# Panel Discussion on

## Custom Synthesis & Contract manufacturing

*In this issue we are glad to present a Panel Discussion on Custom Synthesis and Contract Manufacturing. This topic is of particular interest to our readers and we have testimony of this because of the high number of companies that showed the willingness to participate to this discussion around a virtual table.*

*Among others, panelists treated important topics like the partner selection process in the API manufacturing sector and the "must to have" for a CRO/CDMO to be the right partner for a pharmaceutical company; furthermore the CDMOS evolution process that are transforming them in product partners and the main trends in late stage clinical and commercial scale API manufacturing.*
*The following players have joined the initiative:*

- **Alcami** - Mark Millar - Director and Business Unit Head API and DP
- **Amri Global** - Sripathy Venkatraman - Director Chemical Development and site head Albany site
- **Bellen Chemistry** - Charles Chen - General Manager
- **Capua BioServices** - Elise Mous - Director Sales & Marketing/Business Development
- **CatSci** - Ross T. Burn - Chief Executive Officer
- **Dr. Reddy's Laboratories Ltd** - Rashmi Nair - Technical Manager-Business Custom Pharmaceutical Services
- **EAG Labs** - James M. Schmidt - Sr Scientific Advisor, Custom Synthesis and Radiolabeling
- **Fareva** - Pablo Magnani - Vice President Manufacturing & Sales API
- **Fermion** - Marko Salo - Vice President, Marketing and Sales
- **Johnson Matthey** - Nick Shackley - Global Vice President Innovator Products and Solutions
- **Inventys Research Company** - Deepak Birewar - Chairman & Managing Director
- **PCI Synthesis** - Edward S. Price - President
- **Porton Pharma Solutions Ltd.** - Raj Iyer - Chief Business Officer
- **Richman Chemical Inc.** - Christopher Kulp - Chief Commercial Officer
- **WeylChem International** - Mark Wehner - New Business Developer
- **Ypso-Facto** - Kilian Kobl - Project Manager

# NAVIGATING THE API MANUFACTURING PARTNER SELECTION PROCESS

**MARK MILLAR**
*Director and Business Unit Head, API*
***Alcami***

The accelerated growth, and approval, of new therapies over the last two decades has put outsourcing services for active pharmaceutical ingredients (APIs) in high demand. Consequently, there is an increasing number of API and high-potency API outsourcing manufacturing sites to choose from, which makes selecting the right one that much more challenging. Several critical factors should be considered during selection of an outsourced partner.

### INTEGRATED APPROACH

For a successful collaboration, select a partner with an integrated approach to drug development and manufacture. One that doesn't focus on a single aspect of the program (i.e. API manufacture, drug product, etc.) in isolation, but one that takes into consideration all of the characteristics (solid state characterization, harmonization of analytical methodology, etc.) that are necessary for the eventual formulation at the outset of the program. Consideration of these factors at the beginning of the program can reduce timelines and cost. Examples of tools / approaches used by service providers who offer an integrated approach include:

- A multi-discipline team that understands the intended final formulation (oral solid, injectable, etc.).
- The ability to leverage design of experiments (DOE) and automated platforms to perform higher level process characterization at earlier clinical phases without significantly adding cost or extending the timeline of the program
- Assurance that a robust control strategy is developed and implemented from the outset
- Open and transparent communication - single source program / project management systems and readily available access to subject matter experts
- The ability and flexibility to adapt to changes in the program - whether technically or directionally from the client

> For a successful collaboration, select a partner with an integrated approach to the entire drug development process

### ROBUST INTERNAL TEAMS

Selecting a CDMO partner with experienced internal process development and analytical teams is key— as it is important that both teams are constantly communicating and working together to proactively identify and mitigate any potential problems as well as provide accurate and real-time information to make sure your project is operating as efficiently as possible. In addition, having a strong internal quality and regulatory team is important to ensure the product is manufactured and released under the appropriate regulations to support the intended use.

### AHEAD OF TRENDS

In recent years, the API environment has seen some changes and improvements to the traditional small molecule/batchwise approach, some of which include:

- APIs with less volume and higher potency originating from more targeted therapies
- Increase in the use of pro-drugs and repurposing/ rebooting existing or abandoned therapies
- Hybrid approach to the quality by design (QbD)/ traditional process validation in product lifecycle management— sponsors have not completely abandoned the traditional approach, but have not yet fully embraced the QbD approach
- Utilization of flow chemistry as a replacement for some or all parts of a traditional batch process

Partnering with a CDMO that has experience and proven success in these areas will increase the likelihood of success for your program. From initial project onboarding until the final product is complete, it is important that development and manufacturing teams are connected at every level. To achieve the best outcome for your product, partner with a CDMO that offers and encourages strategic collaborations throughout the entire process.

## COMPANY PROFILE

**Fermion**'s product portfolio of over 30 APIs includes innovative and generic APIs, which are sold to customers located primarily in regulated markets. We have extensive experience in developing innovative APIs from Phase I all the way to commercialisation.

We offer contract manufacturing services for APIs including highly potent compounds (HPAPI), and have a wide range of expertise in manufacturing anticancer products. Together with our parent company Orion we can also offer one-stop-shop solution for our customers including both drug substance and drug product.

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The number of employees of **Fermion** exceeds 330, of which more than 50 are employed in R&D functions. In addition to top scientists, Our R&D is well equipped with state-of-art facilities including laboratory, kilo and pilot scale units. Our aim is to offer you a unique customer experience, characterized by open and transparent communication, innovative spirit and agility. Our staff functions as an extension of your R&D or manufacturing operations and put themselves in your shoes. Since the first FDA inspection in 1979, both of **Fermion**'s plants, Hanko and Oulu, have been inspected regularly by US and EU authorities. The latest FDA inspection at Hanko was in 2016 and at Oulu in 2017. The Hanko plant is intended for large volume APIs, whereas Oulu is dedicated to large and small-scale highly potent APIs (up to OEL class V compounds, 0.1–1.0 µg/m3). Hanko plant will start operating new API manufacturing facilities in 2018, including 76m3 reactor space incremental to the company's current capacity. There will be a reactor volume of 25m3 for OEB5 compounds (containment level of 0.1 – 1 µg/m3) and the rest of the new capacity is equipped for compounds requiring a containment level of 1 - 10µg/m3. In our final handling premises we can perform milling and micronisation for APIs up to OEB5.

