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Scaling up Metal Scavenging Operations for Pharmaceutical Pilot Plant Manufactures

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ABSTRACT: Functionalised silicas, used for selectively removing metal impurities in process streams, are packed in cartridges and inserted into multicartridge filters. The scavenging step that follows a catalytic reaction involves the single pass of the process stream through the multicartridge filter setup at a predetermined linear velocity and temperature. Efficiency in metal reduction as high as 98% has been so far achieved at tens of kilograms scale. Furthermore, the precious metal anchored onto the scavenger's functionalities can be recovered and refined. Our chronological development of a versatile, general, and easily scalable format for metal scavenging at process scales is described, illustrated by application in real time to a range of projects passing through our Pharmaceutical Pilot Plant, employing a variety of metals (palladium, rhodium, iridium). Benefits of the cartridge format in terms of economics and environmental impact are also initially assessed.

INTRODUCTION

Transition-metal catalysis[1] applied to carbon−carbon and carbon−nitrogen bond formation and exemplified by procedures such as the Buchwald−Hartwig, the Sonogashira, Suzuki, Suzuki−Miyaura, and Heck reaction (to name but a few) have become common synthetic tools to the process chemist.[2] Recent reviews on the commercial manufacture of active pharmaceutical ingredients and on the scale-up of drug substance preparations have highlighted a large increase in the incidence of transition-metal-mediated chemistry.[3]

The ability to develop and commercialise industrial processes which are economically feasible and to maximise their environmental sustainability is, nowadays, a key requirement: chemical efficiency and environmental sustainability are strong driving forces in the design of new processes. Such goals can be achieved by researching methodologies which increase the atom economy of the synthetic step, use less harmful and generally greener solvents, introduce catalytic steps where possible, substituting a stoichiometric one, and where possible recycle waste components such as precious metals.

The catalytic approach, for example with transition metals belonging to the group VIIIB, has given the option of introducing more convergent syntheses, later in synthetic sequences, enabling the coupling of very sophisticated building blocks under what can be described as very mild reaction conditions, which generally are inherently unreactive towards other functional groups in the molecule.[4] Furthermore, the level of catalyst can be kept reasonably low.

However, there are some technical challenges associated with such catalytic procedures, predominantly linked to the removal of the metal species: metal contamination can have an unfavorable impact on downstream chemistry, and also strict international guidelines limit the level of metal impurity in the final active pharmaceutical ingredients.[5]

Several methodologies are available for the removal of metal contamination from a process stream, applicable to full scale manufacture: mostly it can be removed by extraction, precipitation, crystallisation of the product, and adsorption onto a solid surface.

It is important to stress, though, that no single technique will fit all metal removal requirements;[6] many will suffer from severe disadvantages including a lack of generality and reproducibility, product loss, and an inability to reach regulatory or process step acceptable levels of metal.

The use of functionalised silicas as metal scavengers is becoming increasingly common within the pharmaceutical industry as a wider range of such materials is made more commercially available. One of the main attractions of a silica-based scavenger is that, at completion of metal adsorption, it is easily separated from the process stream by filtration or can be used in a packed bed format, making the removal process more volume efficient if compared to extraction methods and more product yielding if compared to a recrystallisation method which can result in significant product losses.

Furthermore, the structures of many pharmaceutical compounds bear a number of heteroatoms and electron-rich functional groups, which as well as binding metal strongly (in the case of some adsorbents such as activated carbon) can also result in the pharmaceutical intermediate itself binding to the carbon based scavenger, incurring significant product loss during the metal removal step.[3]

This paper describes the evolution of the operational methodology employed at kilo-lab and pilot plant scale at AstraZeneca R&D Charnwood between 2007 and 2010, for the removal of metal contamination from process streams using modified silicas as scavengers, identified from adsorbent screening exercises: from the classic 'all-in-one' batch mode to a more sophisticated single pass 'semicontinuous' mode where the scavenger is contained in disposable and easy to handle cartridges.

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Figure 1. Multidentate sulphur based silica scavenger.

