TN-9001
Interview with Dr. Ernst Freund
(Group manager of Chromatography Services at CARBOGEN AMCIS AG, Switzerland)

A Look into the Contract Purification Industry from CARBOGEN AMCIS AG, Switzerland.

Dr. Freund has over 10 years experience in the pharmaceutical industry and has a wide knowledge of the contract purification industry. He has previously held the position of group leader in the production department of Bachem AG and project team leader in Chromatography Services of CarboGen AG. He also has for over 8 years of chiral chromatography experience and has been involved with SMB (simulated moving bed) and various other purification techniques. With more than 300 dedicated employees Switzerland-based CARBOGEN AMCIS AG is a pharmaceutical and biopharmaceutica process development and Active Pharmaceutical Ingredient (API) manufacturing company.

We sat down with Dr. Freund, to discuss the trends of the contract purification industry.

Phenomenex:
CARBOGEN AMCIS offers both chemical synthesis as well as preparative chromatography services to the pharmaceutical industry. Do your customers appreciate the availability of preparative chromatography services as a unique selling point of CARBOGEN AMCIS at the time when they approach you?

EF:
This depends on the customers and their type of project. Some customers have purely synthetic problems and are probably not fully aware of the preparative chromatography services we offer. Others contact us because their purification problem can only be solved by preparative chromatography. And sometimes preparative chromatography comes into play during a project, e.g. for a difficult purification. In such cases the customers are usually very happy that CARBOGEN AMCIS can provide adequate preparative chromatography tools to meet their overall purification goals.

Phenomenex:
Could you please explain the various preparative chromatography techniques that CARBOGEN AMCIS is able to offer it's customers?

EF:
We use normal phase flash chromatography for relatively simple purification problems. We tend to not use reversed phase MPLC (Medium Pressure Liquid Chromatography) as the HPLC (High Pressure Liquid Chromatography) technique offers a much higher efficiency with superior performance. CARBOGEN AMCIS has multiple preparative HPLC-systems with column diameters of 5, 10, 20 and 30 cm. For small scale separations we have semi-preparative HPLC-systems available. For binary (primarily chiral) separations, we have two SMB (Simulated Moving Bed) systems that allow the resolution of racemic compounds in a typical range of 3-50 kg. We also have a small scale SFC-system that is available for method development and purification of gram amounts of crude materials.

Phenomenex:
In which technique do you see most interest and growth?

EF:
There is no clear answer to this question. We see a steady flow of projects requiring SMB but also preparative HPLC. SFC is more often cited in the technical information packages of our customers, which I would interpret as a growth of this technique especially in early phase work, where smaller amounts of materials are sufficient.

Phenomenex:
Often chromatography is considered the "last resort" after all other purification approaches have failed. Which role does preparative chromatography play in your strategy when you start a new project?

EF:
In a typical synthetic project based on a medicinal chemistry route our synthetic chemists try to modify/optimize the process in order to avoid chromatography. However, if this is not possible within a reasonable time frame, they know that chromatography is usually a fast purification solution. Especially in the early stages of pharmaceutical development preparative chromatography is more frequently accepted as the majority of the compounds in development will be rejected for diverse reasons in later phases. So all the time invested in a troublesome process optimization may be in vain if the drug candidate fails at a later stage. In such cases, preparative chromatography might be a cheaper overall solution. The synthetic chemist judges for each project when chromatographic process development starts. This can either be at an early stage and parallel with the chemical process optimization or later on, in case that we are sure to work with crude material which is representative for the later production process.

Obviously for standalone chromatography projects, the decision to use chromatography was already taken by our customers before they contacted us.

Phenomenex:
Presumably as a response to the economic recession some major pharmaceutical companies have closed some sites or labs with preparative chromatography capabilities for cost saving measures. Do you think that will lead to an increased outsourcing trend for chromatography services and how will this affect companies like CARBOGEN AMCIS. Is there a shortage of prep chromatography capacity available for outsourcing?

EF:
Supposed that the research activities of these companies remain the same, this should lead to an increased outsourcing tendency which of course should be beneficial for companies like CARBOGEN AMCIS.

Currently I am not aware of a shortage of chromatography capacity in CMOs but I am sure, if this would be the case, more capacity would be created quickly.

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Phenomenex:
There are a limited number of companies in Europe and America offering preparative chromatography services under cGMP conditions. Do you see cGMP competition increasing from countries like India and China?

