Biotage

Metal scavenger supporting GLP/ GMP-compliant API manufacturing

Nippon Shinyaku Co., Ltd makes use of Biotage AB's metal scavenger to attain appropriate management according to GLP (Good Laboratory Practice) and GMP (Good Manufacturing Practice). The purpose of the metal scavenger is to strictly control such residual metals as palladium that are difficult to remove from API by other methods. We have been talking to Mr. Toshio Fujiwara who is in charge of Process Chemistry, CMC Research & Development Department, Discovery Research Laboratories.

— First, please tell me a little about your work.

"Primarily, my role is to develop a synthetic process for pipeline compounds from exploratory studies. We are aiming to establish an efficient, inexpensive and safe synthetic approach in accordance with the production scale. I also supply drug samples for GLP studies and clinical studies, which are required for drug development. After elucidation of the chemical structure of the candidate compound, I participate in a project that involves GLP studies, clinical studies and finally registration application over a long period of time."

No easy job to remove palladium

— What is the role of the metal scavenger in your work?

"In supplying sample for clinical studies, its production should be done according to the GMP Guide for API and a quality level as prescribed by the Guide should be attained. Especially recent medicinal products are often produced via a coupling reaction (ie, Suzuki-Miyaura coupling) using such metals as palladium. Therefore, residual metals should be strictly controlled in the final drug substance. Metal scavenger is deemed as one of the removal methods for this purpose."

— Are there any other removal methods?

"We usually use removal methods involving extraction or crystallization. However, the characteristics of the target chemical may prevent its removal. In such cases, we need to use a reagent such as metal scavenger as described above."

— I see. So, can you tell me how you have employed Biotage AB's metal scavenger?

"Actually, the candidate compound contains a nitrogen heterocyclic ring and the ring is coordinated with nitrogen and palladium, thus making removal difficult. We could not remove the residual metals with extraction or crystallization. In addition, we have searched for an effective method to remove the residual metals at one opportunity because a coupling reaction using palladium should be performed before the final purification process due to the synthetic approach of this chemical compound."

Si-Thiol gets the top rating in test on purchased kits

— It was a real technical challenge, wasn't it?

"Surely it was, but then, I heard about the metal scavenger kit of Biotage AB. Since this kit shows specificities for compounds, various evaluations were performed for each of the 5 types of scavengers included in the kit under a wide variety of solvents and temperature conditions. Of course, we tested other makers' products, but Si-Thiol of Biotage AB gave the best results in terms of removal rate. Furthermore, we can place a large order in bulk to respond to demands for a larger scale production. That was the deciding factor. Recently, the speed in developing new drugs has been emphasized; therefore, a response to a scale-up in production is important."

Biotage

Supplying at a bulk scale is a great advantage

— You considered the adoption of Si-Thiol for the first time around 2009, didn't you?

"Yes. After considering and choosing Si-Thiol, we have proceeded with GLP/GMP productions and the API process is going well. A production scale of tens of kg gave the same results as the smaller production scale. There is no problem."

— What do you feel is the advantage of the metal scavenger after using it in real situations?

"When we first considered the appropriate palladium removal method, we bought the screening kit first. There was a moderate number of the 5 types of scavenger packaged in this kit. Too many scavengers would make finding optimal conditions difficult because we must consider solvent conditions among other factors. Moreover, for those working in the process chemistry field, it is a great advantage that metal scavengers can be supplied at a bulk scale."

First choice for future projects

— You seem to be satisfied with our product. Do you have any requests or suggestions?

"Although the price of the product depends on its demand, we would be happy if you could offer it at a lower price. Also, from a research perspective, we would like to request you to develop a product with high palladium removal capability at low doses by increasing the ingredient amount supported on the carrier."

— Lastly, we would be grateful if you could provide us with your future plan.

"Since we achieved satisfactory results in this research project, I am sure the metal scavenger of Biotage AB will be our first choice when working on a future project in which palladium removal can be problematic. Of course, for any future production involving the candidate compounds used in this project, we will continue to use the product as well."

— Thank you for taking time out of your busy schedule to provide us with your valuable suggestions.

Process Chemistry
CMC Research & Development Department
Discovery Research Laboratories
Mr. Toshio Fujiwara

Introduced Product

Metal scavenger Si-Thiol

http://www.biotage.co.jp/mstk

Resin-supported and silica-supported metal scavengers of Biotage AB are reagents for removing trace metals (platinum group metals (PGM) and so on) from catalytic reaction solutions during the manufacturing process of pharmaceutical drug substances. The metal scavengers are applicable to various industrial fields, not only to those involved in the manufacture of medicinal products but also to agricultural chemistry, waste liquid treatment, and those involved in the manufacture of fine chemicals.

(Photo: Kit for screening)

Name of Client

Nippon Shinyaku Co., Ltd.

http://www.nippon-shinyaku.co.jp/

Nippon Shinyaku Co., Ltd., established in 1919, is a manufacturer of pharmaceuticals whose areas of strength are hematologic cancer drugs and urinary system drugs. In particular, Nippon Shinyaku is promoting drug development for refractory diseases, for which no effective treatment is available, and diseases that require an improved of quality of life (QOL). In addition to developing a functional food business, the company is directing their efforts in research and development for the realization of "hybrid products of foods and pharmaceuticals"

[Established]	October 1, 1919
[Capital]	5.2 billion yen (Listed in the first sections of the Tokyo Stock Exchange and the Osaka Stock Exchange)
[Employees]	1,815
[Head Office]	Kyoto

* As of March 31, 2011