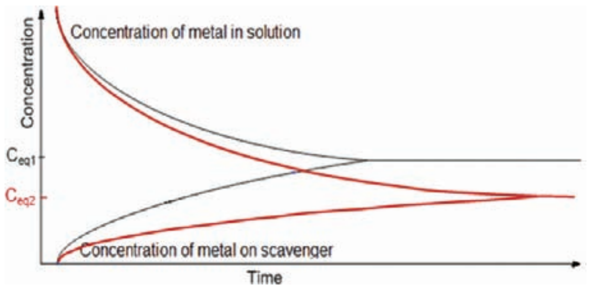

Figure 2. Concentration of metal as a function of time.

Disposable cartridges have been designed to contain silica-based scavengers to answer metal removal demands at kilo-lab and pilot plant scale. They respond to particular requirements such as minimisation of manual handling of loose scavenger pre- and postscavenging, increase process throughput by using a semicontinuous approach, and increase asset availability by eliminating vessel contamination by a loose scavenger.

The cartridges are fitted into a stand-alone compact self-contained filter unit, and the quantity and type of scavenger inside the cartridges can be customised to the particular process.

In this study, various metals from pharmaceutical manufacture process streams have been removed using the adsorption method. Generally, the adsorbents used are based on a modified silica framework functionalised with mercaptosulphide appendages and bisulphide bridges (Figure 1). A key feature of such materials is to possess ligand combinations with overall higher affinity for the metal compared to the pharmaceutical product.

Silica-based materials offer good and broad solvent compatibility, no swelling characteristics, and excellent stability properties even at temperatures in excess of 100 °C, versus similarly functionalised resins based on alternative inorganic, organic, or hybrid support matrices. Moreover these adsorbents can be customised in relation to their particle and pore sizes, accessible surface area, and active site loading according to process requirements.

Representations (1) and (2) are components of the functionalised silicas described in this paper, both offering removal performance for metals in different oxidation states (e.g., Pd (0) and Pd(II)); and where unique internal sulphur atoms, in conjunction with terminal thiol groups, offer bidentate co-ordination sites for the metal, with potential for stronger metal binding and higher metal affinity.[7]

Ready customisation of the component ratio, the particle and pore size, has allowed the use of this particular type of modified silica over a range of metal attenuation requirements for several projects, and they have been successfully applied in the multikilogram manufacture of intermediates and/or final drug substances.

Batch Adsorption. This is possibly one of the more easily employed metal removal methods: the adsorbent is added to the reaction vessel, and after a suitable contact time the metal is removed from the solution phase and onto the adsorbent. As the process proceeds, the adsorbent becomes saturated: the concentration of the metal in solution decreases to $C_{eq\,1}$. The metal enriched inert solid is then separated from the process by filtration.

In order to increase scavenging power (decrease metal concentration in solution, $C_{eq\,1}$), further scavenger can be added to the reaction vessel: metal concentration will diminish, to $C_{eq\,2}$, whilst saturation increases (Figure 2). Metal adsorption onto the functionalised silicas described in this paper should be considered as an irreversible process under general operating conditions.

Adsorption is a dynamic process involving three events: (1) transport of the particle from the bulk liquid to the surface of the adsorbent; (2) diffusion of the metal particle through the liquid boundary to the solid surface; and (3) adsorption onto the adsorbent particle.

With porous materials such as silicas part of this process involves diffusion into the pores.

The first two events are sensitive to the scale of the process as they are both mass transfer processes. As the scavenging operation is scaled-up from a laboratory setting to pilot plant scale, reproducibility of laboratory data may be in jeopardy: the efficiency of metal transport in solution depends on the mixing properties and the geometry of the vessel. An efficient slurry suspension will depend on the agitator characteristics, power input to the agitator, and vessel fill level. Performing the scavenging under batch operation will also require a filtration step and the removal of the adsorbent from the reactor. Typically batch operations vary from 6 to 24 h.

Adsorption kinetics depends on how easily the metal in solution finds free scavenging sites on the adsorbent surface. As adsorption proceeds, the metal concentration in solution decreases and the effective concentration of available sites decreases too. The driving force for adsorption decreases as the metal adsorbent becomes saturated.[6]

There are some shortcomings of the method: product may adsorb onto the solid particles, although this can be easily verified during the development stage by standard analytical methods and can be minimised with the correct selection of the inorganic solid support. The effective cycle time for an adsorption process can be increased substantially by cleaning time for the vessel (see below for further discussion of this aspect).

Column Adsorption. The alternative to batch adsorption is column adsorption where the scavenger is packed into a column and the process stream is passed onto the fixed-bed adsorbent: the column is placed between the feeding vessel and a clean receiver.