COMPANY PROFILE

# ROUTE SCOUTING, SCALE UP & PROCESS OPTIMIZATION (FROM A CRO PERSPECTIVE)

**SRIPATHY VENKATRAMAN**
*Director Chemical Development and site head Albany site*
***Amri Global***

The process for the first synthesis of a candidate that is identified by the medicinal group more often is not suited for scale-up. A modification to the existing route or completely revamping the route is often the starting point when the new molecule reaches chemical development.

> Establishing a route early on and deep diving into unit operations forms the basis of a robust and successful process

However, material needs to support toxicology studies under critical timelines often preclude a full evaluation of the existing route and proceed with minor changes to the synthesis with a short-term focus on safety, reproducibility and quality. Filing an IND is often a rate-limiting step to secure a second funding for several biotech companies and hence, this part until the first clinical batch is produced, is nothing short of a race.

Route scouting and good process understanding are directly proportional to the time available and establishing an optimal route is shelved until later in hopes of finding time and money. Often when positive results are obtained, the situation gets worse and getting the molecule to the market takes precedence and rarely gives you the luxury to reinvent the synthesis. So, the question of when the synthetic route needs to be frozen becomes interesting.

Time and again the final physical properties of the API are not decided early on and heroic efforts to develop a process late in the game to meet the physical properties become inevitable. Late phase process development and process intensification leading to registration and validation batches involve critical thinking in designing experiments. To make sure you are on the right track to develop a scalable process, the right tools will help to minimize the experiments and repetitions. Historical analytical data developed as part of generic or semi-qualified methods in support of earlier developmental efforts are immensely valuable and ability to utilize them effectively to support later phase development need great experience. Changes and improvements to the analytical methods are necessary and need to go hand-in-hand with process development. Edge of failure data and understanding the design space either by modelling or design of experiments constitutes the backbone for a successful process.

Engineering considerations dealt with early on offer relief for later stage production. Starting material sourcing, understanding the quality of these materials from reliable suppliers often gets missed in the grand scheme of things. Systematic impurity purging data prior to validation offers tremendous information in setting-up specifications and justification for deviations during commercial batches.

Establishing a route early on and deep diving into unit operations forms the basis of a robust and successful process. Missed out activities at the appropriate time and disorganized data collection will derail the whole process and delay the progress and filing an Non Disclosure Agreement.

# MEDCHEM OUTSOURCING

**CHARLES CHEN**
*General Manager*
***Bellen Chemistry***

The development costs to discover new drugs escalates every year. However, the enthusiasm to discover them and the relentless pursuit to conquer devastating diseases and improve the quality of lives never wane.

Many untreated diseases lack suitable medication, and drive scientists to research and validate hypotheses, and test potential compounds to treat them. The CRO model is not new to drug discovery and drug companies actively use clinical monitoring, data management CRO and GMP API manufacturers to facilitate their clinical programs, helping reduce the cost of drug development. In the past two decades, CRO have emerged to aid the research process, and it is now feasible to carry out drug discovery "virtually"; with just a couple of scientists and a credit card. Today, each drug discovery function can be managed by CROs and each segment of the drug discovery function can support a viable and independent business. It is a mutual benefit for both the drug companies and the CROs.

Trends have emerged in outsourcing to CROs, especially an increase in early stage medicinal chemistry. Medicinal chemistry is one of the most creative areas in drug discovery, selectively generating compounds with optimal potency, solubility and suitable PK profile before the compounds pharmacology is tested.

During the SAR optimisation phase, a medicinal chemist is required to synthesise any designed structures with ease and to pay close attention to the interrelationship between biological activity and structural changes. In the next blockbuster drug discovery process, you need a team rather than just one or two designers to think about

the project, a CRO becomes even more important within the drug discovery engine. The CRO should be seen as a strategic partner, rather than just an extra pair of hands in the process of drug hunting. Recently, two chemists from a famous CRO joined with Merck scientists and together, were honoured as "Heroes of Chemistry" for inventing ZEPATIER, and is an important step in recognising the role of CRO in the discovery of new drugs.

> In the next blockbuster drug discovery process, a CRO becomes even more important within the drug discovery engine

Currently, two generic models of CRO exist. One, to have every discovery function in one organisation, the other, adopted by most CRO is to be specialised in one function rather than to have everything under one roof. Some specialise in X-ray diffraction and computer modelling (Viva), others in preclinical and toxicology evaluation (Medicilone), and some as a vertical chemistry synthesis company from SAR to manufacturing (Bellen Chemistry). The drug company can use collaborative approaches to outsource their internal needs, and when moving towards a single partner collaboration, it is essential that the right business culture exists across the two organisations.

It is also important to have secure IP protection practices in place, and firewall separation between biology and chemistry is needed, if biology and SAR research are to be done at one company. Currently, we see more drug discovery firms partnering with specialised CROs to achieve their discovery objective, in summary, outsourcing medicinal chemistry shows no signs of abating and will be vital for the next new breakthrough drug.

# OUTSOURCING GROWTH REMAINS

**ELISE MOUS**
*Director Sales & Marketing/ Business Development*
***Capua BioServices***

BioPharmaceutical companies continue to expand and strengthen their outsourcing strategy. Outsourcing no longer seems just a solution to get easy access to flexible capacity; but more and more is applied as a true manufacturing strategy. This also implies that decisions to outsource and to whom are changing. As a CDMO we recognize this increased complexity; the need for strategic alignment, having access to the right level of information, capacity and know-how at the right time, the desire to outsource multiple technologies, the expectations on quality, reliability and expertise.

> We especially value the "people-factor". In the end people buy from people and we are convinced that it also are our people and their capabilities within our plant that make the difference.

