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The contract services landscape: Pharma, CRO and CMO perspectives

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Contract manufacturing in life sciences has always been confined to small Pharma and biotech companies. Big Pharma have used, until now, contract manufacturing organizations (CMOs) only to meet excess demand beyond their own manufacturing capacities or for packaging needs in particular geographic areas. Small Biotechnology firms have hired them because they needed to choose a more logical and economical pathway. Today, increased competition, patent expirations, revenue pressures, mergers and acquisitions have led also Big Pharma companies to recognize the value to outsource chemistry research and manufacturing to contract organizations. The aim of this change is to get safe, efficacious and profitable new products into the pipeline and do so in a timely and cost effective way. Time is in fact a critical factor during the drug development process. Developers calculate the time needed to conduct the required preclinical studies and the phase I clinical formulation. Any time still available prior to the date of the investigational new drug (IND) application is used for further investigation into chemical optimization, scale up and formulation. API delivery is often the critical path of the whole timeline (especially with very difficult biological material and / or accelerated clinical trials). Late delivery can cause significant negative economic consequences. According to analysts this risk can be minimized by using an experienced and easily accessible contract research organization (CRO).

To give an overview of what is going on in the drug development contract services management, Chemistry Today has interviewed experts with various backgrounds. Three different sets of interviews have been organized and addressed to the key people in the outsourcing process. The first set considers the use of outsourcing from the position of pharma companies. In the second set of interviews we have considered outsourcing and partnering from the perspective of Contract Research Organisations (CROs). The final

group of interviews addresses the thoughts of larger Contract Manufacturing Organisations (CMOs).

PART1. INNOVATOR PHARMA COMPANIES

Partnerships

The industry continues to evolve towards a full service model with CRO offering services from the earliest stages of development through clinical trials and post - approval research. This, together with the fact that FDA has increased

requests on safety data, has led Pharma companies to increase their partnerships. Let's enter into details of this decision. According to **Walter Cabri** - R&D - Chemistry and Analytical Development Director - Sigma Tau - one of the targets nowadays is to be flexible and cost competitive. In other words to move from fixed to variable cost. "You spend if you need to carry out some activities taking advantage of the best expertise available on the market", he affirms. "Well, as a consultant in the Pharma market", states **Alan Harris** - Partner - Alacrity Pharma Associates - "I can give reasons from two different perspectives: a larger Pharma and smaller emerging innovator". "There have been many words written and spoken concerning

the plight of big Pharma companies hit by the double whammy of drugs going off patent (often called the patent cliff) and their inability to bring new innovations to the market", underlines Harris. According to Harris the response from **Big Pharma** is therefore twofold: they are looking to reduce costs to remain profitable and also to increase innovation to bring more drugs to the market. Most have the same strategy for cutting costs which is to cut internal manufacturing, where outsourcing of API and drug product production, especially in Asia, is seen as a viable alternative. "By cutting internal R&D they are aiming to achieve both goals through lowering cost of maintaining large R&D sites whilst simultaneously

Time is a critical factor during the drug development process

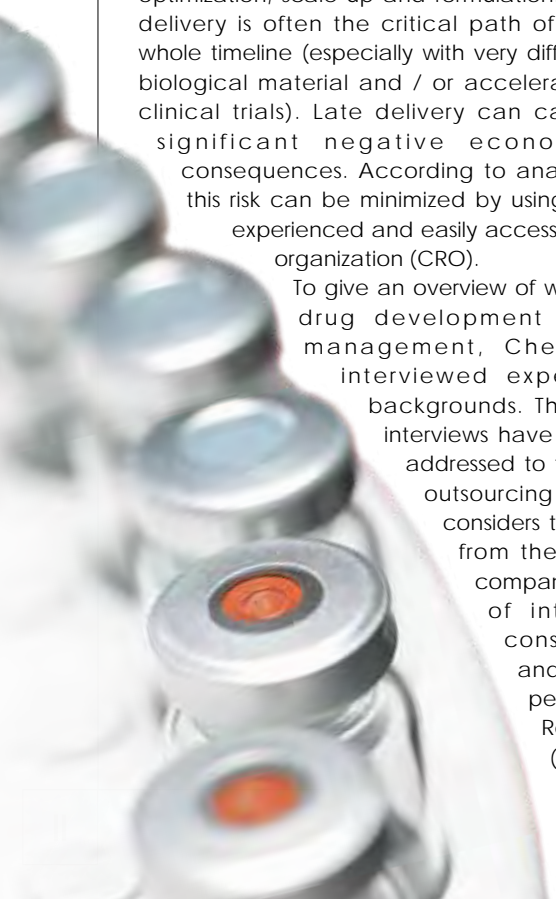
Big Pharma are looking to reduce costs to remain profitable and also to increase innovation to bring more drugs to the market



Walter Cabri,
Sigma Tau



Alan Harris,
Alacrity Pharma
Associates



filling their pipelines through partnering with smaller companies who, they believe, to be better at drug hunting", Harris explains to us. This strategy has been implemented in two waves of externalization. The first wave was the reduction in size or closure of many internal manufacturing sites and outsourcing of commercial manufacturing. For example, Pfizer have closed many sites (1). Chief financial officer Frank D'Amelio, is reported to have said that Pfizer was able to cut manufacturing because it has "a wide array of outsourcing opportunities at various stages of implementation". But Pfizer is not alone as can be seen from a survey of job cuts by large Pharma (2). The second wave is now occurring in R&D. There have been announcements of job cuts and reduction in the number of R&D sites from many large Pharma companies including Lilly, GSK, AZ and Pfizer (3). "Overall, for large Pharma, the internal cuts drive the need for externalisation", Harris confirms. The position is much different from the perspective of **Smaller Emerging Innovators**. In many cases their aim is not to bring discoveries to the market alone but to develop them to stage where they can form Partnerships with Large Pharma companies to perform the very costly late stage clinical trials and other development programmes. "Outsourcing and Partnering are not so much desirable for them but essential and falls into two main stages", Harris points out. The first stage is finding the right companies to work with to help them to perform their early development studies, since rarely will they have the internal experience or resources to do this all on their own. To achieve this they need to be "smart" outsourcers, i.e. they need to understand what is required to be done and what companies are out there that can help them to achieve it. "This is where enrolling the assistance of experienced Consultants in the areas of drug substance/product supply, safety toxicology, clinical trials, regulatory, etc., can help them to make the right choices", Harris adds. The second stage is in Partnering with Large Pharma companies to get the help they need to fully develop the drug. To achieve this they will need to go through a due diligence process to ensure the work performed up to that point is of the appropriate quality. "Forming these Partnerships is often the key to securing the future of the company", Harris concludes.

But which partnering relationships will expand the most over the next five years?

According to Harris there is a large contrast between Big Pharma wanting to cut resources and costs and Small Pharma who simply do not have the right resources available. "For Large Pharma we can expect to see a continuation of the trend in outsourcing of commercial supply of drug substance and drug products, much of which is likely to go to Asia. Many companies are reducing their development capacity in these areas and there will be also an increase in the level of outsourcing of development activities and supply of materials needed for clinical studies", Harris informs us. "Even if I belong to a small-medium sized company in the international panorama and therefore my point of view is quite different, I agree with you: I think that toxicological and clinical services are and will be more and more extramural", states Cabri. "Moreover, Large Pharma are viewing the increasingly affluent

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middle classes in the large Asian countries as an opportunity to sell more drugs. I anticipate that there will be increased sales of generics to these countries with large Pharma branding. This will lead to more partnerships of the type recently announced between AstraZeneca and the Indian generic supplier Torrent Pharmaceuticals (4)", says Harris.

The Emerging Pharma sector has been hit by the recession and the lack of availability of funding. "However, with Large Pharma placing many of their hopes on the success of these ventures, as we come out of recession we can expect many new companies to be formed or existing ones to grow", Harris states. As these companies develop they will need to outsource the supply of API and drug product in order to perform Phase 1/2 studies. Small companies are still reluctant to outsource this type of work to Asia as it is harder to identify the companies required and to manage the situation calls for much effort. They therefore tend to work with local suppliers for this type of outsourcing and will look to form partnerships with small, local, CROs.