The main advantage of using a fixed bed configuration in a semicontinuous mode relies on the fact that the process is now independent of mass transfer laws. Once the optimum linear velocity has been found, defining also the optimum residence time of the solution to interact with the stationery phase and ensure efficient metal removal, this parameter can be easily scaled up and/or down, as long as the packed bed particles are unchanged, using available mathematical calculations.

As the process stream travels through the fixed bed, two important factors take place: (1) the concentration of the metal in the mobile phase decreases; (2) the mobile phase always encounters fresh adsorbent (i.e., scavenging sites). The driving force for the scavenging step is sustained as long as there is fresh adsorbent available.[6]

■ RESULTS AND DISCUSSION

Batch Adsorption: Palladium Attenuation. A project request for 15 kg of API for a respiratory drug candidate was received and required scaling-up a Buchwald–Hartwig amidation, a critical transformation coupling the two building blocks of the molecule to make 20 kg of intermediate per batch.

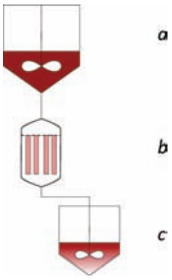

Figure 3. Plant configuration for the Buchwald–Hartwig reaction for scavenging operations: (a) reaction vessel, (b) bag filter, (c) receiving vessel.

Table 1. Efficiency in Pd removal by 'batch mode'

Batch	Pd level in solution prescavenging (ppm)	Pd level in solution postscavenging (ppm)	Pd removal efficiency (%)	Ratio scavenger/Pd (kg/kg)
1	992.1	190.2	81	6.5
2	455.6	25.4	94	12.9

The reaction[8] was run using tris(dibenzylideneacetone) dipalladium(0) (Pd_2dba_3) in catalytic amounts, Xphos as ligand, and cesium carbonate as a weak base. Both the reaction and the following palladium scavenging operations were carried out in a 1200 L vessel, characterised by having a conical shaped bottom and a three blade retreat curve type impeller; this was coupled with a downstream 125 L four bags filter and a clean reactor acting as a receiver for the process stream at the filter's outlet (Figure 3).

At completion of the reaction, a preweighed amount (50% w/w with respect to starting material; unoptimised) of PhosphonicS silica-based scavenger SPM36f was added to the reaction mixture *via* the reactor manway and the biphasic mixture was left stirring at a temperature of 60 °C for 24 h.

When in a batch mode, achievement of a well suspended slurry is crucial to obtain good mass transfer of metal particles through the reaction medium and inside the pores of the silica particles; hence agitation patterns are also critical. Mimicking full scale reactor agitation characteristics in a laboratory environment is not always a straightforward task; this can make the transfer of the process and the scale-up to Pilot Plant somewhat unpredictable.

Two batches were run (at 20 kg starting material): in Batch 1, the starting level of palladium in solution, analysed by ICP-OES, was an atypical 1000 ppm due to extra catalyst added to counteract an unexpected stalling of the reaction. The scavenger was added and left to stir at 60 °C for 80 h before the first sample was withdrawn; once the palladium results were found to have plateaued at around 190 ppm over a period of 10 h, the scavenging was stopped and filtration of the silica was carried out.

Batch 2 presented a more typical profile for palladium content post-Buchwald–Hartwig reaction; starting from 456 ppm (equivalent to 4 mol % catalyst content vs substrate) of palladium dissolved, the scavenging required an overnight stir and reduced the palladium content in solution to the anticipated low levels, in this case just 25 ppm, further highlighting the atypical nature of Batch 1 (Table 1).

In summary, scaling-up of adsorption processes in a batch mode involves the following operations: solid scavenger addition to vessel, vessel made safe (leak tests, nitrogen blanketing), scavenging, solid scavenger filtration, solid scavenger cake wash, filter unloading, filter cleaning, vessel cleaning.

Table 2. Breakdown of the scavenger operation and timings per batch

Operation	Batch 1 (hours)	Batch 2 (hours)
solid scavenger addition to vessel	1	1
vessel make safe	1	1
scavenging	80	18
solid scavenger filtration	4	5
solid scavenger cake wash	4	2
filter unloading	1	1
filter cleaning; vessel cleaning	10	10
TOTAL	101	38

Figure 4. Staining of vessel's walls post Buchwald–Hartwig reaction and scavenging.