## WHAT A CDMO CANNOT MISS: FLEXIBILITY, CAPACITY, STRATEGIC PARTNERSHIPS

Within this complex landscape of outsourcing we have observed that it is very important to be clear in what you can offer and especially also what not. This helps all parties to be as efficient as possible in the early stages of evaluating a potential fit for a development and manufacturing project. Today, many outsourcing discussions are not just about projects, but more and more about true strategic partnerships. As a CDMO, we focus on microbial technologies for especially proteins, enzymes and small molecules. Within our focus on this core expertise, we strive to maximize our flexibility by the way we deal with clients and their process/ product throughout our people and our plant.
We are pursuing a clear growth strategy, not just a strategic expansion. M&A transactions, consolidations as well as investments in new as well as existing assets continue to be announced in the CDMO/Biopharmaceutical space. Operational implementations of such strategies range from broadening the value proposition (towards a "one-stop-shops") to increased focus on core capabilities. We have targeted, to within the niche of microbial technology, combine a bit of both. Important here is to at all times maintain focus on the people, the plant and the processes.

Being a microbial CDMO, for us it's not just about proving the requested solution. For us, it's about providing the right service, at the right time, that based on our experience often goes beyond the initial request. It's about having the ambition to create win-win solutions and knowing what it means to be a strategic outsourcing partner.

## SCALE-UP AND PROCESS OPTIMIZATION: KNOW-HOW; PEOPLE, PROCESS AND PRODUCT

Successful scale-up and robust commercial manufacturing requires consideration of three key attributes: the people involved, including their training, know-how, experience, and flexibility; the process itself, because each has its own unique challenges, characteristics, and requirements; and the desired product, for which the final specifications determine the end-game.

Upon creating and executing the service strategy, it is important to analyze the potential risks and uncertainties upfront and define a custom onboarding trajectory for technology transfer, process development, scale-up, and manufacturing campaigns, which includes definition and agreement of the joint objectives and journey required to achieve them. Such projects can only be successful while working with multidisciplinary teams and close collaboration with the client.

# OUTSOURCING: OPTIMISING AN ASSET AND AN ORGANISATION

**ROSS T. BURN**
*Chief Executive Officer*
***CatSci***

It is not an over-exaggeration to state that outsourcing has transformed the landscape of the pharmaceutical industry, as companies increasingly turn to Contract Research Organisations (CROs) to produce pharmaceutical assets on their behalf. It is now estimated that by 2021, one-third of all global drug discovery projects will be outsourced (1). As this demand for outsourcing organisations grows, so will the supply, with CROs needing to differentiate themselves to stand out from an increasingly crowded market.

A key way of doing this is through understanding the specific needs of each customer, which will often vary depending on company size. Smaller and emerging pharma companies, who were typically early adopters of the CRO model, often use outsourcing to control budgets and to get access to state-of-the-art facilities and expertise for innovative and specialised process research and development. Compounds must often be driven into the clinic as quickly and efficiently as possible due to financial constraints, meaning that tasks like route optimisation may, at risk, only come into play later in the pipeline. However, larger organisations are also increasingly using CROs for agile and effective process research and development. Whilst they may have differing longer-term objectives in comparison to smaller companies, collaborating with the right CRO also provides an opportunity to save money and plug a resource gap without compromising on the quality of the science.

Project objectives are differentiated by many more elements than just company size, so CROs must deliver a personalised and strategic service to meet all customer needs. A consultative approach allows CROs to scope and scale projects that deliver appropriate results, while factoring in speed, quality and cost issues. Building a strong relationship through meaningful and knowledgeable communication has a two-fold benefit. Firstly, the customer gains an inherent trust that the collaboration will deliver the best outcome for their asset; and secondly the CRO is able to gain a deep understanding of the asset, enabling them to advocate with confidence the correct approach to efficiently meet all objectives in the evolving drug development project.

However, relationship building isn't the only hallmark of an exceptional CRO. When developing a robust and commercially viable drug manufacturing process, it is good practice to refer back to the age-old adage: a stitch in time will save nine. Within this context, this signifies how good process research and development helps to pre-empt or circumnavigate complications otherwise encountered further down the development timeline – usually at far greater cost. Optimising drug manufacturing routes is often neglected, as the ticking clock of patent deadlines pressurises companies getting their drugs to the market as swiftly as possible. However, doing so can actually lead to more delays when unforeseen hurdles, such as delays in plant or missed quality targets, can necessitate costly material re-processing. Employing appropriate route exploration and design space understanding, alongside rigorous scientific methodology, at an early stage can help companies to avoid this. Partnering with a CRO that understands the significance of process research, development and optimisation allows pharma companies to stay ahead of the curve and avoid manufacturing delays and material supply risks, issues that are plaguing the industry.

From plugging a resource gap using facilities and expertise of the highest standards, to driving forward exciting innovations within the pharmaceutical industry, CROs must be able to deliver all targeted objectives and contribute to truncating the drug development timeline. Building exceptional relationships and understanding the chemistry needs, opportunities and risks of customers' projects inside out are the foundations upon which a CRO builds its success story.

## REFERENCES

1. https://www.kaloramainformation.com/Outsourcing-Drug-Discovery-Contract-Research-Organization-CRO-Edition-11506775/

# EVOLVING COLLABORATION MODELS IN CDMOs: FROM SERVICE PROVIDERS TO PRODUCT PARTNERS

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Last decade has been one of the most dynamic times for the pharmaceutical industry. Big and medium businesses are re-focusing on core strengths and key areas of interest. An intense churning has precipitated few important opportunities for the Contract Development and Manufacturing Organizations (CDMOs). Outsourcing companies want to ensure that they do not dissipate their energies (both manpower resources and money) working with different CDMOs, worrying about their quality, information security, regulatory status, product logistics etc. A professional, integrated service provider who can address above stated concerns, offers technical expertise in developing complex chemistries and drug products (like modified release products, pre-filled syringes, inhalation products etc.), handles potent new chemical entities and drugs, provides high standards of project management, operational

> Coupling technical expertise, above stated features and a strong cGMP manufacturing network creates an ideal CDMO partner

flexibility to accommodate supply demands and various scales of production, effective communication and lean decision making is most preferred. Similar work culture & organizational values are other important parameters for successful long-term partnerships of CDMOs & outsourcing companies.

CDMOs like Custom Pharmaceutical Services (CPS) are creating distinction in this space by offering integrated drug substance and drug product development services from US FDA inspected R&D center, being one of the few ISO Information Security Management System (ISMS) certified CDMOs and one of the earliest players in introducing Information Technology (IT) enabled 21 CFR part 11 compliant documentation systems like electronic note books (ELN), analytical data collection in Empower software, employee trainings in learning management system (LMS) etc. As part of Dr. Reddy's, Custom Pharmaceutical Services (CPS) exemplifys the global work culture and echos the values of accelerating access to innovative & affordable medicines.

