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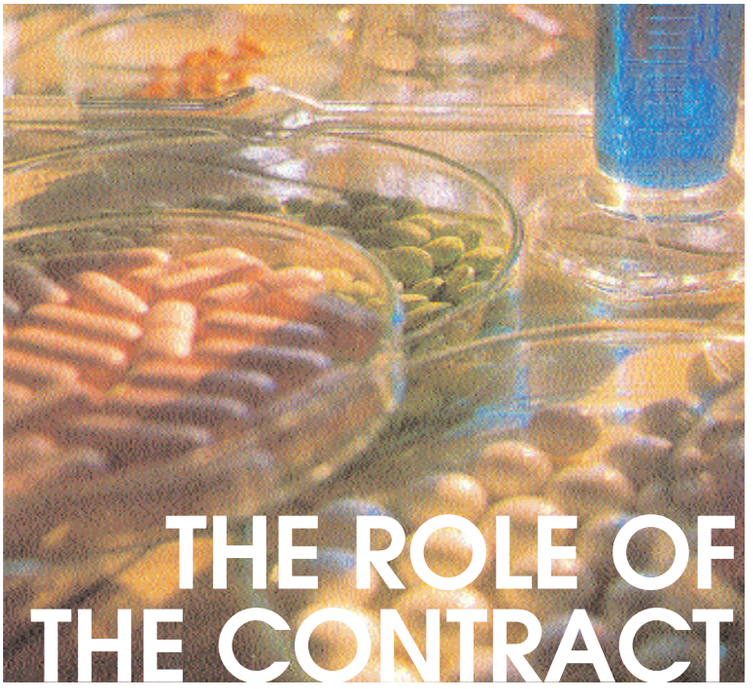

# THE ROLE OF THE CONTRACT RESEARCH ORGANIZATIONS WITHIN THE FINE CHEMICAL INDUSTRY

**Contract Research Organisations, such as Caffaro's new Serichim Research Centre, design synthetic methods for new drug molecules and develop viable production processes.**
There is an increasing demand for these services, mainly from the pharmaceutical and fine chemical industries. The discovery of "breakthrough processes" has become the key differentiator against the growing competition from India.

Following the example of other industries, such as automotive, fashion and IT, also the pharmaceutical industry is recurring more and more to outsourcing non core activities. The single most important piece of the total "outsourcing pie" is the production of intermediates and active pharmaceutical ingredients (= API) by the fine chemicals/custom manufacturing industry (Figure 1).

Although the majority of this production is still done in-house by the drug companies, it nevertheless accounts for about $ 7 billion of the total outsourcing market of approximately $ 30 billion. Dosage form production, clinical and formulation development are all also outsourced in multi billion dollar per year amounts. Process development is one of the two main domains of the Contract Research Organisations (CRO). Their task is best described as follows:

- design of synthetic methods for the preparation of specific API molecules;
- development of efficacious and efficient processes for their industrial scale production.

Print version of a paper titled *L'importanza delle Organizzazioni per la Ricerca a Contratto nell'ambito della Chimica Fine* presented in occasion of the dedication of Serichim's new Research Centre at Torviscosa on 29 May 2004.

In order to identify business opportunities for CRO's, it is worthwhile to look at the life cycle of a drug (Figure 2).

The support of Contract Research Organisations is sought primarily at the beginning of the life cycle. Actually, at "entry gate no. 1" samples of the new drug molecule are needed for *in vitro* tests. Provided the results are encouraging, the laboratory method of synthesis needs to be scaled-up to a viable industrial scale process in a second step. Entry gate no. 2 is at the interface between CRO's and CM's (= Custom Manufacturers). The definitive production process has been established at this point, and semi-commercial

scale quantities of the new API have to be produced for extended clinical tests. Depending on the availability of an appropriate pilot plant, this can either be done by CRO's or CM's.

At entry gate no. 3 competition from "we-too" drugs within the same therapeutic class and with similar structure begins to emerge. More economic manufacturing processes are now required. Due to their year long manufacturing experience CM's have aggregated a substantial know-how on all aspects of the chemistry of the target drug molecule. They have, therefore, a better starting position for looking at alternative syntheses. At entry gate no. 4, the drug is about to loose patent protection and generic companies are preparing to enter the field. They usually source the active substances from fine chemical companies.

The business condition of the CRO's is mainly driven by four elements, two of each on the demand and the offer side. On the former, it is the number of new lead molecules and the outsourcing policy of the pharma industry, on the latter is the competition from both Western and Far East CRO's. Within the global pharma industry, there are about 5,000 molecules in the various phases of drug development at present. The number is likely to increase because the new research tools, such as rapid throughput screening and combinatorial chemistry generate new lead compounds at a higher rate than before. Therefore, it can be reasonably assumed that internal chemical synthesis capabilities of the innovative pharma companies will become a bottleneck and CRO's will be asked more and more to provide samples as well as developing viable synthetic routes.

