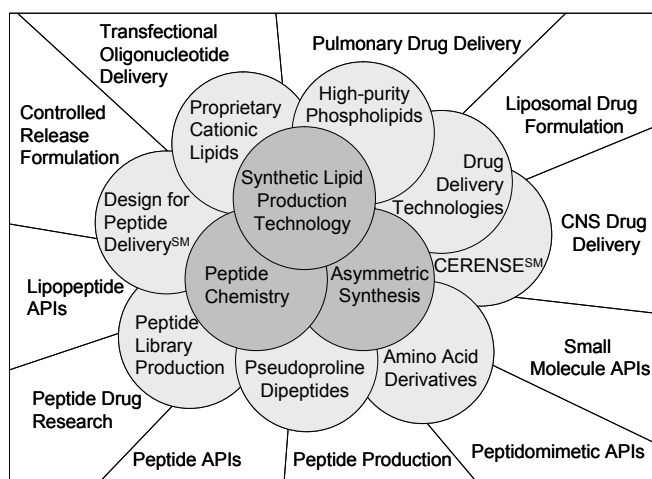
At Genzyme Pharmaceuticals we believe the industry has shifted towards a new paradigm. Complying with GMP requirements and meeting the customers’ quality criteria are considered a must. Today, customers expect timely delivery of compliant goods at the best possible price and in addition seek effective project management that includes open communication, regulatory consulting, and filing support.

The drug development process is complex and non-linear with varying priorities. Custom manufacturers must manage the uncertainties of the drug development process with flexible facility and resource planning. Effective project management therefore requires frequent communication with the customer to facilitate the adaptation process, manage internal and external stakeholder expectations, and direct cross-company and cross-cultural team interactions towards valued outcomes.

In trying to answer the question “What are the important differentiators that distinguish the winners?”, three decisive criteria can be listed in line with Peter Pollak’s view on the industry<sup>1</sup>: a) the suppliers commitment to make their fine chemical business a key contributor to the overall company success; b) a global presence with objectives to expand the market area as well as benefit from regional manufacturing cost differences; and c) differentiating technologies.

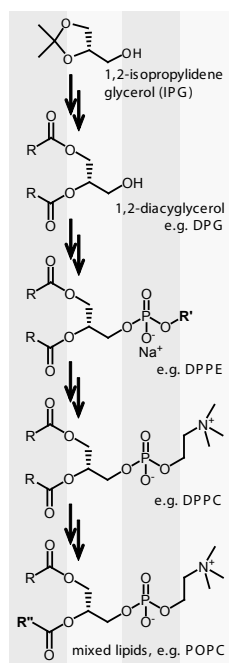
## Technology-driven custom manufacturing at Genzyme Pharmaceuticals

With a track record of more than 20 years in the fine chemical business, Genzyme Pharmaceuticals, a business unit of Genzyme Corporation, fosters a number of core competencies that provide a solid foundation for future business. Genzyme Pharmaceuticals not only offers contract manufacturing capabilities to the pharmaceutical industry, but has also been involved for many years in the large-scale production of high-value components for the electronics industry, thereby developing special expertise in polymer chemistry and cross-coupling reactions.



As illustrated, Genzyme Pharmaceuticals' fine chemical business is based on differentiating capabilities in synthetic lipid production, peptide chemistry and asymmetric synthesis. A catalogue of core technology-derived GMP product and service offerings complement the custom manufacturing business in niche markets ranging from peptidomimetic API manufacturing to oligonucleotide delivery. Some selected offerings are presented below in more detail.

**Phospholipids:** Phospholipids, a class of lipids and the main component of cell membranes, are normally isolated from natural sources such as soy bean extracts. Genzyme Pharmaceuticals, however, is the leading company in the scale-up manufacture of purely synthetic phospholipids under GMP conditions. The multi-step synthesis starts from 1,2-isopropylidene glycerol and gives access to a wide range of phospholipid compounds with consistent batch-to-batch quality. Synthetic phospholipids have the advantage of being highly pure, single compounds which render them particularly suitable as pharmaceutical excipients for liposomal and pulmonary drug delivery.