In order to understand the impact of each of these operations on the batch cycle time, a thorough analysis of batch data was carried out (Table 2), with batch 2 for the reasons described considered more typical.

With both batches, palladium staining was observed on the internal surfaces of the filter and on the reactor walls, leading to requirements for extensive cleaning operations between batches using a variety of solvents and cleaning agents (Figure 4).

A further important aspect to consider when transferring a process from laboratory to a pilot scale environment is its HSE impact: although each unit operation is carried out within the standard envelope of an HSE and GMP regulated plant, it was thought that the overall HSE rating of this operation could certainly be improved, in terms of material handling pre- and post- scavenging and solvent usage for cleaning.

The high number of unit operations within the scavenging operation, requiring manual intervention, has a high economical impact on the overall batch cycle time, and whilst possible in suitable apparatus it may not be desirable or sustainable in the long term at large process scale.

Fixed Bed Adsorption, Recirculation Mode. *Rhodium Attenuation.* The enantioselective 1,4-addition of an aryl boronic ester to an α,β-unsaturated ester mediated by a rhodium based catalyst (cyclooctadiene rhodium chloride dimer $[Rh(COD)Cl]_2$) affording compound **3** (Figure 5) is the key chirality-inducing step for the preparation of an active pharmaceutical ingredient.

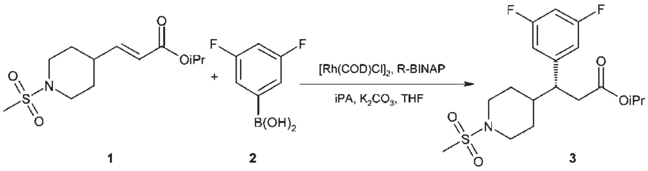

Figure 5. Rhodium catalysed 1,4-asymmetric addition to substituted isopropyl acrylate.

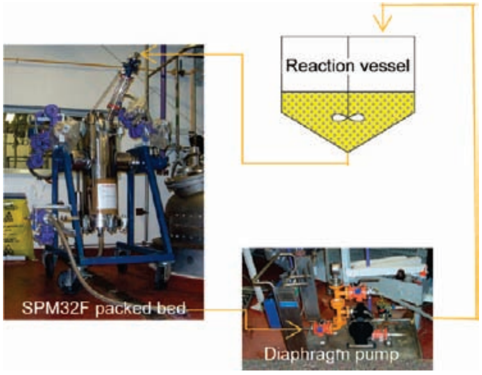

Figure 6. Recirculation mode scavenging setup.

This synthetic step was scaled up in the AstraZeneca R&D Charnwood pilot plant facilities to produce 120 kg of pharmaceutical intermediate in four batches.

Whilst this synthetic approach showed a substantial improvement from the initial medicinal chemistry route, it still had to deal with the attenuation of the rhodium content in the process stream.

In a first pilot plant campaign the rhodium attenuation was achieved by slurring Smopex-234; although the result was very satisfying with rhodium content in the isolated intermediate below 40 ppm, the overall plant procedure was somewhat cumbersome: pretreatment of Smopex-234 resin in a filter with recirculating reaction solvent, analysis of solvent stream for detection of leachables, and pretreatment of the reaction mixture with a solid oxidant, to oxidise the metal for increasing Smopex-234 scavenging activity.[9]

Development work carried out for the up-coming pilot plant campaign identified scavenger SPM32f, another PhosphonicS silica-based metal scavenger, as a good candidate for the removal of rhodium: during the laboratory development it provided consistent low levels of rhodium in solution and superior handling performance versus Smopex 234 and Quadrapure BZA.[9]

Learning from the experience acquired with the batch mode scavenging, the scavenging process was this time accommodated utilising a long and thin existing hastelloy filter housing packed with the modified silica, SPM32f: at its outlet a diaphragm pump would recirculate the solution through the packed bed (top to bottom) back to the reactor as in Figure 6.

The downside of scavenging using such a configuration is that as the process stream is exiting the packed bed and has been stripped of metal content, it is pumped back to the single vessel in the equipment loop, where the solution at higher metal content is being held. The overall effect is a slow scavenging action obtained by dilution with each recirculating loop.