But is Outsourcing always the right choice?

"Yes", replies Cabri. "You move from fixed to variable cost and therefore this introduces a large amount of flexibility". "Well, if you have the capability and capacity to do it in-house there are potentially no advantages to outsourcing - if you outsource you are paying for it twice over if you have internal resource which is under-utilised", Harris says. "But, I agree with you when you say that outsourcing often has real advantages in costs and delivery, as well as potentially offering better control because changing internal project priorities often lead to wasted usage of internal resource", Harris outlines. "If you lack the ability to complete the programmes you need in-house then outsourcing will almost always give you a cost saving, and a potential speed advantage, over trying to establish an in-house capability", Harris concludes. "The lack of new blockbuster and the generic competition is determining a change in the pharmaceutical industry. This is not the golden age of the pharmaceutical industries. It is only a matter of time, the change is on the news every day. All the companies are announcing restructuring, closure of facilities in all areas from discovery to development and production. How many Big Pharma are now disinvesting in Europe? Then the choice is to invest in emerging areas or use contract services. Medium small size companies prefer to use contract manufacturing service organisation", points out Cabri.

Of course the choice of the right supplier is key and sometimes communication problems are an issue especially if emerging markets are taken into consideration. "You are right", Cabri affirms. "This is the most difficult task. During the selection process, the outsourcing Manager must identify the distinctive competences of the supplier from a technical and cultural point of view, namely technical/scientific know how, culture, pro-activity, communication skills, customer oriented project leaders etc.", he explains to us. There are in fact various aspects to communication. The first is the time differences "and there is not much you can do about that", Harris says. "However, companies in emerging markets tend to be very flexible in their approach and if winning the business means staying very late, or getting up very early, they will



usually compromise to work to your time zone", Harris underlines. The second is the mechanics of communications. With modern email systems and teleconferencing this area of communication can be mostly overcome. "However, people often manage to deal with details as they arise in their own organisation but a lack of attention to detail can be dangerous if you are working remotely and relying on a weekly telephone call with a CRO", Harris warns us. Detailed, face to face meetings can be repetitive, but, as a basis for effective communication, are absolutely essential. The third area is in the language barrier. The language of business is English, but although many people speak it there are often nuances that need to be understood. "This is not just an issue with emerging markets though, even the US and the UK speak slightly different languages although both claim to be speaking English!", Harris says. "There is really no substitute for a series of face to face meetings if you are to overcome the language barriers. Verbal communication is only a small part of it and you often don't pick up every nuance in a teleconference", Harris states. For Emerging Pharma venturing into emerging markets is a huge challenge.

According to Harris if you are a small company with limited resource it is very difficult to justify the cost of sending people to distant countries to identify the right people to work with, even if anyone actually has the time to do it. This is even before you reach the challenge of working with the cultural differences. If you are a large multinational it is relatively simple to work with different cultures. You can employ people "on the ground" who are either natives of the country you are working with but have extensive experience of working in your own country, or you can employ someone from your own culture who has experience of working in many different ones. You can second people to work in foreign countries for periods of time to help them to understand the culture and this can be a big advantage if working on a late stage development or commercial project with a long delivery timescale. "There is one overriding golden rule though in all business interactions. You must be absolutely clear about the scope of the work to be performed and your expectations for delivery. It is also essential that these requirements are reflected in any contract drawn up", Harris concludes.

Contract Research and Manufacturing Organizations (CRMOs)

CRMOs are hybrid companies combining the services of CROs and CMOs, which are also abbreviated by some as CRAMS (Contract Research and Manufacturing Services). Their history is either a forward integration of a CRO, which adds industrial scale capabilities or backwards integration of a CMO. Are there pros and cons as opposed to stand-alone CROs and CMOs?

"I would say, one shop is always a preferred choice, however, there are no rules!", comes up Cabri. "For me, the only real advantage of a CRAMS company is for Small Emerging Pharma companies where they can find all the services they need in one place. This is less of an issue, and is a potential disadvantage, for Large Pharma who usually have relatively independent functional areas that each will handle the outsourcing in their area of expertise", states Harris. "In any CRAMS type company there will be strengths and weaknesses. Also it is not necessarily less expensive to use a single supplier for all your needs. So my personal view is even for Small Emerging Pharma there are potential pitfalls in using a single company and it is better to find and use the right stand alone CRO/CMO for the job in hand. This will require some

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The lack of new blockbuster and the generic competition is determining a change in the pharmaceutical industry

management but again is an area where Small Emerging Pharma might want to enlist the help of experienced Consultants", concludes Harris.

Key selection criteria

What are the key selection criteria sponsors expect from outsourcing partners?

"There are standard requirements like technical/scientific know how, quality, reliability, flexibility, track record, cost, pro-activity, communication skills and customer oriented project leaders" Cabri says. "In addition, in my experience, the capability to react when you have "deviations" or unexpected results is critical. In this context, scientific competence with speed is a determinant of distinctive competence", underlines Cabri. According to Harris there are six key selection criteria to every project which are displayed below.

1. The CRO/CMO must have the right level of technical competence to deliver to the company's needs. This can be difficult to ascertain by audit alone and so one is often reliant on the reputation of the company in the industry. For Large Pharma this is not too much of an issue as they can afford to run some projects at risk with supplier. In order to assess their capabilities in more detail and over a series of projects, they will be able to work out the strengths and weaknesses of the companies they deal with in order to decide which project are best fit with each supplier. For Emerging Pharma the issues are greater as they won't have the volume of projects to take this route and so they are reliant on external advice or the reputation of the company they wish to work with.
2. The supplier must have the right equipment and/or facilities to deliver the project. This criterion can quite easily be established by a site visit.
3. The approach of the supplier to their Safety Health and Environmental (SHE) risks is important. This can be established by an audit of the supplier. Working with a supplier who has a poor SHE record could jeopardize delivery and reputation.
4. There needs to be an appropriate Quality system for the work to be undertaken. This can be assessed by audit but this can be dangerous in the development phase unless it is focussed on risks to the project and the auditors fully understand any specialised areas and requirements.
5. The suppliers approach to corporate responsibility (CR) is also important particularly in emerging markets. Areas such as employee relations, use of child labour, etc could impact on the relationship with the supplier and with their ability to deliver the project. This could have consequences on the image of the company and can impact on investor decisions.
6. And finally cost. The price has to be right. "To me this is always the final criteria, the supplier needs to meet the minimum standards you require in all the other areas before you consider the price they are offering", Harris concludes.

Negative experiences

An example reported by Cabri

A company was supposed to produce material for toxicological studies. Instead of 1.5kg they delivered 1kg with a delay of 1 month. We found out later that they carried out extensive purification studies losing 30% of the material because a new peak was present in the chromatogram. The specs were clearly "draft" and the material for tox. We rapidly identified the impurity as a normal process related impurity coming from a starting material that did not add any toxicity to the target compound. Since the supplier did not inform us, the problem could easily have been solved by a simple change of the specs, we missed the opportunity to qualify a potential process related impurity and lost 30% of the product.

Contractual arrangements

For both our interviewees the typology of contract arrangements in the outsourcing arena is very dependent on what you are outsourcing.

Harris indicates several situations which are reported below.

- If it is a late stage project the ideal is to have a per Kg (or per tonne) price based on a forecast for volume requirements that you will provide to the supplier (in order for the required delivery timescales to be achieved by the supplier). At the other end of the spectrum for early phase laboratory development work an FTE (Full Time Equivalent) approach may be more appropriate.
- A fee for service type agreement is often appropriate for a chemistry project involving first scale-up where the expected yields may be uncertain. It can be agreed to process x Kg of starting materials through the process for y cost, with the supplier delivering all the material they obtain from the process.
"A development project is by its very nature not well defined in many cases. It is important to have a realistic relationship with some shared risk, so that unforeseen challenges can be handled on a reasonable financial basis. All relationships have to be professional, and this includes a reasonable fee for work done in return for reasonable behaviour in the face of new information", underlines Harris.
- For in-licensing or out-licensing then a milestone payment agreement is probably more usual. *"And milestone payments are the preferred choice of Sigma Tau"*, informs us Cabri.