The situation is less favourable with regard to the competitive situation. Although the new Research Center of Serichim is rather unique in Italy, a large number of similar CRO's exist already in countries like the U.S., England, Germany and Switzerland.

The world's largest CRO, Albany Molecular, has sales of about $ 35 million, and the no. 10, Girindus, about $ 15 million. Within the top ten companies, there are also three leading Fine Chemical/CM companies that offer contract research, namely DSM (The Netherlands), Rhodia-Chirex (USA/UK) and Lonza (Switzerland). These companies have integrated backwards in order to be able to participate right from the beginning at the new drug development of their partners in the pharmaceutical industry. It is difficult, however, to reconcile two activities requiring totally different cultures under the same roof. Contract research is a pure service business. The price that CRO's charge is based on the time the research chemist spends on a given assignment. The most frequently used unit is the "Full Time Equivalent" (= FTE), meaning the price of a chemist (plus ancillary services) working for one full year on a given project. In sharp contrast, CM is a product business, and the CM's charge prices on a dollar-per-kilogram basis.

Serichim, with its highly qualified scientists on the one hand, and its state-of-the art research and analytical laboratories on the other hand, is well poised to challenge its Western competitors. The situation is less comfortable with regard to the competition from CRO's established in Far East countries, which are mushrooming. They offer a combination of high skill and low cost, which is difficult to beat. Thus, FTE's charged by Western CRO's are in the area of $ 150,000 per year, those from Indian companies are about $ 30,000! As a result, the top two Western CRO's, Albany Molecular and CarboGen, had to reduce personnel in the course of the last two

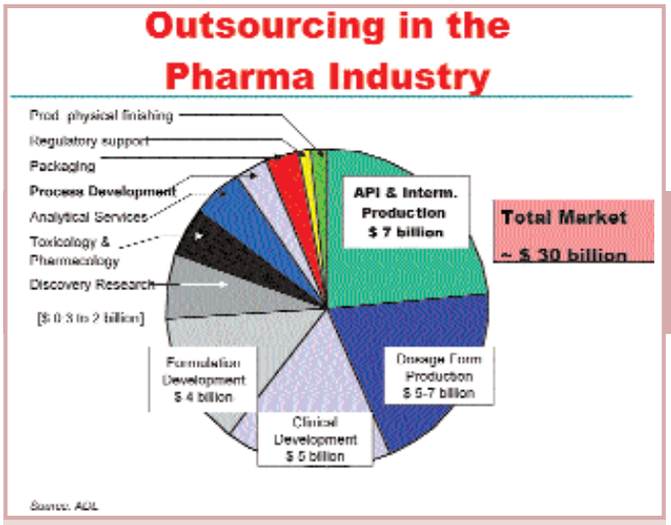


Figure 1 - Outsourcing in the pharma industry

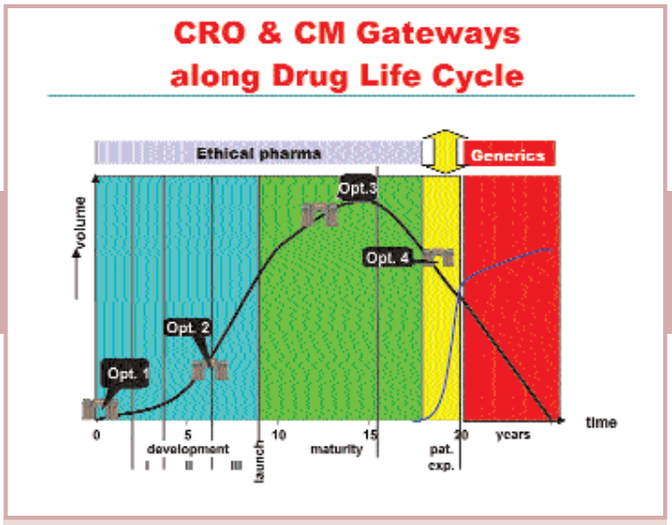


Figure 2 - CRO & CM gateways along the drug life cycle

years. A convenient yardstick for measuring the output of the CRO's is the number of Drug Master Files (= DMF's) developed. The DMF's are the documents which contain all data on the synthesis of a new drug. They have to be submitted to the FDA in order to get the authorisation to produce it. Until the turn of the century, Italy has always held the largest number of DMF submissions. The situation has deteriorated in the recent past: with 42 DMF submissions, Italy still was ahead of India with 38 submissions in the year 2000. Only two years later, the situation had changed dramatically. Whereas India has submitted 82 DMF's, Italy had dropped to 25!

