Interview with Jan Hoogendoorn

(Independent Consultant for PrepHPLC, former Solvay Pharmaceuticals/Abbott Laboratories)

Chiral and Achiral Media Trends in Large Scale Purifications

For more than 40 years, Jan Hoogendoorn has been active in the pharmaceutical industry, with over 25 years of experience in process and preparative chromatography. His interest in process chemistry began in the early 1980s, to replace several crystallization steps by chromatographic techniques in existing routes for API's. Since that time, Jan has held several roles and worked in multiple areas of the chemical development process, including process research, process development, troubleshooting, and after care.

We sat down with Jan to discuss trends in preparative chromatography, and gain his expert perspective on chiral separations.

Phenomenex:
As a pioneer of process scale chromatography in the pharmaceutical industry, what are some of the notable techniques you've used and seen developed since its introduction over 20 years ago?

JH:
In the beginning, I used normal phase separations using silica gel and/or aluminium oxide. During the second half of the eighties, reversed phase separations became a focus, and then special non-aqueous reversed phase systems (NARP). Since the mid mid-nineties, chiral phase separations become of interest and we used them for numerous projects in the discovery and development phase from mg up to kg scale. For [the] discovery and early development phase, the use of preparative chromatography is no longer an issue. For late development and production scale there is still a long way to go.

Phenomenex:
Preparative chromatography is still considered a niche technology by some pharmaceutical companies . What do you think is the reason for that?

JH:
The general opinion is that the technology of preparative chromatography is too expensive, too complex and has too low a capacity. Even the proven examples will not change that. As for flash chromatography, by using silica gel, I agree with the idea that chromatography must not be the way to go on a production level. In such cases the main purpose is the removal of very polar byproducts. These byproducts will be adsorbed at the column entrance and will be difficult to remove. But for chiral separations and especially the separation of racemates, I fully believe that preparative chromatography must be a standard tool during the development phase for a new API. The goal must be to find the right parameters to operate in a continuous mode (SMB/Varicol).

Phenomenex:
What are the challenges of chiral chromatography as you see them.

JH:
For a binary separation, like the enantiomer separation, there is a big chance in finding good operating parameters, which can be economically feasible. The economic feasibility is not dependent on the chromatography step only, but also on the downstream processing, including the recycling of the mobile phase. The problem is that the process chemist only takes into account the data from batch separations of enantiomers. This data is coming from a very early phase, without any optimization and/or full screening of the various possibilities in CSP/MP-combinations. In principle for the scale-up of a chromatographic step the same strategy must be followed as during the development/scale-up of a synthetic step.

Phenomenex:
Do you think that synthetic chemists lack understanding of the development process of a chromatographic separation?

JH:
The point is that the separation is seen as a purification step and not as an equivalent to a synthetic step in the whole process. There is an increasing choice of synthetic tools available for the synthetic chemist to produce pure enantiomers by using selective enantiomeric reagents. This is much more challenging for the chemist than using preparative chromatography. This is more a cultural than an economical decision but I am convinced that preparative chromatography could at least sometimes show the better economical parameters if a fair comparison was made.

Phenomenex:
Prep chromatography has sometimes been seen as "the last resort if everything else failed." What is your perspective on this?

JH:
From [the] chemical point of view, and especially the process chemist point of view, the use of preparative chromatography is seen as a failure. This is mainly due to the fact that some chemists are not familiar with the power of this technique and they try to avoid this technique unless there is no other way for purification. Personally, I

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don't agree that preparative chromatography must be seen as the last resort. In my opinion, preparative chromatography is an essential tool for chemists and process engineers, which must be part of the development process for a new API or API intermediate.

Phenomenex:
Though continuous techniques such as SMB (simulated moving bed) can show excellent economics, why are there relatively few large-scale continuous processes established in the industry?

JH:
Simulated moving bed technology is a proven technology nowadays with several industrial applications, especially for the separations of enantiomers, despite a big restraint in the pharmaceutical industry. This is because synthetic chemists consider preparative chromatography as a ready-to-use black box which will instantly solve their problems. At the same time they ignore that the development of a synthetic route is also a laborious process with failures and dead ends.

The same criteria must be handled for the development of a chromatographic step as for a synthetic step. Next to that, it is very important that in an early phase the process chemist and separation chemist work in cooperation to collect data for finding the best position in the synthetic route for a chiral separation. This may need to be done in the discovery phase. This strategy must result in a better understanding of the power of the technique for the chemists. The chromatographic community must work on that.

Phenomenex:
If you were to write a wish-list to the hardware and media suppliers of preparative chromatography, what would be on your list to make your job as a preparative chromatographer easier?