Four batches were run at 30 kg scale: the scavenging in recirculation mode (overnight recirculation at 60 °C) provided a consistent reduction of rhodium content in solution in all batches (Table 3).

Table 3. Results of rhodium removal using a ‘recirculation’ plant setup

Batch	Recirculation time (h)	Rh in solution prescavenging (ppm)	Rh in solution postscavenging (ppm)	Rh removal efficiency (%)	Ratio scavenger/Rh (kg/kg)
1	21	583	41.3	94	18.17
2	19	553	22.3	97	
3	22	554	47.3	93	
4	24	686	49.9	93	

Table 4. Averaged breakdown of the scavenger operation and timings

Operation	Average over 4 Batches (h)
solid scavenger addition to vessel	Not applicable
vessel make safe	Not required
scavenging	22
solid scavenger filtration	Not required
solid scavenger cake wash	2
filter unloading	Not applicable
filter cleaning; vessel cleaning	Not applicable
TOTAL	24

The consistent results obtained over the first two batches allowed for predictive reduction in the analytical support during the scavenging operation for the following two batches: only one sample per batch was withdrawn and analysed before ending the scavenging operation.

The flow rate used to pump the solution through the packed column was mainly dictated by the activity of the diaphragm pump and limited to the equipment available at the time, rather than a true scale-up of parameters identified during laboratory development work. In fact, removal of the metal worked on the basis that the reaction stream was recirculated through the bed for a minimum of 20 h until a constant level of rhodium in solution was achieved. Nevertheless, this setup brought a number of improvements compared to the previous operational mode where the scavenger was slurried in the reactor. As for the palladium scavenging in the previous case study, also in this example a review of the unit operations was carried out, to enable an objective evaluation of the timings (Table 4).

The main advantages identified in recirculation mode were (1) a reduced number of unit operations, (2) reduced batch cycle time (increased productivity), (3) a dedicated piece of equipment holding the scavenger, preventing silica contamination of the reactor, and (4) reduced postbatch cleaning activities with solvent usage for cleaning purposes also substantially reduced.

On the other hand, overall, the HSE rating of the scavenging operation still presented an opportunity for improvement as it was perceived that the manual handling of loose silica powder before and after scavenging could be eliminated if using ready to use cartridges filled with the appropriate scavenger.

Furthermore, on unloading the filter postscavenging, it was noted that areas of the bed had been left untouched by the process stream, indicating a nonhomogeneous distribution of the rhodium throughout the modified silica bed. The reaction mixture had a deep red colour before being treated with SPM32f, turning to a yellowish colour postscavenging. Similarly, the silica-based scavenger would acquire a deep brown-red colour after successfully adsorbing the metal from the process stream.

It is unclear whether the channelling effect had taken place due to the filter being loosely 'filled' rather than uniformly 'packed' with the scavenger or because the nonoptimised flow rate through the column had given rise to axial flow. Unused scavenger, in the equipment, brings a percentage of wastage which needs to be addressed in the attempt of optimising the manufacturing process.

Palladium Attenuation. A further scale-up of the Buchwald–Hartwig reaction was carried out on a 50 kg scale (with respect to starting material), this time as one batch. The removal of palladium (720 ppm initial palladium concentration in solution) was carried out using the recirculation method.

PhosphonicS SPM36f metal scavenger (ca. 22 kg equating to 44 wt %/wt with respect to starting material; unoptimised) was packed into the tubular filter housing and the process stream was circulated at 80 °C through the filter bed, with periodic monitoring of the palladium content.

The ratio of scavenger versus palladium catalyst (kg/kg) was still 12.9, as in the Batch Adsorption: Palladium Attenuation section. Effective palladium removal was achieved overnight, and the process was allowed to continue for 36 h to maximise metal removal (see Figure 7).

The metal content of the isolated API-intermediate was found to be reduced from 720 to 75 ppm in solution (40 ppm in isolated material) within the 36 h process step time scale, with no loss of intermediate indicated by appropriate analytical assays. The API-intermediate was advanced to the next process step, allowing the API to be delivered on time and within regulatory guidelines for metal content.