The ascent of India becomes also evident when one analyses the situation of the ten top selling drugs in the world (Table). Despite the fact that the patent expiration for these blockbuster drugs is still up to seven years away, Indian companies already have submitted DMF's for seven out of the top ten drugs. No submissions have been made so far for Johnson & Johnson's Erypro, a biopharmaceutical requiring a special manufacturing know-how, for Glaxo SmithKline's Seretide, which is a combination drug and for Takeda's Ograstro (Lansoprazole).

Whereas the situation is particularly difficult with regard to the "quick and dirty" synthesis of small samples, it is more comfortable with regard to the second key activity of CRO's, namely process development. The challenge here is to find new, breakthrough processes for the industrial scale production of API's of major drugs.

In order to create a distinct competitive advantage, process development must not be geared at gaining a few percentage points of yield here and there, or improving on the recovery rate of solvents. The prime targets must rather be:

- to cut significantly the number of steps required to make a given API;
- to switch to more readily available raw materials;
- to have a close look at work-up.

Drawing a mass balance of a process will reveal that the number of pure chemical reaction steps accounts only for a quarter of the total process steps, the rest being work-up. In most instances, work-up means separations, and separations are seldom neat. In liquid/liquid separations, there are intermediate fractions, in liquid/solid separations filtration problems to cope with and so on.

Or, talking in the language of alpinists, the challenge is not to improve marginally on your existing track - comprising several bivouac s -, but to find the diretissima leading directly from a conveniently located base camp to the peak!

Sertraline (Zoloft) (Figure 3) is an example in case for such a breakthrough process development. Zoloft is a blockbuster antidepressant drug of Pfizer (global sales: $ 3.4 billion (2003), Table). The original synthesis had been developed in the company's own research laboratories in Groton (CN, USA). The pivotal intermediate, 4-(3,4-dichlorophenyl)-3,4-dihydro(2H)1-naphtalenone ("Tetralone") was obtained in a demanding four step synthesis starting from diethyl succinate, benzoyl chloride and *o*-dichlorobenzene. The situation changed dramatically, when Guy Adrian, at that time head of R&D of the independent French fine chemical company Finorga (Finorga has been acquired by the German company Dynamit-Nobel in early 2001), succeeded in developing a one step process. It consists of a Friedel-Crafts reaction whereby one mole of α-napthol and *o*-dichlorobenzene each are reacted with two moles of aluminium trichloride. Thanks to this breakthrough, Finorga became the no. 1 supplier of tetralone intermediate to Pfizer.

The most recent development in the Sertraline process concerns the transforma-

## *Contract Research Organisations are sought primarily at the beginning of the life cycle*

**API-for-Generics… the Ascent of India**

| no. | Exp.[1] | Sales[2] | Name/Company | Challenger |
|---|---|---|---|---|
| 1 | 09 | 10.3 | Lipitor/Pfizer | Ranbaxy |
| 2 | 06 | 6.1 | Zocor/Merck | Ranbaxy |
| 3 | 11 | 4.8 | Zyprexa/Eli Lilly | Dr. Reddy's |
| 4 | 06 | 4.5 | Norvasc/Pfizer | Dr. Reddy's |
| 5 | 09 | 4.0 | Orgastro/Takeda | |
| 6 | 04 | 4.0 | Erypro/J&J | |
| 7 | 08 | 3.8 | Nexium/AstraZeneca | Dr. Reddy's |
| 8 | 11 | 3.7 | Plavix/Sanofi | Dr. Reddy's |
| 9 | | 3.7 | Seretide/GSK | |
| 10 | 05 | 3.4 | Zoloft/Pfizer | Dr. Reddy's |

[1] *Year of patent exipiration (indicative)* [2] *$ billion (2003). Source: IMS Health*

tion of the tetralone to the final Sertraline. This involves a cumbersome racemic separation through the mandelic acid salt of an advanced intermediate. The introduction of the "Simulated Moving Bed" technology for the isolation of the chiral form might enable Pfizer, to retain a competitive edge even after patent expiration.