EF:
For non-GMP work the competition is certainly more noticeable than for cGMP-projects. This is especially true for synthetic projects more so than for chromatography projects. The reason for this is certainly that there are still less competitors in Asia who are specialized in preparative chromatography. In general, there are still a good number of customers who rely on European or US companies if it comes to quality systems and even more to the protection of their intellectual property.

Nevertheless, through the Dishman Group, our India-based parent company, CARBOGEN AMCIS has a very significant presence in Asia. This gives our customers the advantage of leveraging the right skills and assets at the right time throughout the drug development process and during product lifecycle management.

Phenomenex:
CARBOGEN AMCIS is focusing on small synthetic molecules rather than biopharmaceuticals whereas some see biopharmaceuticals as the APIs (Active Pharmaceutical Ingredients) of the future. From your perspective, do you see the industry is putting fewer resources into the development of small molecules and what would that mean for a company like CARBOGEN AMCIS?

EF:
The biopharmaceuticals are certainly booming at the moment and many blockbuster drugs belong to this class of molecules. Nevertheless small molecules remain attractive, as their development and manufacturing is less cost intensive. We also purify molecules which are generated by fermentation or extracted from plants and their semi-synthetic derivatives. These molecules cover fields (e.g. antibiotics), where large biomolecules are not required. Additionally, the so called drug-conjugates (a pharmaceutically active molecule e. g. a cytotoxic compound chemically linked to a docking molecule, like a peptide or protein) which can also be synthesized in house are objects of our purification work.

I do not think the biopharmaceuticals will replace the small molecules but they rather complete the pharmaceutical arsenal.

Phenomenex:
The majority of the small molecule NCEs (New Chemical Entities) are chiral. Nevertheless our industry has only seen a few examples of chiral APIs which are made by continuous chromatography at the commercial stage. Have SMB and similar techniques failed to take advantage of this trend and why?

EF:
No, I do not think so. In the development of new chiral drugs, the SMB technique is routinely being used. However, chiral preparative chromatography is in competition with various other approaches to make chiral drugs and once an API gets commercialized, the overall costs determine which synthetic route will be chosen. If a cheap starting material from the chiral pool is available or an efficient enantioselective transformation can be applied this often seems to be the more economical alternative. However, if the unwanted enantiomer of the API can be easily racemized, often SMB is more cost efficient also for large scale production.

Chromatography might still not be well accepted by process chemists and companies do not want to make considerable investments for large scale chromatography equipment as long as their classical techniques are working well.

Phenomenex:
Phenomenex has recently put a lot of resources into a new group called “Phenologix” which offers phase screening and method development. How do you rate the significance of such services to a company like CARBOGEN AMCIS and to the pharmaceutical industry?

EF:
I think these services are generally valuable for the pharmaceutical industry as a part of the problem solving can be outsourced at a low cost. Small companies will probably benefit more frequently from these services as their in house knowledge for preparative chromatography is lacking. However, these services are usually limited to the products of the corresponding vendors. Even if a solution for the problem is identified, it is not necessarily the optimal one. For small scale separations or analytical methods, this might be of low importance. However, for commercial processes even apparently marginal increases of the productivity might have a big impact on cost and timelines.

Phenomenex:
If you were to write a wish-list to manufacturers of the various type of phases used in different modes in preparative chromatography, where do you see the most potential for improvements and which new phases would help you achieve your purification goals?

EF:
Over the last few years we have seen a considerable drop in the prices for RP-bulk phases. However, we have not seen this happening for the chiral stationary phases even though there is more competition than before. As the material costs for chiral separations are significant, a price reduction would certainly promote more chromatographic solutions for racemate separations. Cost efficient chiral stationary phases with smaller particle size would especially be of interest for preparative chiral SFC applications.

Even if many of the available phases solve existing separation problems, a higher selectivity and/or loading capacity would always be welcome by the preparative chromatographer. Stationary phases, which show no tailing for polar or basic compounds or do not require the use of (non-volatile) modifiers could also aid in the purification tasks.

An ultimate challenge remains in the purification of compounds which show a good solubility only in solvents as DMF, DMSO or the like. Often the crude mixtures are injected in such solvents, however, in some cases it might be necessary to use these strong solvents also as part of the eluent system. New technologies like nanofiltration might allow an easier removal of the solvents, so that these eluents could be acceptable. This leads to a need of stationary phases which show retention under these conditions.