From the interviewees' feedback we understand that there is a strong demand for early stage services from the supply side (Pharma) that could translate to higher business for CROs if their services are positioned to meet the demand and requirements of sponsors.

PART 2. CONTRACT RESEARCH ORGANIZATIONS (CROS)

CROs comprise Clinical CROs and Chemical CROs. The former address the clinical part of pharmaceutical development at the interface between drugs, medicinal devices, physicians, hospitals and patients. The latter provide primarily discovery chemistry, process research and development services (5).

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The CRO/CMO must have the right level of technical competence to deliver to the company's needs

CROs in general provide services to clients who seek a more cost-effective answer to their development needs. What is happening now is that the industry keeps on evolving towards a full-service model, with CROs offering services from the earliest stages of development through clinical trials and post-approval research. Moreover, because of FDA request for more safety data and increase of trial sizes, Pharma is outsourcing large global mega-trials now more than ever. This because the aim of Pharma is to shorten the drug development cycle time by using CROs, which may have greater expertise in a therapeutic area and/ or offer greater efficiency at lower cost.

Drug development process timeline

Time is a critical factor during the drug development process. This is well known by our experts who have indicated the factors contributing to the timeline, from when the work is commissioned until it is delivered. According to **Volker Wolfart** - Head of Process Research & Development - CARBOGEN AMCIS AG - there are a few different factors contributing to the overall cycle time: availability of raw materials, personnel and plant capacity at the CRO, the chemical workload and its complexity.

"The timeline is typically determined by the project scope and can vary from days to years" adds **Michael Trova** - Senior VP Chemistry leader - AMRI. *"A key factor in the successful outcome of the project is achieving the timeline set by the customer; AMRI prides itself on meeting and/or exceeding our customer's deadlines and creating added value by generating more efficient processes, deliverables, and intellectual property"*, he says. *"The time element is a critical factor in process development and API manufacturing as it has a direct impact on the clinical development of a drug candidate and varies with the phase of development. The time element becomes more critical for the biopharma clients in the early stages of development. Timely expeditious performance during this phase requires a combination of scientific knowledge and scale-up expertise. IRIX has earned a well deserved recognition in this space by scaling up successfully green chemistry and delivering the product to its clients typically in four to six weeks from initiating a production campaign"*, affirms **Mike Cruskie** - Vice President of Business Development and Supply Chain - IRIX Pharmaceuticals Inc.. *"In some cases, Pharma companies have ordered raw materials prior to the CRO selecting process, thereby cutting out this potential delay"* explains Wolfart. *"Personnel and plant capacity are highly dependent on market conditions, general availability of specialist equipment may also be a bottleneck. The chemical complexity and workload is highly variable too. In general time becomes an issue when the chemistry shows scale-up problems. Typically*



Volker Wolfart, CARBOGEN AMCIS AG



Michael Trova, AMRI



Mike Cruskie, IRIX Pharmaceuticals Inc.



Geoffrey Glass,
Patheon

timeline to deliver the first kgs of API is between 3 and 7 months (Labwork, production, release etc) depending on the length of the synthesis and the quality of the initial data provided" he underlines. "In the drug development business speed and agility is essential, in fact" states **Geoffrey Glass** – Patheon's Executive Vice President of Global Strategy, Sales and Marketing. To this end, Patheon launched an award winning program called the 4-6-8

promise. 4- Quick To Clinic™ solid dose molecules will be formulated and ready for distribution to phase 1 clinical trials in four months from receipt of API. "We have actually done this successfully for clients in less than four months", underlines Glass. 6- Quick To Market™ solid dose or liquid products will be transferred and ready for regulatory filing in six months from receipt of analytical methods and API. "This enables clients to move products very quickly out of their plants and facilitate rationalization programs" he says. 8- Quick To Market™ aseptic liquid or lyophilized sterile products will be ready for regulatory filing in eight months from receipt of analytical methods and API. "We must not forget that there is a strong dependency of the criticality of timelines related to the client" states Wolfart. "Biotech startups, new and virtual companies are often very aggressive in their timelines, take best case assumptions and plan i.e. the animals and patient tests immediately after a first anticipated delivery of API is scheduled, resulting in a lot of time pressure on the CRO to make it in time in order not to lose their slots. Big Pharma and companies with a long track records plan more realistically and anticipate reality in their planning. They also know about potential problems and plan accordingly. For companies with a smaller household of experts the CRO can provide valuable council in plan and to realize realistic scenarios", he concludes.

Small CROs versus full service CROs

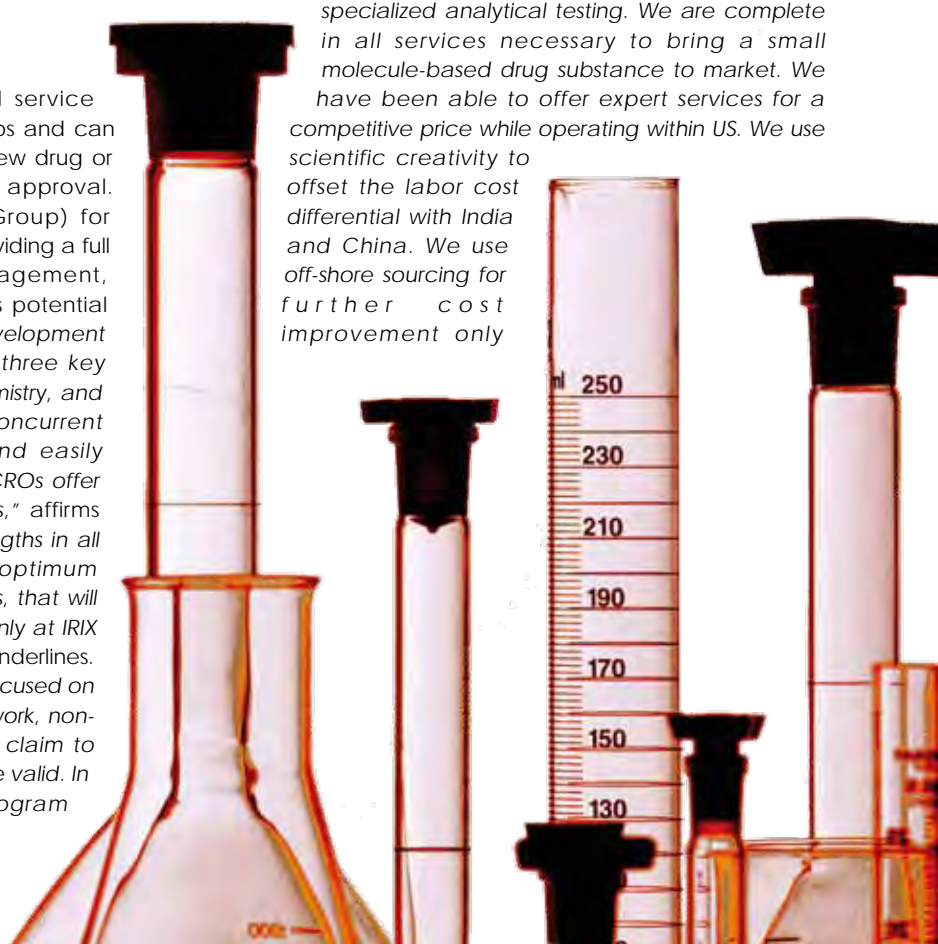
CROs range from large, international full service organizations to small, niche specialty groups and can offer their clients the experience of moving a new drug or device from its conception to FDA marketing approval. CARBOGEN AMCIS AG (and the Dishman Group) for example provides a full service CMC offer by providing a full range of chemistry, analytics, project management, regulatory and consultancy services, as well as potential multiple sites of supply. "Successful process development and API manufacturing must incorporate the three key disciplines of Organic Chemistry, Analytical Chemistry, and Chemical Engineering in a concerted and concurrent approach. This formula creates a robust and easily transferable process. Not all of the full service CROs offer the appropriate strength in all three disciplines," affirms Cruskie. "IRIX maintains a good balance of strengths in all three disciplines and seeks to develop the optimum process, free of esoteric conditions and reagents, that will enable its clients to manufacture their APIs not only at IRIX facilities, but by other CRO/CMOs as well ", he underlines. "Well you see smaller CROs by nature are often focused on only part of the service offer, whether it be lab work, non-GMP synthesis, stand alone analytics etc. They claim to offer a faster service, which in some cases may be valid. In the context of a complete development program