JH:
The existing column hardware commercially available for batch and continuous preparative chromatography is sufficient from a technical point of view, but the price for these systems is sometimes a bottleneck. For equipment, and especially in process preparative chromatography, the recycling of solvents is crucial. Hardware system integration with continuous evaporation systems is a must. The cost of media is also an issue.

For preparative chromatography, there is a wide range of straight phase silica. For the small molecules world, reversed phase silica is not interesting for production scale, due to limitations for the solubility of the molecules in the mobile phase. Reversed phase silicas are of course very important during process development for isolation of impurities and/or degradation products. These types of isolations, followed by structure elucidation, are very strong tools. For the isolation of very polar degradation products, new reversed phase materials can be interesting.

Phenomenex:
There are plenty of reversed phase and normal phase media available from a number of suppliers. Do they satisfy the needs of the customers or are there still phases missing?

JH:
I don't have the feeling there are any phases missing. [There may be] a need for phases which can handle very polar molecules.

Phenomenex:
Compared to reversed phases, there are relatively few chiral chemistries in use at preparative scale. Do the chiral stationary phases available on the market satisfy the customer needs in terms of variety?

JH:
Nowadays there is a wide variety of chiral phases available. From these, the polysaccharide backbone chemistries are the most widely used in preparative chromatography with a >95% usage rate. But the loading is not always great and it is also very difficult to predict the best stationary phase based on the chemical structure. Because of the predictive difficulty, a broad screening must be done with a lot of trial and error to find the most optimal conditions.

Phenomenex:
What is one change or improvement you hope to see in the chiral separations industry over the next few years?

JH:
I hope to see more use of continuous chromatographic technique and SFC for enantiomer separations. In principle, setup of experiments to generate data for parameter calculations and simulation is not too complex and there will come more and better software available on the market. The screening to find the optimal stationary/mobile phase combination must become more predictable. As said before, what users are looking for nowadays are unique CSP.

Phenomenex:
Do you believe that silica based phases will continue to dominate over polymeric phases for small molecules purification?

JH:
I think silica based phases will continue to dominate small molecule purifications. In fact personally I don't have any experience with polymeric phases.Phenomenex:

Which type of molecules do you think will increase in the coming years?

JH:
I think there will be an increase in biochemical molecules.

Phenomenex:
Do you believe in a breakthrough of any new separation technology and are you evaluating any such new technologies?

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JH:
Next to HPLC, SFC is a very strong technology. This technology will become more and more important for the production of supplies used in (pre)clinical studies. For production scale, at the moment, SFC is not economically feasible. So utilization of SFC depends on the production scale and with the economics for alternative purification.

Phenomenex:
What major purification cost cutting efforts do you think corporations will employ in the coming years?

JH:
That depends on each specific company. At our Abbott facilities in Weesp, we are/were focused in reducing the costs for mobile phase. A project was started for the realization of falling film evaporators for the batch chromatography unit but due to planned reorganization, this project has stopped. But, recycling of solvents and automation is a must for preparative chromatography on a production scale.

Phenomenex:
Some pharmaceuticals companies increasingly outsource their purification of clinical phase batches to CMOs. Do you believe that this trend will continue and will – for cost reasons – be taken over by Asian CMOs?

JH:
The purification outsourcing trend will continue. It is very important to have a good relationship with CRO's and CMO's to utilize their capabilities. But in my opinion it is a must to have the expertise and purification capacity in-house.

Phenomenex:
Some pharmaceuticals companies increasingly outsource their puThe PhenoLogix group within Phenomenex offer services such as phase screening and process development to our customers. Are such services relevant for the kind of work you are doing?

JH:
These kinds of services are very relevant for our kind of purification work, especially during the media screening phase.

Additional Information about Jan Hoogendoorn:

He started his career in 1970 at the company Philips-Duphar, The Netherlands. He reached a Bachelor degree in Organic Chemistry in 1973. In 1980 the company Duphar was taken over by the company Solvay and was renamed to Solvay Pharmaceuticals. Recently Solvay Pharmaceuticals was integrated into the company Abbott. During the past 40 years he was mainly active in the Chemical Development area. He was operational in process optimalisation for early and late development projects and aftercare for several commercialized products.

From 1985, he was active in several aspects, like screening, scale-up and production, of process Chromatography for achiral and chiral separations, using batch and continuous techniques. His last position within Abbott Healthcare Products was as GroupHead/Sr.Scientist for PrepHPLC-activities. Due to the worldwide reorganization within Abbott the R&D-facilities, amongst others the PrepHPLC-facilities, were closed in Weesp, the Netherlands. From April 2011 Jan is started as an independent consultant in the field of PrepHPLC.