Coupling technical expertise, above stated features and a strong cGMP manufacturing network creates an ideal CDMO partner. From a transactional mode of operation where CDMOs were considered only as service providers, today most outsourcing companies view this association as a collaboration sharing the vision and purpose of the drug product program. This is majorly because of the confidence that CDMOs have been able to instill through continuous effective engagements providing technical solutions, foreseeing project risks, devising risk assessment and mitigation plans, upgrading quality of operations as per regulatory expectations (such as serialization) as well as keeping pace with technical demands, like peptides, activated mPEGs, soft gel capsules, liposomal products etc. With our current long term partnerships for drug substance and drug product projects, which span from development to commercial manufacturing and commercialization in various markets, we see that the relationship between sponsors and CDMOs is truly evolving into product partnerships.
*The views expressed are personal and do not necessarily reflect those of my employer or any other organization with which I am affiliated.*

## COMPANY PROFILE

Research driven Innovative Process Design is the cornerstone of **Inventys** growth. With more than four decades heritage of demonstrated excellence in process development, scale-up, and manufacturing of products in Agrochemicals, Pharmaceuticals, and Fine / Specialty Chemicals applications. Currently more than 95% of our customers are based in advanced markets such as Western Europe, USA, and Japan. **Inventys** has a proven track record of delivering outstanding performance to its customers. We are committed to create value for our customers by:

- delivering on-time, in-full and in-spec solutions
- innovative chemistry
- world class engineering
- state-of-the-art automated process plants

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**Inventys** offers a wide range of chemical reactions in batch or continuous mode from few kg up to one thousand MTs scale. The focus on advanced technologies stands for innovative, cost effective and safe processes.

A WHO-GMP and US-FDA compliant API manufacturing facility is undergoing pre-production trials.
A new intermediate plant will be inaugurated in Q4 2018 at the current manufacturing facility.
**Inventys** has implemented on manufacturing scale chemistries such as Cyanation, Hydrogenation, Esterification, Cyclization, Bromination & Chlorination, Nitrile Synthesis, Hydrolysis, (air) Oxidation / Reduction, Organo Metallic Reactions, (100+ MTs). **Inventys** can conduct reactions from -40 to 360 C, pressures from 1 mm Hg to 35 atm, plus catalytic t as well as gas phase reactions, in batch or continuous mode - with a large variety of unit operations. Fluorination is expected be implemented in 2020.

**Inventys** has also started developing additional three new state-of-the-art new production facilties - for API´s, AI´s, and advanced intermediates respectively - totaling about 20 acres. These three new (adjoining) sites are expected to commission production starting 2021.

COMPANY PROFILE

# TYING METABOLISM EXPERTISE TO CUSTOM SYNTHESIS EXPERTISE

**JAMES M. SCHMIDT**
*Sr Scientific Advisor, Custom Synthesis and Radiolabeling*
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From the perspective of a CRO offering custom synthesis services, especially non-regulatory and GMP radiolabeling, but with significant expertise in stable-label and non-labeled test substances, there are a number of services and areas of expertise that are essential.

One is some expertise in drug metabolism and metabolite profiling. Determination of the optimal position of the radiolabel in the test substance is a critical decision point before proceeding with the synthesis. Ideally, the radiolabel should be incorporated in the molecule at a metabolically stable site (or multiple sites, for complicated chemistry), so that it will be conserved in the degradation products observed in plasma, tissue, excreta (or environmental matrices). It's important to note, however, that incorporating the radioactive isotope into the test substance sometimes involves developing a new synthetic pathway. You will want to ensure that your contract synthesis laboratory has the expertise to provide advice on preferred radiolabel position(s) and suggest the merits of possible synthetic pathways.

> You will want to ensure that your contract synthesis laboratory has the expertise to provide advice on preferred radiolabel position(s) and suggest the merits of possible synthetic pathways

That expertise extends to advice on the design (and practicalities) of synthesizing stable label test substances, whether for their traditional use as internal standards for bio-analytical methods, as an aid for determination of absolute bio-availability in pharmacokinetic studies, or other uses. Stable label materials may employ two or even three distinct isotopes and when matched with high resolution mass spectrometry and/or ion trap technologies, provide valuable diagnostics ions for MS analysis.

Likewise, bench synthesis is often suitable for "Phase I" metabolites such as dealkylations, oxidations, and carbonyl reductions, etc. However, novel metabolites, especially phase II metabolites, may not be synthetically accessible at the bench owing to difficult routes, stereo-selectivity, very low yields and or/other challenges. A good laboratory will survey the literature and advise you of the feasibility of bench synthesis of a metabolite or impurity. If it does not appear to be accessible, they should offer other alternatives, such as forced degradation of parent material, isolation from in vitro and/or in vivo samples, or a growing arsenal of nontraditional methods such as microbial bioreactors or biomimetic oxidation.

Robust analytical support is also important when selecting a custom synthesis CRO. The unequivocal identification of what once may have been referred to in the Sponsor's laboratory as "Unknown X" is a particularly satisfying conclusion. If you are still at the "Unknown X" stage, but eventually intend to have the analyte synthesized, talk with your custom synthesis laboratory. A good laboratory will offer both synthesis services and trace analysis and structural chemistry support, so they can put a face and name to the unknown.

These complementary services are not effective, though, without solid quality systems. The consideration of regulatory requirements (non-regulatory, GLP certification, or GMP synthesis and release) in your custom synthesis program is very important and should be made as early as possible in the process. The choice can affect timing and cost, but the most important factor is how it matches with your own study design and regulatory needs. Effective, timely, and quality production of radiolabeled Clinical Trial Materials (CTMs) requires radiochemistry expertise and rigorous CGMP-compliant facilities, processes and systems. There are special considerations related to CGMP compliance (and patient safety) during the clinical trial. Be certain to inquire about the laboratory's inspection record with regulatory authorities; you may also want to schedule your own technical and/or quality assurance audits.