however, having multiple service providers with many interfaces will add complexity and time to the project in its entirety" Wolfart counteracts. "What we can do is to continue to emphasize our strength in chemistry and extraordinary process development capabilities", comments Cruskie. "AMRI's strategy has been to improve our competitiveness by continually expanding our scientific services platform and global footprint" explains Trova. Examples of expansion in both technology and geography over the past five or so years have included an expansion of development and large scale manufacturing in the UK through the very recent acquisition of Excelsyn Ltd.; establishing medicinal chemistry and custom synthesis in Budapest, Hungary, also through acquisition; building out chemical development, cGMP scale up and manufacturing, and commercial manufacturing capabilities in India through both acquisition and green field initiatives; and establishing medicinal chemistry and in vitro biology services in Singapore. "AMRI now spans operations in the US, Asia, and Europe providing customers with a broad range of services, technologies, geographic proximity, and cost models. To further accelerate its market penetration, AMRI has established sales offices around the globe including Japan, Australia, France, Sweden, Hungary, India, the UK, and the US", Trova informs us.

The supplier must have the right equipment and/or facilities to deliver the project

There needs to be an appropriate Quality system for the work to be undertaken

"Another platform for competition is low cost and again where infrastructure requirements are low this may be valid, however, often keeping costs low is done by reducing the scope of the work quoted. This may be an attractive proposition to some of the less experienced customers, however, they can soon come to realize that the additional tasks are needed and either end up paying more or losing time" states Wolfart. "In order to keep costs low they also employ recent university graduates with little industry expertise. Smaller CROs as well as we do outsource very specific activities to 3rd parties such as microbiology or chromatography. The smaller the CRO the more they need to outsource" he underlines. "IRIX subcontracts only highly specialized analytical testing. We are complete in all services necessary to bring a small molecule-based drug substance to market. We have been able to offer expert services for a competitive price while operating within US. We use scientific creativity to offset the labor cost differential with India and China. We use off-shore sourcing for further cost improvement only



based on the client's appetite and only for non-GMP production. We produced 50 APIs last year for clients and worked on additional ones in the lab. None of the clients we approached to outsource any aspects of development or cGMP production to partner companies off-shore were willing to take the risk. Major pharma is reaching more and more off-shore but not our main client base, the biopharma companies", states Cruskie. "We believe there is real value for clients in providing high quality integrated solutions for development. No one company can handle everything 'in-house', including Patheon", Glass affirms. "Therefore we have established some key partnerships that allow us to offer holistic solutions for clients large or small that want to outsource development completely to achieve a more virtual variable cost model. In these cases we partner with other CROs who have services that are complementary to our own -with equal quality and proven performance" he informs us. "Yes, providers need to be fully qualified", adds Wolfart. "Universities for example do not seek to be qualified as cGMP or cGLP providers. The handling of the IP is too sensitive and critical as many times the science behind the future product is not even (fully) patented (yet)" he underlines. "Patheon is fully qualified and its focus is in clinical development, on dose form formulation, analytical, and the manufacturing of clinical supplies. Integration with API suppliers and/or CROs focused on clinical site and data management create a one-stop-shop for clients" Glass says. "While subcontracting may be a viable option for CRO service providers to consider, AMRI instead pursued a strategy of growing services and technology internally", Trova informs us. "In order to address specific challenges related to capacity and cost, we implemented a global expansion plan and we are now able to provide our customers with a flexible range of cost structures, technologies, and manage project logistics across all of our sites in an integrated project model", he tells us. Various aspects of a project can be completed across multiple locations to leverage cost benefit based on the complexity of the work. Trova indicated to us a few examples: advantages of AMRI's integrated US-Asia manufacturing model includes a cost competitive environment for producing raw materials and intermediates, the capacity to

make APIs in a lower cost structure environment, and the ability to leverage AMRI's small scale/development pipeline and capabilities on two continents. The Hyderabad, India site provides low cost, high value, custom synthesis service offerings in process R&D.

The future of outsourcing

▄ We see a bright future as our primary market consists of service to the emerging pharmaceutical sector and this sector continues to grow, despite many challenges. Even though some emerging companies suffered from a lack of cash flow in 2009 we find that the emerging sector continues to grow as is our client base", states Cruskie. "Yes this is true", adds Wolfart. "There has definitely been a drop in demand for early

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phase services, due to M&A and rationalization from large Pharma as well as reduced VC funding available to biotech and small Pharma. There are early signs that this trend is starting to reverse, indeed there will be more of a drive to outsource as the need for innovation increases and internal capacity has been reduced", underlines Wolfart. "AMRI in fact is experiencing a growing demand for services based on a drug discovery and development model that includes the full continuum of Discovery, Chemical Development, and Manufacturing technologies and that begins as early as the identification of lead compounds through lead optimization to drug manufacturing and commercialization", says Trova. "The ability to provide this full service offering has been the outcome of a deliberate plan to expand AMRI through globalization and acquisitions, enabling us to offer a flexible model for cost, geography and technologies all managed through a central point of contact and/or project leader. Being established in locations such as Europe and Asia has significantly increased AMRI's ability to penetrate a much larger customer base; we see the future of global outsourcing as quite promising", he concludes. "Patheon too is expanding its development service offerings",

states Glass." In Bourgoin, France we are investing in a world-class high potency solid dose scale development scale-up facility that is seamlessly integrated into our commercial manufacturing plant. This offering allows our customers choosing to do development in Europe to move from PI all the way through commercial Launch in Patheon European facilities", he explains. Patheon also believes in establishing local infrastructure near the key global hubs of innovation to work with their clients in a very integrated way. "Our facility in Milton Park, UK near Oxford serves as an example of such a facility, but we're looking to buy or build near other hubs of innovation including: San Diego (USA), San Francisco (USA), Boston (USA), and Scandinavia", informs us Glass.

"We need to emphasize also the fact that there has been an increase in demand for late phase services as companies drive their lead candidates, either to market or to secure partnerships or additional funding. This will plateau in the market as a whole, however, we believe that CARBOGEN AMCIS has the knowledge, experience and capabilities to gain market share in this area",

adds Wolfart. "Moreover, price pressure and the need to drive value are definite trends", he underlines. CARBOGEN AMCIS offers a quality service out of Switzerland, with many customers, notably small customers with little in-house expertise as well as large Pharma who are looking for reliability and quality from a supplier partnership. There is, however, a trend to source more from Asia. "Being part of the Dishman Group positions us to be able to access a higher volume facilities with economies of scale and a lower cost base on behalf of our customers (most commonly, back integration of intermediates into a single-contact supply chain.) As such, we feel that the Dishman Group presents a highly competitive range of services, including those offered from Switzerland and that we are extremely well positioned to compete on both a value and a price level" concludes Wolfart.