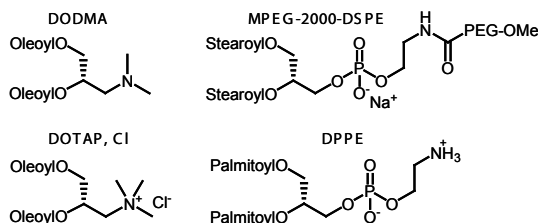


Liposome research led to the commercialization of a number of therapeutics such as Doxil® (Alza/J&J), AmBisome® (Gilead), Myocet® (Elan), and DaunoXome® (Gilead/Fujisawa). Liposome encapsulation generally sustains drug delivery, is suitable for both passive and active drug targeting, and thus reduces drug toxicity. Furthermore, clearance by opsonization and liver up-take can be slowed using polyethylenglycol conjugated lipids (also known as “sterically stabilized liposomes” or “stealth liposomes”).

With a strong standing in synthetic lipid production and extensive GMP manufacturing experience, Genzyme Pharmaceuticals is well positioned in this market. Some phospholipids are offered directly off-the-shelf. Yet, there is an increasing demand for custom manufactured lipids with special product purity, degradation stability and quality acceptance specifications in order to ensure a consistent formulation process and drug product performance.

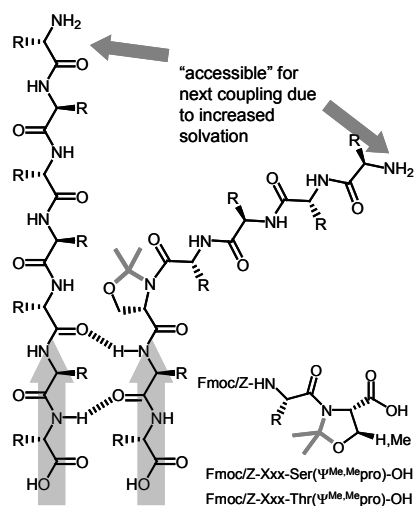
**Helper and cationic lipids:** Strong lipid chemistry capabilities allowed Genzyme Pharmaceuticals to enter new markets such as the custom manufacturing of lipopeptide APIs, lipidated vaccines or proprietary cationic lipids. The latter emerged as a preferred

choice for the non-viral delivery of oligonucleotide-based therapeutics, in particular RNAi therapeutics. Cationic lipids can complex nucleic acids, thereby forming so-called lipoplexes which have been shown to deliver oligonucleotides into the cells, a process known as cell transfection. Lipoplex encapsulation is achieved, in a nutshell, by preparing empty liposomes with cationic lipids and mixing them with the oligonucleotide of interest. Cationic lipids such as DODMA or DOTAP have been used early on in liposome-mediated transfection. In the procedure for cationic liposome-mediated transfection, the cationic lipid is usually mixed with a “helper lipid” such as MPEG-2000-DSPE or DPPE to increase its transfection potency.



Meanwhile, research laboratories around the globe are searching for safe and effective transfection reagents and delivery platforms,<sup>4</sup> the single largest barrier to the broad development of RNAi therapeutics<sup>5</sup>. Genzyme Pharmaceuticals successfully collaborates with a number of pharmaceutical and biotechnology companies to identify and custom manufacture lipids for oligonucleotide delivery.

**Peptide production and Design for Peptide Delivery<sup>SM</sup>:** Genzyme Pharmaceuticals entered strategic technology alliances with Mimotopes ([www.mimotopes.com](http://www.mimotopes.com)) and SurModics Pharmaceuticals ([www.surmodicspharma.com](http://www.surmodicspharma.com)) to complement its peptide manufacturing capabilities and extend offerings on both ends of the pharmaceuticals value chain.



Mimotopes is a global leader in high quality research-grade peptide products and applications for the drug discovery industry. Mimotopes’ proprietary peptide library synthesis technologies and hit-to-lead chemistry services complement Genzyme Pharmaceuticals’ offerings in the GMP custom manufacturing market place. The companies exchange technology know-how to the benefit of mutual customers ([www.peptidechain.com](http://www.peptidechain.com)), for example to overcome peptide synthesis difficulties or in the field of lipid-vaccine conjugates which are known to be powerful adjuvants<sup>6</sup>. Mimotopes is an industry pioneer in applying pseudoproline building blocks<sup>7</sup> which Genzyme Pharmaceuticals offers off-the-shelf in high quality suitable for peptide API production<sup>8</sup>. There is a noticeable industry trend to longer peptide drugs, often containing difficult sequences that may cause aggregation, insolubility, and ultimately poor product yields.