# THE MUST TO HAVE FOR A CRO/CMO TO BE THE RIGHT PARTNER FOR PHARMA COMPANIES

**PABLO MAGNANI**
*Vice President Manufacturing & Sales API*
***Fareva***

Between 2006 – 2015 there were 7,455 development programs, across 1,103 companies [Biomedtracker database (BIO, 2016)]. In 2017, the FDA approved 46 new drugs, more than twice that of the previous year. With the sheer number of projects under development, available capacity, both in terms of process and analytical development resources and actual reactor capacity is an important factor to evaluate when selecting a new CDMO. If a company is running near 100% capacity, they may not be in position to take on your project when you need them. If your program is in late clinical phase, you must evaluate whether the CDMO has the flexibility to meet your long term needs especially when your product grows. Another way to evaluate future capacity is to look at a company's recent investments. If the CDMO has a history of investing in new technologies and capacity, you can imagine that they are willing

to continuously invest and grow to meet the demands of their customers and the market.

A commitment to quality and deep knowledge of the regulatory environment are also very important characteristics to consider, especially when thinking about your own long term needs. Where do you intend to file for approval? Has your CDMO been successfully audited by the relevant regulatory agencies for your intended commercial geography? Do they have experience filing Drug Master Files in your countries of interest? How frequently have the facilities been audited? Regulatory requirements are increasing and changing, and you want to select a CDMO that is anticipating what changes will come next. Specific topics have received increased attention by regulatory agencies in recent years, like data integrity for example. Find out if your CDMO is on top of the latest developments and if they are proactive or reactive when it comes to working with regulatory agencies.

> Sufficient capacity and flexibility to meet your long term needs? History of investing in new technologies and capabilities? Commitment to quality and deep knowledge of the regulatory environment? Communication and responsiveness? Important questions to be asked when selecting your C(D)MO.

It's important to understand that each CDMO has their own strengths. Some companies specialize in early stage development and delivering a few kilograms quickly starting from a medicinal chemistry route. Other companies focus on process/analytical development & optimization, with the eventual commercial scale and regulatory compliance in mind. You may end of working with both types of companies if you have projects in different phases of development.

Also keep in mind that communication and responsiveness are key characteristics that you can evaluate during your RFP process, no matter what phase of development your project is in. How well does the CDMO communicate with you to understand your needs and requirements? Are you able to have detailed discussions with the appropriate people at the manufacturing site during the evaluation phase? Are they engaged and do they bring new ideas to the table? A high-quality proposal along with responsive, clear communication from the CDMO throughout the evaluation process can give you an idea how important the project is to the CDMO and what it could be like to work with them.

## COMPANY PROFILE

**FAREVA** is a global CDMO with 39 production sites, with a Pharma Division that specializes in the development, commercialization, and launch of API and Drug Product. **FAREVA**'s API group has industry leading expertise in the areas of development & optimization of complex synthesis, High Potent API, aseptic processing, cryogenic, hydrogenation, steroids, spray drying, PSD and polymorph control with volumes ranging from 10 kg to 250 MT. Our Drug Product and Formulations group specializes in sterile solutions / suspensions, lyophilization, tablets, capsules, sprays / aerosols, liquids / gels, powder filling, Ophthalmics (BFS, bottles, tubes), suppositories, and high potent oral formulations. All sites are FDA / EU approved and our packaging is fully serialized to meet the newest regulations.

FAREVA

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**FAREVA** is continually expanding to meet our customers' needs. The most recent example is the completion of a 30 Million €, world-class, high potent API building for large scale manufacturing at our La Valle site located in France (Le Puy en Velay). The new building has 12 m3 of commercial manufacturing capacity in addition to a high potent pilot plant and high potent process and analytical labs. The capacity expansion program started in November 2016 and the facility is now fully qualified. During the same time, **FAREVA** La Vallée tripled the size of its process and analytical development group. The La Vallée site offers a full range of capabilities, from chemical & analytical development through pilot and commercial manufacturing of highly potent APIs.

**FAREVA** has also expanded high potent capabilities on the drug product side investing over 10 Milllion € on a new analytical lab and roller compactor at our Excella site in Germany. Excella is the first and only site in the world that is Safebridge certified for both HPAPI and High Potent OSD at the same facility. Lastly, **FAREVA** has just initiated a new investment in spray drying at our Valdepharm site in Normandy, France.

COMPANY PROFILE

# TRENDS IN LATE STAGE CLINICAL AND COMMERCIAL SCALE API MANUFACTURING

**MARKO SALO**
*Vice President, Marketing and Sales*
***Fermion***

Business environment in API custom manufacturing for new chemical entities is constantly changing. Changes are sometimes slow but, on the other hand, the development time of a NCE is long. Therefore most of the projects from preclinical to registration have enough time to be affected by business environment related changes to some extent. We can perceive at least two kinds of trends. Those which are related to stricter industry standards, which mostly are driven by industry guidelines, and those related to market environment.

> We can perceive at least two kinds of trends; those which are related to stricter industry standards and trends in market environment

A trend part of the first group we have seen at Fermion is stricter impurity control, especially in terms of mutagenic impurities (ICH M7). This requires emphasis on control strategy. One key element of this strategy is starting material designation. This together with possibility for quality by design (ICH Q11) requires more process knowledge by a CMO.

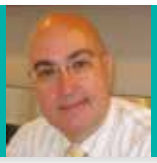
The trends in market environment have also an important influence for CMOs. According to FDA's list of new chemical entity approvals during the recent years, the share of oncology molecules and molecules for rare deseases is increasing, also when only small molecules are taken account. During the last few years, the number of NCEs approved has been high but the average sales expectation of a new molecule is lower than during the wave of blockbusters. When having a limited sales potential, drug candidate attrition risk mitigation is even more important for innovators.
API CMOs see this change indirectly from many perspectives: firstly CMC files or DMFs need to be of top quality without compromises and risks for lengthy deficiency letter rounds. The topics discussed hereinabove must be carefully addressed. Secondly, requirements for physical properties, especially for crystal habit, have increased. Partly this is due to the increased share of orally administred oncology molecules. When administered orally, crystal habit plays a key role in bioavailability and solubility.

Crystal habit management in a robust way can be very tricky. Emphasis for physical properties is driven by another market environment change, too. Cost austerity policies which drive lower drug prices put more pressure towards innovators to show the superiority of their drugs against the products already on the market. There is less room for compromises than in the past as far as efficacy of the drug product is concerned, and in this scenario API physical properties have their important role. The companies having the capability to produce desired crystals in a robust way and mill or micronize the material to a right particle size distribution will be preferred. Robustness is then calling for process automation and QbD.