Intellectual Property issues

Intellectual property (IP) plays an important role in an increasingly broad range of areas and is certainly gaining importance in outsourcing services. With the help of our experts we have tried to understand the role of IP in the relationship between sponsors and CROs. *"Intellectual property considerations are in fact critical to our customer's decisions on outsourcing services. Intellectual property generated at AMRI on behalf of the customer is fully assigned to the customer and is defined by the contract and the regulations of US Patent Law"* says Trova. AMRI scientists are named on over eighty US issued patents; for those cases in which intellectual property is generated on behalf of their customers that intellectual property is assigned to the customer. *"IP is a very sensitive topic to our customers and to us as well. All IP brought to us belongs to the customer. Anything process or compound related developed during a project also belongs to the customer. We do not have a large internal IP portfolio which we use to limit clients freedom to operate, unlike some of our competitors"*, underlines Wolfart. *"Well you see, IRIX Pharmaceuticals made a decision early in its 14 -year history not to be an IP repository but rather to use the real IP we develop as an added benefit for the client. If a client invests in process development for their molecule, the resulting IP belongs to them. We have filed 34 patents to-date for our clients based on real IP developed by IRIX"* Cruskie explains. *"The same for us"*, says Glass. *"Where we act as a fee-for-service partner our clients retain their IP. With over 100 PhDs and almost 1,000 scientist world-wide Patheon has considerable scientific depth. This group has independently developed Patheon owned IP around many areas including drug delivery techniques. Additionally, Patheon partners with clients in collaborative deals that may involve the sharing and exchange of IP from both groups"* concludes Glass.

Success factors

Competition and differentiation may very well be a CRO's toughest challenge. In today's market, full service CROs need to maintain a cost-competitive position, while mid-sized CROs need international alliances and smaller CROs need to be more and more specialized and experienced, and maintain global alliances. There are a lot of companies jumping into the CRO arena and those that are already in it have to get more aggressive in order to continue growing. Every CRO therefore needs to differentiate itself. The three most important success factors of the companies we have interviewed are indicated below.

AMRI

We believe AMRI's long term strategy is a three prong approach. The first is globalization; our ability to offer services across facilities in the US, Asia, and Europe as best fits the unique needs of each customer project. Our service offerings begin at the identification of lead compounds through lead optimization chemistry to drug manufacturing and commercialization. The second is continued growth and diversification of services and technologies across the drug discovery and development spectrum including our Discovery, Chemical Development, and Manufacturing

capabilities. For example, the US-Asia Manufacturing Model provides AMRI the capacity to make active pharmaceutical ingredients in a lower cost structure environment as well as provide a cost competitive environment for producing raw materials and intermediates. The third is AMRI's internal R&D division, which is making significant investment in the discovery and development of novel drug candidates with the long term goal of out licensing to a partner, an area often viewed as a higher value added service to the many companies with which AMRI is working.

A key factor in the successful outcome of the project is achieving the timeline set by the customer

CROs range from large, international full service organizations to small, niche specialty groups and can offer their clients the experience of moving a new drug or device from its conception to FDA marketing approval

there will be more of a drive to outsource as the need for innovation increases and internal capacity has been reduced

**CARBOGEN AMCIS
Technology, Service and Partnership**

Technology: CARBOGEN AMCIS and Dishman are constantly evaluating new technologies, aiming to offer customers technical solutions to the broadest range of problems. Recent examples are investments in SMB, large scale chromatography, micro-reactors and High Containment facilities. *Service:* Over 50% of our staff – our biggest asset - have a PhD in chemistry with expertise in all fields of modern organic chemistry. Having excellent technical staff and training them in project management and customer communication helps us to ensure that we offer solutions to technical problems and guide customers to making decisions on critical chemical and project decisions. Our company philosophy of problem solving also ties in to the continuous maintenance and investment programme which underpins our ability to respond flexibly to the inevitable changing needs of our customers. *Partnership:* We work with our customers, sharing common project goals, offering support and advice, not just an extra pair of hands. We have built up relationships, communication channels, technical understanding of their product portfolio, common expectations and ways of working. All of this forms a bond between the two companies and has resulted in more than 80% of our business is from repeat customers, many of whom have worked with us for over 10 years.

IRIX PHARMACEUTICALS, INC.

A full service company that unifies Outstanding Process Technology Expertise, Compliant API Manufacturing, and Value Adding Relationship. *Process Technology Expertise:* The company philosophy is to utilize all available science, process technology, and facility tools to develop the best manufacturing process for APIs not to shoehorn a process to proprietary tools. *Process Development* is driven by the company "ESPRIT" principle; Economical, Safe, Portable, Reproducible, Innovative, Timely Process. Its performance is supported by scientific staff with an average of more than 15 years of pharma industry expertise half of which have a PhD degree. IRIX has a strong record of 34 process patents issued on behalf of its clients worldwide. *Compliant API Manufacturing:* The company has state-of-the-art manufacturing facilities with broad capabilities and reactor sizes up to 24,000 L, including Class 4 high containment, to execute the manufacturing processes for client APIs. Both sites of the company share clean regulatory compliance records since inception. *Value Adding Relationship:* The primary objective at IRIX is to create value for its clients. It starts with the scientific creativity and processing expertise that the company uses to counteract the lower labour costs from India and China in an

effort to improve the economics for the client and continues with the development of an optimized easily transferable process supported in every step of the way during the entire clinical development timeline, whether within the companies facilities or during transfer to other sites when needed. It is all tied together with an effective project management incorporating strategic planning, timely execution, global sourcing strategy, and clear communication with clients for a hassle free one stop CMC service.

PATHEON

Our biggest differentiator is that we provide a breadth of development offerings, across almost every dose form, with integrated links to commercial supply. This integrated offering, at the scope and scale we possess, cannot be matched by anyone in the industry. We backup our promises with real guarantees. To date we are the only company in the industry (that we know of) guaranteeing, as a given, on-time product delivery in every new commercial manufacturing agreement. A global integrated Quality System and unmatched quality record. We are audited by a regulatory agency and/or our clients, on average, every single day. Since the end of 2005, of the 66 regulatory agency inspections, 22 were completed with ZERO observations of any kind. This includes our world-class large sterile facilities.

Safety procedure

CROs contribute to ensuring the safe conduct of procedures through discipline and wide expertise. "In contrast to many of their clients CRO walk through quite a lot of different chemistry. Thus they get to see almost all modern as well as extraordinary chemistry. Feasibility studies, categorization routines and safety evaluation ought to be a firm part of any project planning. Therefore established processes and responsibilities ensure a safe assessment of their endeavors. In general procedures come from a small scale lab environment and thus need considerable changes and adaptations to fit large scale requirements", explains to us Wolfart. "Prior to scale up in fixed equipment, in fact, we investigate internally the HAZOP information and process conditions that provide the confidence that the respective process will scale up without unforeseen problems", says Cruskie. "Given that we have a substantial commercial manufacturing business, in addition to our development business, Patheon focuses on global health and safety as a priority. One of our top high potency facilities in Toronto, Canada eclipsed three million man-hours without a lost time accident last year", states Glass. "Also for AMRI safety is a core value" says Trova. "AMRI has an extensive safety program that includes chemical handling, emergency procedures, incident reporting, occupational health, MSDS and hazard information, PPE, and training programs" he underlines. AMRI has recently been SafeBridge certified for safe handling of potent active pharmaceutical ingredients. Engineering and administrative controls are the preferred means of protection; PPE is designed to protect the employee from hazardous substances and is meant to be the last line of defense. AMRI has a strong history of compliance with Federal, State, Local and International regulations for Environmental, Safety and Health and has been

audited by numerous agencies with positive results confirming AMRI's commitment to Safety and Health in the workplace.

Sustainability

"Sustainability has a lot to do with economy, safety and quality of processes", states Wolfart. "And it is dependent also on the continual investment in your people and infrastructure" adds Glass. "Patheon places a high value on training our people to assure they are well versed in the latest techniques and trends in the scientific community. We also have a comprehensive program within our company to deliver leading IT solutions, and other tools, to manage development in the most rapid, yet flexible, way possible", he says. "Fierce competition in fact in the market requires a focus on all aspects of a project, such as sourcing of sm, recycling opportunities, waste handling and labour. There is a strong interaction between all these aspects when a new process is designed. Large Pharma have dedicated staff to take care of this aspects whereas small and medium sized Pharma do have to outsource and buy this knowledge externally. They do have experts in various fields who contribute to the success of the clients projects" explains Wolfart. "The evaluation of new technologies and equipment is key component of this", he states. CARBOGEN AMCIS recently signed an agreement with Codexis to be its supplier of choice for their biocatalysis technology in the pharmaceutical market. With the correct application, this technology can offer shorter processes, reduced solvent requirements and improved yields, which all lead to a more sustainable process. "Irix, from its part, has the ability to protect a client with an 'original process' which provides a longer life cycle for the finished product and helps the client compete on

a global basis, based on better chemistry", affirms Cruskie. "One of AMRI's core values is to work in an environment that promotes environmental well being and one of our objectives is to reduce our waste", Trova tells

us. AMRI has made a commitment to a Continuous Improvement program designed to reduce waste throughout its organization.