Pseudoproline building blocks are peptide backbone protection groups which disrupt secondary structure formation during the chain assembly process and ultimately result in crude peptide material with higher yield and improved purity<sup>9</sup>. For illustration, the insertion of a single pseudoproline enables a more economical scale-up production of glucagon-like peptide (GLP-1) hormone derivatives which are currently in late-stage development for Type 2 diabetes treatment.

Peptide drugs are typically designed by discovery chemists for potency, molecular target selectivity and if possible, increased serum stability. The collaboration between SurModics Pharmaceuticals and Genzyme Pharmaceuticals focuses on the delivery aspects of the peptide drug development process. Scientists at SurModics Pharmaceuticals draw upon a long track record of successful projects centered around long-acting parenteral (or local) formulations using biodegradable polymers (e.g. PLG) to achieve systemic and site-specific delivery for days, weeks, and months. The result of the collaboration is a formulation service with integrated peptide production capabilities known as Design for Peptide Delivery ([www.d4pd.com](http://www.d4pd.com)) that is tailored to screening and optimizing peptide properties for drug delivery. The Design for Peptide Delivery approach identifies and, if necessary, optimizes peptide physical and chemical properties early in drug development, so as to match a peptide with the properties of microparticles, implants and other drug delivery formulations required for optimal drug delivery. Combining the capabilities of both companies generates new market opportunities in drug manufacturing and formulation, which benefits customers and ultimately patients by jointly developing sophisticated pharmaceutical products.

## Conclusion

---

Global competition in custom manufacturing has dramatically shifted. Formerly dominating suppliers from the West are facing competition from nearly all over the world. Responding to the threat that business might go elsewhere, some companies are changing business strategies to extend geographic presence for more low-cost production capacities or closer access to attractive markets, develop investment-intensive chemistry capabilities, or further leverage existing economies-of-scale.

Genzyme Pharmaceuticals' custom manufacturing business is based on long-standing competencies and technologies. By striving for leadership in niche technologies, Genzyme Pharmaceuticals has the strategic vision to strengthen its business and develop new market opportunities.

## References

---

1. Peter Pollak (2007), *Fine Chemicals – The Industry and the Business*, Wiley-Interscience
2. Ann M. Taylor (2007), *For Better or Worse*, C&EN, Feb. 12, 2007, pp. 21-34
3. Bethan Hughes (2009), 2008 FDA drug approvals, *Nature Reviews Drug Discovery*, Vol. 8, pp. 93-96
4. For example see Akin Akinc et al. (2008), A combinatorial library of lipid-like materials for delivery of RNAi therapeutics, *Nature Biotechnology*, Vol. 26 No. 5, pp.561-569
5. Alan Sachs, Merck & Co, online publication, January 20, 2009
6. BenMohamed, L., Wechsler, S. L. & Nesburn, A. B. (2002), *Lancet Infect. Dis.* 2, pp. 425–431
7. W.R. Sampson, H. Patsiouras & N.J. Ede J. (1999), *Peptide Sci.* 5, p. 403
8. [http://www.genzymepharmaceuticals.com/pdf/Genzyme\\_Pseudoproline\\_dipeptide\\_flyer.pdf](http://www.genzymepharmaceuticals.com/pdf/Genzyme_Pseudoproline_dipeptide_flyer.pdf)
9. T. Woehr, F. Wahl, A. Nefzi, B. Rohwedder, T. Sato, X.C. Sun and M. Mutter J. (1996), *Am. Chem. Soc.* 118, p. 9218



AMERICAS  
Tel +1 800 868 8208; +1 617 374 7248  
Fax +1 617 768 9765  
Email [pharmaceuticals@genzyme.com](mailto:pharmaceuticals@genzyme.com)

REST OF WORLD  
Tel +41 61 906 5959  
Fax +41 61 906 5958  
Email [pharmaceuticals.swiss@genzyme.com](mailto:pharmaceuticals.swiss@genzyme.com)

[www.genzymepharmaceuticals.com](http://www.genzymepharmaceuticals.com)