Thirdly, one aspect of risk mitigation innovators are looking for is the improved compliance in quality systems. Suppliers with proven track record are preferred partners for more than one activity. Especially, companies with capability to manufacture both the drug substance and drug product will definitely have an advantage.

Fourthly, financial risk of R&D projects can also be mitigated by ordering the products from a CMO later and asking for shorter leadtime. Companies capable to meet tight timelines will succeed.

# MAXIMISING EFFICIENCY TO MINIMISE RISK



**NICK SHACKLEY**
*Global Vice President Innovator Products and Solutions*
***Johnson Matthey***

The demand for innovative and complex pharmaceutical drugs that treat a range of illnesses is changing the pharmaceutical industry. Nowadays, the industry is becoming increasingly dependent on outsourcing drug development and other clinical services to contract development and manufacturing organisations (CDMOs) like Johnson Matthey (JM). Outsourcing brings a multitude of advantages to both parties, as innovator pharma companies can focus on building a robust and efficient pharmaceutical pipeline, while ensuring development and manufacturing is handled by experts in the field. The key to successful outsourcing is about choosing the right partner with the right capabilities and proven experience.

Pharmaceutical development is a risky process, and one of the key reasons for pharma companies outsourcing processes to CDMOs is to minimise this risk. But, risk is one point of a triangle, alongside time and cost, that all must be optimised or balanced for any given project. It is important to consider all three parameters such that the customers' interests are maintained while still working within the scope of a project. To achieve this, a

CDMO's experience and range of capabilities are key differentiators.

> The key to successful outsourcing is about choosing the right partner with the right capabilities and proven experience.

A CDMO's offerings are influenced by a client's requirements. For instance, if a company requires a small molecule to be developed, then capabilities such as chemical synthesis and solid form will be key considerations. One such aspect of synthesis is route screening, where multiple viable chemical routes must be investigated to potentially synthesise an entity. The challenge is in optimising the reaction. Hypothetically, syntheses can be facilitated using catalysis or biocatalysis that improve yield and purity of the product at that stage. In these instances, experience in catalysis can help companies to overcome potential issues they may face when instigating such reactions.

Certain projects may require a combination of capabilities, such as formulation and solid form optimisations to ensure that the drug has the appropriate bioavailability. JM's approach is both consultative and executional, combining the collective skills and experiences of employees to provide companies with guidance on which appropriate capabilities best address specific problems faced. But again, this must involve balancing the risk, cost, and time variables while remaining within the clients' scope. It is then a matter of executing these capabilities and, in JM's case, using the wide range of both personnel expertise and assets to meet established goals.

Considering specific applications for outsourcing, such as API development and manufacture, there are many ways outsourcing is beneficial for the pharmaceutical company. Financial investment is a strong driving-force: instead of investing in the physical capabilities themselves, they can partner with a company having a proven record and experience in manufacturing across a range of assets. In most cases, this is more economically favorable, freeing investment capital for the further development of their own pharmaceutical portfolio. For a major pharmaceutical company that possesses in-house manufacturing capabilities, outsourcing can allow them to focus on the development of priority products, with CDMOs supporting others in their portfolio.

Pharmaceutical development is changing. Outsourcing processes to key partners will continue to drive innovation. Selecting the right partner is a matter of determining who can offer and execute on the capabilities and services that best address the customer's needs.

# PRE-REQUISITES OF BEING A PREFERRED CDMO IN PHARMA SEGMENT

**DEEPAK BIREWAR**
*Chairman & Managing Director*
***Inventys Research Company***

In order for the pharma companies to select it as the right partner, the Cdmo must possess several strong key competencies:

- Route Synthesis
- Process Development
- Quality by Design
- Analytical Development
- Stability Testing
- Scale Up Studies
- Pilot Production
- Process Engineering
- Plant Design
- Project Management

> Sustainable Responsive CDMOs offering a full gamut of services are preferred by modern Pharma Companies

Innovation is the key success factor in the Cdmo business. without innovation, a company is seen not even as a contender - in today's fast changing world of global competition. State-of-the-art research taking in account modern technologies like microwave technology, ultrasonic chemistry, biotransformation by enzymes as well as green chemistry could be important for the growth strategy. The cornerstone of a competent Cdmo is R&D. Full range of capabilities: from route scouting à all the way to à full-scale production; preferably in an integrated site, coupled with good project management are critical for a Cdmo. Experience in a large range of chemical reactions as well as the capability to go with this from gm to Kg to Mt scale is another prerequisite for being selected as a Cdmo business partner.

To use the capabilities to create value understanding the needs of a pharma company is essential. It means looking at the business through the customers' eyes. Always answering the questions which needs do our customers/partners have? What is creating value for them? Which solutions should be offered? How to drive communication and touch points.

Smooth communication is important too. As aptly described by Konrad Lorenz (Nobel Prize 1973):

- Said is not heard
- Heard is not understood
- Understood is not agreed
- Agreed is not being able to do so
- Being able to do so and agreed is not done
- Done is not continued

The last statement is probably the most important. Pharma companies need sustainable supply. The costs of disruption cannot be overemphasized.

# THE CHEMISTRY BETWEEN SPONSORS AND CDMOs: THE IMPORTANCE OF WORKING COLLABORATIVELY BEFORE THE PROJECT BEGINS

**EDWARD S. PRICE**
*President*
***PCI Synthesis***

While most of a project's focus is on the chemistry and processes necessary for regulatory submission, there is another crucial, sometimes overlooked consideration: the chemistry between the sponsor and outsourced CDMO.

The most successful programs are those in which the sponsor's business model aligns closely with that of the CDMO's, and when both teams are prepared to work closely and collaboratively with an understanding of expectations before the project even begins.

Once it does, as with all new chemistry, in the early stages neither team yet knows how the chemistry or manufacturing processes will behave when put to the test. Although our experience as an API developer and manufacturer allows us to set realistic timelines and budgets, we make clear that an additional investment may be required. We typically suggest a 15%-20% set-aside for such contingencies. If all goes well, it will not be needed. But we have seen projects fail or falter due to lack of adequate capital for overcoming hurdles. We now shy away from underinvested projects. They do not align with our goals of developing and manufacturing high quality APIs. As a regulated GMP facility, cutting corners to save costs is out of the question, and ultimately costs more.