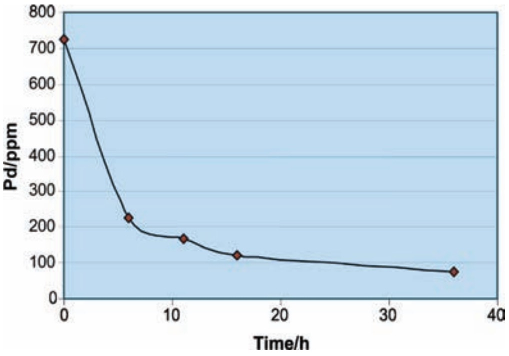

Figure 7. Palladium attenuation versus time.

Similarly to the rhodium case study, an analysis of the broken-down plant activities was carried out and similar results were obtained, although a longer scavenging time was employed for this project.

Scavenging: Looking for an Improved Format at Pilot Plant Scale. As more processes requiring metal removal post-transition metal catalysis were transferred to the pilot plant for scale-up, there was a clear requirement for the scavenger operation to be a 'fast and efficient process' ideally where the process stream could be purified by single pass through a stationary phase, with 'ease of operability', where manual handling of the scavenger was minimised. Finally the scavenging operation ought to be a 'clean modular process' where the metal removal could be carried out in dedicated equipment (to be taken out of the equipment chain at completion of operation without impacting on batch cycle times) which would be flexible to accommodate processes at different scales within a range of 5 to 10 kg of solid scavenger material, and with the potential for larger scales.

In collaboration with PhosphonicS and Amazon Filters Ltd. a new cartridge design was engineered as illustrated in Figure 8.

The main feature of this cartridge has to be the simplicity of its design, made of three main parts: tubular body (approximately 50 cm length and 5.1 cm external diameter), inlet end, and outlet end. The three parts are held together by the threaded end-caps, and appropriate "O" rings are in place to ensure proper fitting in cartridge housings and filter elements are in place to retain all grades of functionalised silica scavengers, down to a 20 μm particle size.

The prototype was made of polypropylene which is a common polymer used in many operational applications in pharmaceutical manufacturing, presenting wide chemical and mechanical compatibility and meeting regulatory requirements. Furthermore, tapered seal and thermal bonding processes eliminate the use of adhesives and sealants to ensure zero extractables from the materials of construction of the cartridge.

Each cartridge can be packed with up to 500 g of PhosphonicS modified silica scavenger (depending on the exact scavenger variant) and can be advantageously fitted in existing plant equipment regularly used to house cartridge filters of identical geometrical shape (Figure 9a)

As a drug candidate proceeds through its development path, the chemical synthetic process evolves to aiming for more viable solutions from an operational, commercial, and environmental perspective. In the field of metal scavenging, such novel cartridge

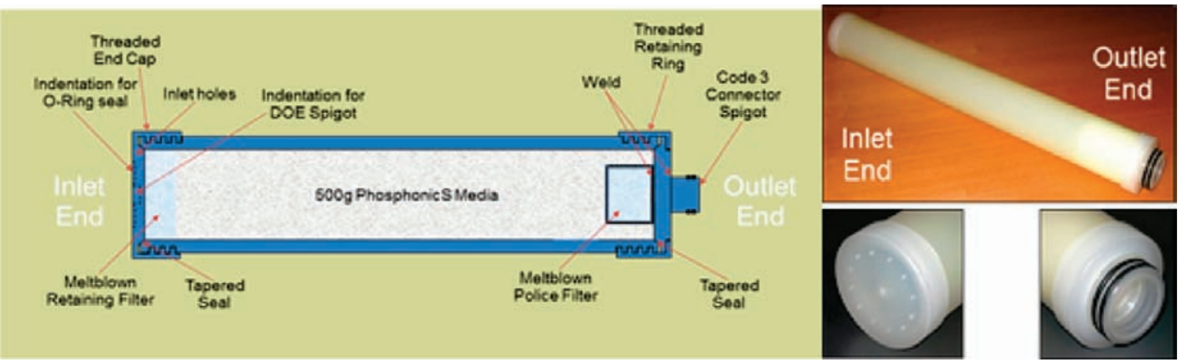

Figure 8. New scavenger cartridge prototype.