"Applying proven methodologies for examining work environments and process flow has positively impacted such things as cost and time savings, decreased errors, and increased employee engagement and morale", he says and underlines "these are all important factors that contribute to a uniform and exceptional quality customer experience wherever doing work with AMRI". AMRI also supports an internal campaign called REACT

(Reduce Excess and Conserve Together) as part of its green initiatives. A few of the programs that are currently in use include recycling paper, technotrash recycling program, methylene chloride reclamation, battery recycling, and printer-cartridge recycling, among many others.

Despite the drop in early stage research, recent reports foresee a growth in the CRO market. The global CRO market is expected to grow by 14%/year during the next three years, making contract research a \$35 billion industry by 2013. R&D spending growth by pharmaceutical and biotechnology companies is another measure and predictor of the CRO market. The health of Pharma and biotech companies and particularly their research budgets is crucial because that is the source of funding for CROs. And now more than ever CROs are competing for fewer customers. The CROs with strong performance

records, solid financing and established specialty capabilities will be the survivors in the coming years.

price pressure and the need to drive value are definite trends

Intellectual property (IP) plays an important role in an increasingly broad range of areas and is certainly gaining importance in outsourcing services

Competition and differentiation may very well be a CRO's toughest challenge

CROs contribute to ensuring the safe conduct of procedures through discipline and wide expertise

PART 3. CONTRACT MANUFACTURING ORGANIZATIONS (CMOs)

CMOs are companies that offer manufacturing services, with volume capabilities ranging from small amounts for preclinical R&D to larger volumes necessary for clinical trials purposes and commercialization.

On the demand side, there are three trends affecting the demand for CMO services: 1. all Big Pharma companies announce that they will produce less APIs in-house and outsource more in the future; 2. all Big Pharma are reducing their inventories and therefore postpone orders from CMOs; 3. CMO business is shifting more and more to Asia.

That being so we have asked R&D directors and managers of some CMOs how these trends will affect their company in the next few years.

"First of all I need to inform you that I do not agree that these three situations are so clear", states **Roger Laforce** - General Manager M&S, R&D, Logistics F.I.S.

- Fabbrica Italiana Sintetici S.P.A. "Some Big Pharma reduce their internal API manufacturing, others do not. But if only 3 - 4 Big Pharma outsource more, CMOs take advantage", Laforce says. "The trend that we see at DSM, in fact, is an

increased consolidation of the supplier base which coincides often with internal reorganizations at Pharma. Years of hard work with some companies is now starting to pay off and more strategic partnerships are now being formed", points out **Ronald Gebhard** - Director, DSM Innovative Synthesis BV, a unit of DSM Pharma Chemicals. "And certainly the trend for Big Pharma to outsource is welcome. Albemarle has the capability to take on projects that the Big Pharma companies need to outsource", states **John Parks** - R&D Director - Albemarle. "Well we must think that Big Pharma have to face also their own competition with the reduction of their pipeline and the growth of the generic market", underlines **Fabrice de Panthou** - R&D manager - AETGROUP SAS. "Outsourcing the chemistry is a way to cost reduction as CMOs are usually more competitive. On the other hand some companies choose to in-source as much as they can in order to fill up their plants, avoid social expenses incurred when closing industrial sites, and globally keep the know-how and the gross margin all along the value-chain", he states. In both cases CMOs have a role to play; in the first case for manufacturing products from A to Z and in the second case for implementing specific steps of synthesis where the technology is not available within the customer's organization. "With its ongoing development strategy around niche technologies and chemistry AETGROUP is definitely an innovative and reliable partner for Big Pharma companies. In particular when Big Pharma comes to performing hazardous chemistry or when looking for cost-competitive solutions requiring continuous processes, less wastes or improved yield and purity for the end-product", de Panthou affirms. "As regards the reduction of inventories

Sustainability has a lot to do with economy, safety and quality of processes

and the consequent decrease of business for CMOs this is not a long term trend. Most customers who have weathered the storm during the 2008-2009 period of global crisis by reducing their inventories are coming back to inventory build-up" informs us de Panthou. "In addition the Pharma business was the less impacted by these reductions within our portfolio, the serious difficulties were more in the cosmetics and specialty chemicals business" he explains. "Let's say that Pharma companies try to better manage their inventories, and this may lead to postponements but also anticipation of demand, this means we have to be flexible", states Laforce. "And to do this one needs also to be integrated into Asian supplier networks to be able to meet increasing cost pressure" Gebhard affirms. "According to me", says Laforce, "CMO business is not overall shifting to Asia. Rather are Pharma customers trying to take benefit where feasible and possible from lower cost", he states. "That is true!", comes up Parks. "The concept of CMO business shifting to Asia is purely a competitive one. Albemarle is positioned to provide unique value through our service offerings that stand against our competition regardless of location. Each project that Big Pharma outsources has its own specific needs. We just make certain that the services we are capable of providing are clearly communicated to the customer", he says. "Correct", states Gebhard. "Quality, responsiveness and on time delivery of the requested amount of material remain as important as cost, especially with increased focus on quality by the authorities", he concludes. "Our perception in fact is that the Asia hype has calmed down and decisions to move products to Asia are much better evaluated today", Laforce affirms. "I don't think this perception is totally correct", says de Panthou. "Shifting of business to Asia is definitely a heavy trend for two reasons. First because the first market in the future will be there, and second because the Pharma big players look for low-cost manufacturing even for products that will be marketed in Western countries", he underlines. De Panthou explains to us that the development of the Asian market is a tremendous opportunity for all companies, including CMOs, especially for those who own differentiating technologies which are not available there. The development of these new markets will come along with the growing of the living standard and therefore the increase of the manufacturing costs. "That's why, at AETGROUP, we believe that there is still a place for CMOs who never gave up developing innovative technologies which can already today compete with standard technologies at Asian prices. In the future, as the cost gap between Asia and Europe will decline, these technological advantages will become more and more important to remain in the global competition" he states.



Roger Laforce,
Logistics F.I.S.



Ronald Gebhard,
DSM Innovative
Synthesis BV



John Parks,
Albemarle



Fabrice de Panthou,
AETGROUP SAS

API plants for sale

During the gold period of blockbuster drugs pharmaceutical companies invested the surplus of money they had in manufacturing plants built in countries where they wanted to get products approved. In the last few years Pharma companies due to patent expirations, mergers and new trends coming up have been looking to close or sell several underused plants. Moreover they have started to outsource the majority of their APIs production. CMOs consequently are trying to take advantage of the situation and buy these plants. But what are the pros and cons? *"I think there are two types of facilities that become available. Some are sold empty, others are sold with an ongoing contract to produce certain products for a fixed number of years"* says Parks. *"It is obviously not in the interest of the selling party to guarantee over 10 years of stable production volume"* affirms Gebhard. *"Win-win scenario's are possible, but in my opinion scarce. I can imagine certain niches where CMO wins by taking over a specialized production infrastructure which is out of focus for Pharma due to e.g. changes in pipeline"* states Gebhard. *"Albemarle has been cautious in this area because frequently these plants were engineered with one or few product families in mind. Albemarle looks at its sites with an eye towards speed and flexibility as well as strong regulatory compliance"*, states Parks. *"There are pros if your strategy includes expansion or the addition of special facilities that may become available this way. Else, it does not make sense to acquire such plants just because they are around"* says Laforce. *"The story may be different if the management of such plant tries a buy-out in order to become independent, while, at least at the beginning, still continuing to manufacture products for the former owner"* he continues. *"Another advantage may be to extend geographical presence (India, China, USA or US companies in Europe and vice-versa) presuming it is at least a state-of-the art plant"* he underlines. FIS is getting offers very frequently and it is evaluating such options carefully, but so far it has not considered an acquisition. AETGROUP instead has the experience of buying a plant from a big organization. The last project was the purchase of Kodak's chemical site in Burgundy: AETGROUP decided to face the growing of the demand in the cosmetics market back in 2007. The advantages of such a deal were numerous: capacity increase at reasonable cost, incorporation of qualified manpower, manufacturing contract to ease the transfer and the shift of business. The disadvantages were mainly cultural. *"Turning the mindset of people who spent tens of years within a market leader company to a customer oriented and mainly quality of service mindset is not an easy task"* points out de Panthou. Notwithstanding AETGROUP is still considering the acquisition of an API manufacturing plant as far as it may fit with its criteria and find its place within its existing facilities. *"It's a good way for medium-size companies like ours to reach a critical size, preserve the employment and also keep industrial capabilities in Western countries as we strongly believe that they will lack in a near future"*, affirms de Panthou.