In mid-stage and later development, a fully integrated CDMO with core competencies that include Process Chemistry, Analytical Methods Development, Quality Control and Stability capabilities is the most productive and cost-effective in terms of project timeliness and efficiency.
In addition to these core competencies, practicalities, such as mid-stage scale up, should be built into the program and undertaken. No one wants to do first time process development in a GMP environment. The costs and loss of time if unpleasant surprises arise can be significant.

Times have changed. A decade ago if a CRO or CDMO developed a drug for a sponsor, and that sponsor was acquired, API development would likely have been transferred either to the acquiring pharmaceutical company or one of its preferred suppliers.

The trend now is for pharmaceutical companies to forego the expensive, time consuming and risky transfer process *if* the CDMO has solid capabilities and GMP manufacturing facilities. It is widely recognized that critical knowledge gained during API development is often difficult to transfer. Many companies who try to do so have realized they are not only putting their project in jeopardy but are also significantly delaying commercialization.

As well, since successfully navigating FDA and EMA regulations can be challenging, pharmaceutical companies are more inclined to continue projects with a CDMO with a track record of adherence to the highest GMP standards. With competition keen and demand for APIs high, time to clinic is of utmost importance.

> The trend now is for pharmaceutical companies to forego the expensive, time consuming and risky transfer process

Ultimately, projects at all stages move more swiftly and smoothly when the contract manufacturer is viewed as, and performs as, a trusted extension of the pharmaceutical company, and when there is ongoing and open communication between teams.

# EXTERNALIZING MEDICINAL CHEMISTRY FOR HIGHER PRODUCTIVITY IN THE POST-PROTEOMICS AGE

**RAJ IYER**
*Chief Business Officer*
***Porton Pharma Solutions Ltd.***

The global outsourced drug discovery services market is valued at approximately USD 21 billion, and is expected to double by 2025. Medicinal chemistry and lead optimization (including Pharmacology and ADMET) presently account for approximately 60% of outsourced drug discovery expenditures. Pharmaceutical and biotech companies in North America, EU and Japan are the predominant sources of outsourced drug discovery services revenues.

Notwithstanding recent M&A and consolidation, the CRO provider landscape remains fragmented geographically and in terms of service differentiation. Similarly, CMOs have sought to transform themselves into CDMOs to address outsourced demand for early-phase development services via M&A and/or internal capability expansions.
Due to recent shifts in how large pharmaceutical and smaller biotech companies access drug discovery services, providers have witnessed demand in both traditional outsourced and newer, in-sourced paradigms (the latter especially from larger buy-side companies with broader R&D portfolios and extensive internal infrastructure to house / equip external CRO scientists). In-sourced models can clearly provide increased proximity for buy-side and CRO teams, potentially leading to more effective knowledge-sharing

and faster decision-making. However, only a few companies (typically large multinationals) possess the necessary (and under-utilized) internal infrastructure – hence placing substantial limitations on scaling this model.

> In-sourcing is an attractive externalization option for some larger pharmaceutical companies; however, outsourced drug discovery and early phase process chemistry are likely to remain the industry standard

Despite phenomenal strides across target ID, assays and in-vitro screens, etc., small molecule-based medicinal chemistry and early-phase process chemistry activities remain siloed in terms of human skill sets and execution modalities. While overall IND-enabling program attrition rates have declined, the transformation of a discovery asset into a development candidate is still seen as a gap to be bridged, rather than being approached as a smooth continuum. Lead candidates accruing from medicinal chemistry efforts are often presented with minimal definition of synthetic route, potential for genotoxic impurities and scaling suitability. When undertaken within a traditional outsourced environment, RFP processes and secondary technology transfers to CDMOs can engender significant opportunity costs.

A CDMO with an integrated medicinal and process chemistry platform offers considerable opportunities to chemically de-risk and accelerate IND-enabling strategies. Rather than await sequential transfers from pharma and biotech medicinal / process chemistry groups, an integrated CDMO should inhabit the dynamic space between these two functions, proactively identifying and addressing synthesis scalability and analytics issues for likely lead candidates. Averaged over several molecules and an extended reporting period such as a year, such an approach can save dozens of development-months while providing chemical scalability POC and confidence at least through the FIH stage.

In-sourcing is an attractive externalization option for some larger pharmaceutical companies; however, outsourced drug discovery and early phase process chemistry are likely to remain the industry standard – given recent trends such as CRO-CDMO platform integration and technology-based improvements in productivity, service reliability, data security and materials transfer speed.

# ROUTE SCOUTING, PROCESS OPTIMIZATION, AND SCALE-UP CONSIDERATIONS: DRUG DEVELOPMENT FIRMS AND CROs

**CHRISTOPHER KULP**
*Chief Commercial Officer*
***Richman Chemical Inc.***

The current landscape for drug development has changed from decades ago when in-house "big pharma" candidates dominated clinical trial pipelines. While the largest pharmaceutical firms in the world still possess the rights to most investigational new drugs (INDs) undergoing clinical trials, many candidates have been plucked from either the development groups of aggressive, private-equity backed start-ups or spin-offs from IP-laden universities. And, these candidates- as well as those driven through clinical trials by independent start-up outfits themselves- typically still require extensive efforts regarding route scouting and final synthetic route selection, final process optimization, and successful scale-up of the selected route of the promising drug substance molecule. The right CRO partner proves invaluable for all three of these objectives.

> For instances where a synthetic coupling step dominates the preparation, a convergent synthesis approach leveraging fragment coupling and independent but concurrent synthesis efforts could prove vital for success

## ROUTE SCOUTING AND SELECTION

While initial drug development efforts focus solely on synthesizing and isolating the molecule of interest, the focus shifts very quickly to identifying a feasible synthetic scheme for efficiently preparing material. Route scouting initiatives address this, as experienced CROs will concurrently and efficiently evaluate various methodologies for achieving the same end molecule. For instances where a synthetic coupling step dominates the preparation, a *convergent synthesis* approach leveraging fragment coupling and independent but concurrent synthesis efforts could prove vital for success. However, determining the best route takes into account many other factors including: effective and regulatory-friendly solvent selection, hazardous waste minimization, high-yielding reaction steps, reduction of the number of synthetic steps required, IP considerations, and ultimately cost controls. In a holistic sense, sustainability of the process for preparing the drug candidates remains paramount, and a well-organized and highly skilled approach to route scouting accomplishes this!