The development of Oseltamivir Phosphate (Tamiflu), Figure 4, is another example for breakthrough process development. Roche's anti flu drug was running behind the development of Glaxo Wellcome's "Relenza" right from the beginning. Therefore, Roche was forced already in phase I/II of the project to develop a competitive process. The results of the process development which where presented by Dr. Karpf at the 10 years anniversary of CarboGen, a Swiss process development company (acquired by Solutia (USA) in 2000) are really fascinating:

The original 16-step (!) process had been developed by the licensor of Tamiflu, GILEAD (GILEAD still holds rights for the USA). It started from the expensive natural raw material (-) quinic acid, comprised a hazardous azide intermediate and had an overall yield of about 10%. Roche first substituted quinic acid with the more readily available shikimic acid, eliminated the azide intermediate, reduced the number of steps to about 10 and increased the yield to 35%.

- A completely new synthesis based on cheap raw materials was developed. It comprises a.o. the enzymatic resolution of the Diels-Alder adduct obtained by the reaction of the key raw materials, furane and ethyl acrylate.
- A second new process, dubbed "meso concept" was developed, starting from pyrogallol resp., a pyrogallol derivative. In order to facilitate catalyst recovery, supercritical carbon dioxide is used as solvent.

So, the CRO CarboGen was a major contributor to the development of substantially improved processes for Tamiflu!

The last question to be addressed, which of the two customer categories, the fine chemicals or the pharmaceutical industry, are the more attractive "hunting grounds" for CRO's.

The advantages and disadvantages of doing business with the fine chemical companies are:

- they are under great pressure to develop more performing manufacturing processes;
- there are many such companies in Italy (typical examples are Dipharma, Erregierre, Fis, Flamma, Procos, Recordati, Sims and Zambon), and therefore within easy reach of a local CRO;
- as the custom manufacturing agreements are confidential, it is not publicly known what kind of products and processes they are involved in. Therefore a proactive approach (in the sense of making concrete proposals for innovative processes) is almost impossible for a CRO.

With regard to the pharmaceutical companies the situation is as follows:

- at least the leading drug companies have large portfolios of API's and therefore there are a priori more opportunities than with small fine chemical companies;
- they outsource both the sample synthesis and process development tasks (fine chemical companies typically do only the latter);
- the competition for obtaining business is fiercer.

All in all, the creation of the Serichim Research Centre adds a bright and vivid colour patch to the tavolozza (palette) of the Italian fine chemical industry!

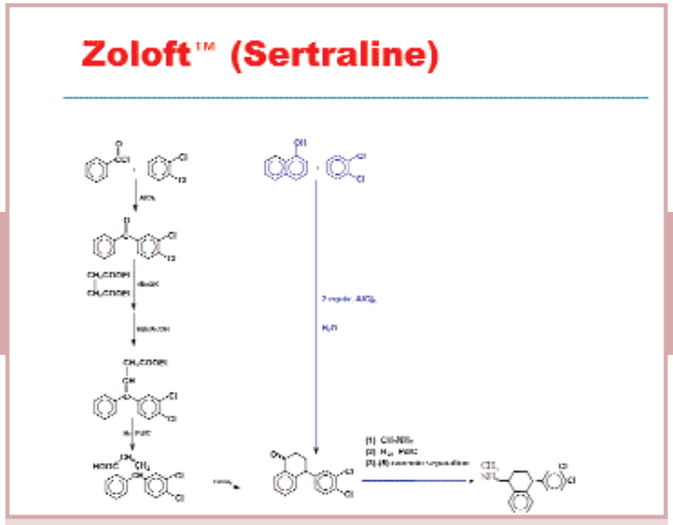


Figure 3 - Sertraline (Zoloft)

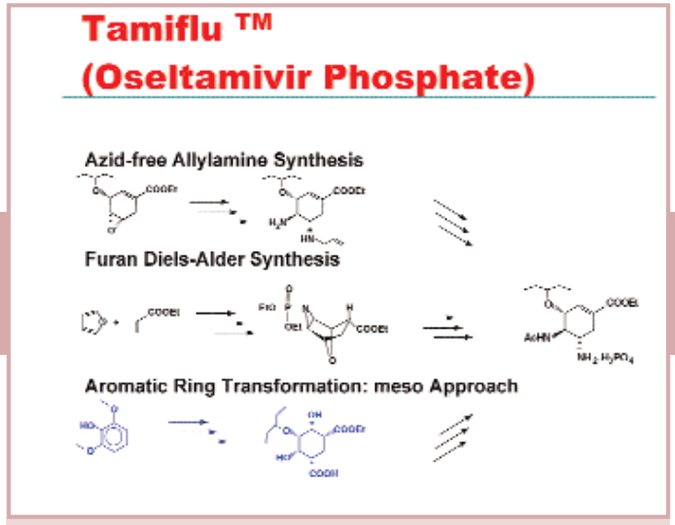


Figure 4 - Oseltamivir Phosphate (Tamiflu)