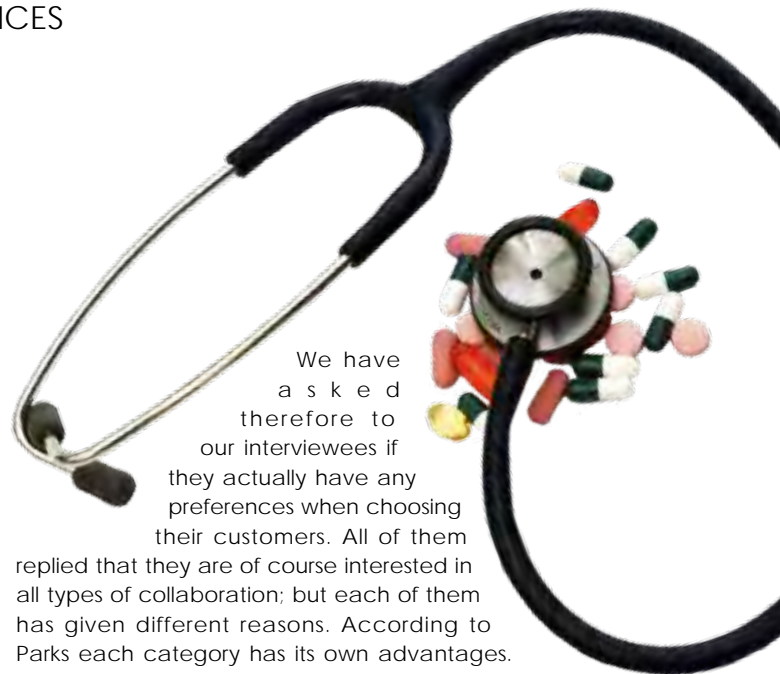
The ideal customer

The differences among Big, Medium and Small Pharma are evident from the beginning of the outsourcing relationship with CMOs.

The global CRO market is expected to grow by 14%/year during the next three years, making contract research a \$35 billion industry by 2013

The CROs with strong performance records, solid financing and established specialty capabilities will be the survivors in the coming years

CMOs are companies that offer manufacturing services, with volume capabilities ranging from small amounts for preclinical R&D to larger volumes necessary for clinical trials purposes and commercialization



We have asked therefore to our interviewees if they actually have any preferences when choosing their customers. All of them

replied that they are of course interested in all types of collaboration; but each of them has given different reasons. According to Parks each category has its own advantages.

"Big Pharma tend to bring bigger projects and they are much closer to being plant ready. The scopes are usually well defined, and they know in fine detail what they need from us" says Parks. *"To Small Pharma we bring a different advantage, in that we can better use our know-how*

in process development, scale-up, analytical, regulatory, project execution etc for their benefit. There is great value in being able to advise and guide smaller companies along a broad front of issues in order for their product to be successful" he affirms. *"One should make smart picks with emerging Pharma and have a good relation with large Pharma"* says Gebhard. *"You are right"*, comes up Laforce. *"As FIS is a large, or better, one of the largest independent cGMP manufacturers in Europe and perhaps even worldwide, we are very interested in collaborations with Big Pharma companies since they have large products. But we are trying to follow a balanced portfolio strategy, including all kinds of Pharma companies"*, he states. *"This is a way to split risks. Furthermore, pharma market is still shared among many small companies. The merging movement started 10 years ago is probably not ended. It means that a small company can become a big customer very rapidly!"*, underlines de Panthou.

Asian competition

During the last 30 years the chemical manufacture of active pharmaceutical ingredients (APIs) have undergone a major transition. The increased R&D costs, unsatisfactory R&D productivity, pressure to reduce global healthcare costs and the rise of generics have forced global pharmaceutical industry to sourcing APIs from cost - competitive destinations. Asian pharmaceutical companies are now the world's lowest-cost producers of small-molecule APIs. While selecting between Indian and Chinese companies, Western

Pharma companies look at both countries as each offers distinctive advantages to the big companies. China has the advantage of manufacturing bulk intermediates of economic scale with low labour cost. While, India offers highly skilled labour at 40 percent-50 percent low cost as compared with

Western countries. Besides, India offers high-end capabilities in contract research. Western companies need therefore to adopt survival strategies which could be identified in the following: 1. Setting-up manufacturing capabilities in Asia; 2. Partnering with an Asian company; 3. Subcontracting non regulated intermediates to Asian companies; 4. Wait and see. Will the costs of Asian players match European levels soon? Entering into details these are the strategies adopted by our interviewees.

AETGROUP

"Wait and see certainly not! It usually leads to regression, and at AETGROUP we don't like remaining passive. Running to Asia is also an extreme position, not easy for a medium-size company, and also a kind of «do like the others» attitude we have never favoured in the past. We strongly believe that the main driver for the growth of our company is to keep our customers satisfied with the quality of our products and services at reasonable costs. Therefore partnership or/and subcontracting in a win-win arrangement with Asian companies for non-strategic/non-regulated products, while keeping in-house the strategic steps involving innovative technologies and/or key steps for insuring the quality of the end-product is probably the most clever attitude. It allows our end customers to have access to competitive costs with the benefit of the quality reproducibility and the service that they expect from their CMOs", de Panthou says.

Albemarle

"As it happens, Albemarle has a fairly large presence in China, including manufacturing, purchasing, R&D and logistics. The Custom Services Group uses these assets to help in locating sources for non-regulated intermediates, negotiating prices locally, overseeing production, insuring proper labeling and shipping, and in general, making sure that things work smoothly to get material made and shipped from China. We don't believe a wait and see option is a good strategy. Of course, we understand that costs in Asia are moving towards parity with the West. As that happens, we will adapt", says Parks.

DSM

"We prefer to do regulated steps in house and rely on a solid supplier network in Asia to meet our requirements for the non-registered steps; when taking the full cost picture into account, the costs for registered steps often come close to western costs", says Gebhard.

FIS

"So far, FIS has not invested in Asian operations for manufacturing. The demand raw and starting materials in CMO is continuously changing with respect to quantities, technologies involved etc that one single plant could not cover them all. The FIS group has started a joint-venture in China for process development work and for learning more about the Chinese market. We are therefore partnering in these countries, and we are investing in a strict supplier qualification policy, since we are part of the pharmaceutical supply chain, and so are our suppliers. These must therefore comply with the requirements of pharmaceutical products to the patients as we do. Moreover, the Asian markets bear a high market potential in themselves. I personally believe that this is a key topic to invest in operations in Asia. Indecision is worse than wrong decision (D.A. Poling, Sunday

Herald, 18 feb 1951). Wait and see is not an option while we measure our steps carefully", says Laforce.