## PROCESS OPTIMIZATION & SCALE-UP CONSIDERATIONS

An optimal CRO partner realizes and understands that process optimization and successful scale-up are *not* mutually exclusive. Rather, integration of the two occurs in lockstep as the selected drug candidates transitions toward process validation status. First, the best CRO partners properly advise drug development companies on important optimization and scale-up considerations, including (but not limited to): raw material availability, commercial equipment compatibility and

capacity, safety and regulatory compliance requirements specific to the process, and key analytical chemistry/ impurity profile considerations for the anticipated commercial product. Reviewing and addressing all such factors allows the manufacturing process to be optimized at a representative scale in the pilot plant. Ultimately, this leads to a consistent, validation-ready process as the candidate progresses toward commercialization. Further, depending on the strategy of the drug development firm, it may be crucial that the partner CRO providing both route scouting and scale-up services ALSO possesses the capability to produce commercial quantities of material. The ability of a CRO pilot facility to mirror its own full-scale production capabilities may offer the advantage of minimizing future technology transfer risk.

# IN-SOURCING SYNTHESIS AND MEDICINAL CHEMISTRY: IS IT STILL A VALID MODEL FOR COMPANIES?

**MARK WEHNER**
*New Business Developer*
***WeylChem International***

In order to answer the question if in-sourcing is still a valid model for companies we take a look at the most important pros and cons.

One of the most important arguments for in-sourcing is the current supply security from Asian sources or rather the lack thereof. Due to the shutdown of several industrial parks in Asia the dependency of these sources for the European chemical companies has become apparent. So in-sourcing could be a good option to recover a certain independence from these situations in the future.

As modern API's have an increased potency, less material is needed for one dose so less capacity and smaller plants are used. This avoids higher costs for the company.
On the other hand, a broader range of chemical reactions is needed, e.g. Raney-Nickel hydrogenation, Birch Reduction, customized Phosphine ligands or catalysts, etc.

> A trustworthy and agile partner within the EU acting as a one-stop-shop for non-GMP and GMP production is an excellent alternative

This makes it more challenging to adapt and optimize the existing in-house production plants.
Companies developing API's normally do not have the same expertise in scale-up and production. When companies want to do in-sourcing they have to realize that manufacturer must always go through 3 long phases of development and this takes around 10 years. If the chemical plants stay still for this long time they will bring higher costs and lower profit in the future.

A different option would be to focus on European suppliers as outsourcing partners. These are typically medium- to small-size companies. A possible drawback is that one has to deal with several manufacturers. For both non-GMP intermediates and the late stage GMP steps including the API itself.

Streamlining the purchase process in such an environment would ideally call for both to be under one roof.

A trustworthy and agile partner within the EU acting as a one-stop-shop for non-GMP and GMP production is an excellent alternative to a costly and time consuming in-sourcing

# SMART DIGITAL TOOLS AS DRIVERS TOWARDS CMO COMPETITIVENESS

**KILIAN KOBL**
*Project Manager*
***Ypso-Facto***

Contract manufacturing organizations (CMOs) operate in a very competitive environment driven by quality and regulatory pressures, uncertainties on expected production volumes as well as tight cost constraints and time schedules. Improving competitiveness and attractiveness with respect to increasingly demanding customers is a daily challenge for CMOs, especially since they are expected to deliver on a wide variety of items like: product quality, service, price competitiveness, capabilities, customer proximity and relationship, etc.
These criteria are all important but take various forms depending on the development stage:

- Call for tenders – reactivity and commitment
- Process research and development – €/day matter
- Manufacturing - €/kg matter

> Flexible simulation tools support the smart optimization of a relevant process

### CALL FOR TENDERS – REACTIVITY AND COMMITMENT

Obviously, this stage has prerequisites like historical customer-supplier relationship, track record of the CMO and availability of key-technologies. But, above and beyond that, the main challenge for a CMO at this stage is to take quickly important decisions, based on a low level of information, with high budget constraints and with a strong commitment on future development and production.
To best position their offer, CMOs rely on the knowledge gained in previous projects and on technical and economic evaluations. At this stage, smart software solutions can bring a real competitive advantage (and some peace of mind), especially when they compile data on the company's historical cases, internal expertise, publicly available knowledge (to bridge the gaps), etc. and when they offer user-friendly modules to make most of all the information available to obtain the best forecast possible.

### PROCESS RESEARCH AND DEVELOPMENT – €/DAY MATTER

The process research and development phase is a race against time with the often paradoxical objectives to design and optimize the process while delivering product batches in various quantities for tests. It is critical at this stage to be able to adjust the level of effort to the target objectives.
As such, it is crucial to perform a thorough analysis of the whole process to identify and keep a watchful eye on the steps, operations, parameters, etc. that have the biggest impact on the key performance indicators of the process. Moreover, streamlining process development (design, optimization, scale-up) is a real competitive factor for CMOs allowing them to offer shorter timelines. Combining the skills of chemists and process engineers early in the process development allows to optimize the lab-/pilot-scale work and to design an efficient and robust process meeting the project requirements. Flexible simulation tools support the smart optimization of a relevant process by identifying optimal operating conditions, they also prepare for a seamless scale-up, help overcoming process bottlenecks and, eventually, lead to optimal equipment utilization, material and waste reduction, etc.

### MANUFACTURING - €/KG MATTER

At the manufacturing level, what matters is the production cost for the CMO and the manufacturing price for its customer. The production process inherited from the development phase is adapted to the production unit. The robustness of the process and the ability to control deviations to minimize off-specification batches are critical and they are the direct outcome of sound process development practices using quality by design approaches that can also be supported by process simulation tools.

### IN A NUTSHELL...

The attractiveness and performance of CMOs rely on their ability to be reactive, work fast, bring expertise and methodologies to their customers, take the right decisions and adapt to/anticipate the needs of their clients. To secure and gain competitive advantages in this tough environment, the CMOs need to embrace digitalization and strengthen their process development approach, both of which can be supported by smartly designed software tools. ■