Quality, responsiveness and on time delivery of the requested amount of material remain as important as cost, especially with increased focus on quality by the authorities

In the last few years Pharma companies due to patent expirations, mergers and new trends coming up have been looking to close or sell several underused plants

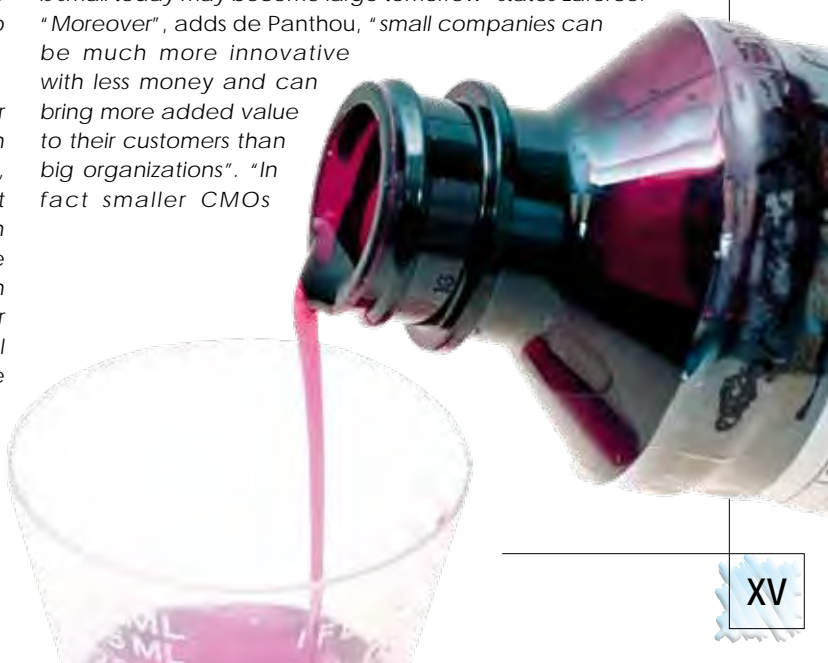
The differences among Big, Medium and Small Pharma are evident from the beginning of the outsourcing relationship with CMOs

Successful projects

After learning what strategies companies are following to survive the successful burst of Indian and Chinese contract services, we have asked our experts to give us some examples if any of projects signed with a new customer in the past two years. Albemarle has had a number of successful projects in the last two years, some they can discuss openly such as Siga and Anthera, and some they hold confidential. "Our success is in the pharma area and is supplemented by many successful projects in other areas such as agriculture, lubricants (with ExxonMobil) and some business segments that are new to us", says Parks. "We in DSM have several late clinical and pre-launch projects in our pipeline of customers which came to us for the first time in the past two years; or course it remains to be seen how these products develop and whether Large Pharma takes over in the end", states Gebhard. FIS has more than one project but they can't give any information on this issue. According to de Panthou, AETGROUP's success in closing several projects is due to their continuous reactor RAPTOR (c) which brings a serious advantage over traditional technology of batch reactor in term of cost, safety for hazardous reaction, quality improvement and environmental impact reduction. "As well as most of us in our private life, customers are becoming more and more concerned with environmental issues", affirms de Panthou.

The ideal CMO

Taking into consideration size as a parameter all our experts agree in saying that there is no ideal CMO. "The pharmaceutical industry needs a population of different providers with regards to size, capacity, location, technologies and more factors. It is therefore vital that the pharmaceutical industry is served by a number of different providers to take advantage of their best skills", says Laforce. "The ecology, if I may say so, of pharmaceutical service providers needs CMOs and CROs of all sizes and compositions, large ones and small ones occupying specific niches such as oligonucleotides. What is small today may become large tomorrow" states Laforce. "Moreover", adds de Panthou, "small companies can be much more innovative with less money and can bring more added value to their customers than big organizations". "In fact smaller CMOs



are more competitive if they own particular technologies such as HPAI technology, oncology or controlled product handling" underlines Laforce. "However a critical size is required to be considered by Big Pharma companies as a reliable partner" says de Panthou. "Yes because large CMOs can support the customer for large drugs, size is a competitive advantage" Laforce adds. "This critical size is also important for weathering the storm during periods like the one we had to face these last two years. The lower limit should probably be around € 50 millions", de Panthou concludes. "There could be also an upper size limit since working as a CMO (= industrial service) means full dedication to project management, industrial flexibility, financial strength. Having a CMO division within a larger group with other strategic fields may limit the strategic importance within the overall company strategy. This can be a reason why in the meantime a number of larger chemical groups have again quit the pharmaceutical CMO business since they did not have the right fit (Clariant, Rhodia to name a few)" adds Laforce. "Also, important decisions on investments or customer relationship aspects need the almost daily attention of top management, which could be a limit in very large companies. Privately owned companies can also make other decisions in times of crisis rather than public ones. As an example: quarterly results that need to be published by public companies are not a good indicator of how CMO business goes, our time horizons are longer. Therefore, quarterly results that indicate a drop in sales can send wrong messages to the shareholders and investors. CMO business is not an optional, rather a key strategic field" he states. Well, I think there are so many factors that make a quality service provider, not only size" affirms Parks. "For example, Albemarle's largest single reactor available for custom manufacturing is sized at 16,000 gallons. That has absolutely no value to a customer that requires flawless execution on the preparation of 100 grams of a highly valued new active ingredient. We are comfortable operating on and between both ends of the spectrum. Albemarle likes to think of itself as a large, well-resourced company that feels like a small custom manufacturer by providing personal attention to every project entrusted to us by our customers" he concludes. And trust is certainly a value which is required in the Sponsor / CMO relationship, together with clear, open, fearless communication and a willingness to resolve problems as they arise. "When you have that, both sides are engaged and a successful outcome is certain" says Parks. "And real partnership in the noble sense of this word can start" affirms de Panthou. "Sure but we must accept that the role that pharma wants CMOs to play comes at a certain cost. And with increased needs for quality systems, there is an end to costs going further down. We need to work together with their suppliers towards sustainable production processes, rather than focusing on cost alone", Gebhard underlines. "And this is one of the key success factors for a CMO. Other qualifiers are being a reliable supplier and deliver the right quality at the right time for a realistic cost. One of the

The increased R&D costs, unsatisfactory R&D productivity, pressure to reduce global healthcare costs and the rise of generics have forced global pharmaceutical industry to sourcing APIs from cost - competitive destinations

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CROs and CMOs that will be able to provide global and specialized services are definitely going to succeed

differentiators is to surprise your customer in a positive way (e.g. deliver earlier, more material or openly discuss early and

future options for process improvement)" he explains to us. "Don't forget reactivity/flexibility, reliability and innovation. Being able to propose innovative solutions to meet customer's requirements is leading to think chemistry out of the box. For example, being able to propose continuous process intensification at industrial scale is a way to be different and efficient, that's what AETGROUP is looking after" says de Panthou. "You are right" comes up Parks. "One key factor is having the right breadth of assets to handle a wide variety of projects. The kinds of available projects vary from year to year. If your assets are tuned to one segment, such as large pharma, and there is a dry spell in those projects, that can really hurt" points out Parks. "At Albemarle, we understand that every project is different. We must find the right way to match our capabilities to the specific needs of our customer's project. Ultimately our success is measured by our customer's success. If our customer is delighted with the way we have handled and delivered their very important project, then we know we have done our part in making them successful" he concludes. "The same thing happens in FIS", states Laforce. "This means, we are able to adapt our production trains, to add new equipment in short time and to change our production scheduling almost weekly according to customer demand and having the financial strength to realize investments even before getting the full commitment from our customers. A smart operational management is therefore key to stay atop in contract manufacturing", he concludes.

CONCLUSIONS

More than ever Pharma companies have recognized the value of CRO and CMO services and are beginning to take full advantage of them. CROs and CMOs' operations and business models have evolved and changed in response to external events. Some of the recent trends that have influenced the changes include the need to improve efficiency to increase competitiveness, pressure from financial constraints, increased use of specialty technologies and FDA changes. In order to stay competitive CROs and CMOs are increasing efficiency, reducing cost and offering value-added services. One of the biggest issues is competition. CROs and CMOs that will be able to provide global and specialized services are definitely going to succeed.

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