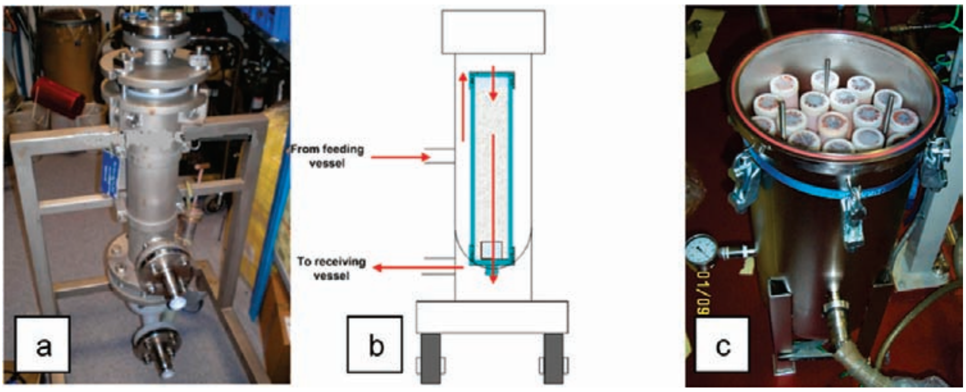

Figure 9. Plant filter housing: (a) single cartridge housing, (b) schematic of single cartridge housing, (c) 19-cartridges housing, open showing used cartridges.

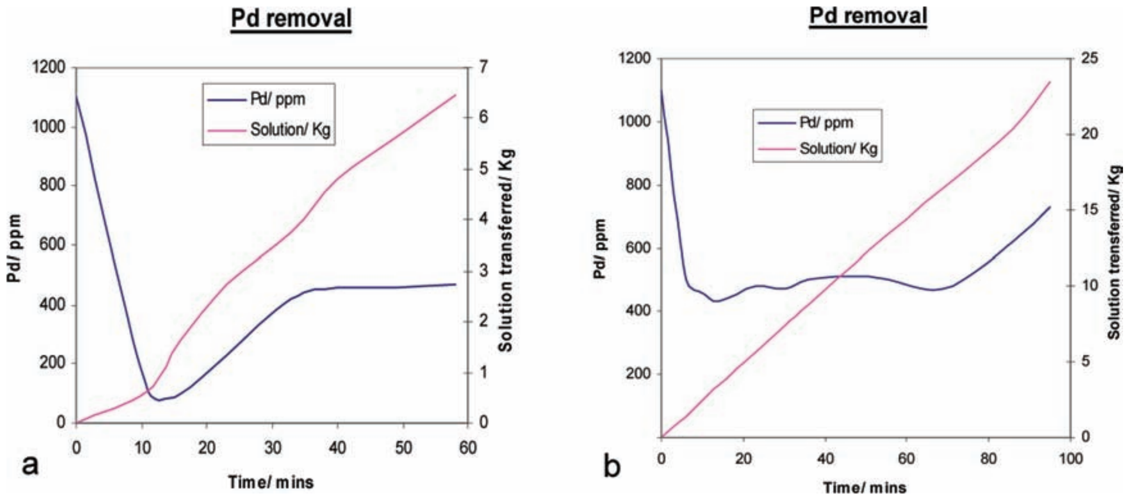

Figure 10. Semicontinuous, fixed-bed adsorption results and flow rates: (a) after prewetting cartridge with process solvent and (b) with no cartridge preconditioning (breakthrough after ~50% of solution has been treated).

design has the potential to be adopted quite early on in the process development (Figure 9) and used in manufactures of toxicology batches (0.5 to 1.5 kg).

As the request for the active pharmaceutical ingredients increases, the scavenging step can be accommodated with potentially no further development work for the manufacture to 10+ kg by scaling-out the operation using the required number of cartridges and a bigger cartridge housing (Figure 9c). The 'scale-out' option from a single to multiple cartridges will involve a mathematical adjustment of the flow rate, with linear velocity being maintained constant to ensure sufficient contact time for the metal scavenging step.

Metal Removal, Using the Single Pass, Semicontinuous Method. Initial trials were run at kilo-lab scale where a prototype cartridge packed with PhosphonicS silica-based scavenger SPM36f was used to purify an acetonitrile solution containing homogeneous palladium species and around 10% of an API intermediate.

During this initial proof-of-concept phase, the plant setup included a feeding vessel connected to a small diaphragm pump followed by the filter, housing the scavenger cartridge, and a receiving vessel placed on a weight scale for flow-rate evaluation. Samples were regularly withdrawn at the cartridge exit.

The solution was artificially spiked with Pd(0) catalyst prior to use, to achieve a palladium content of *circa* 1100 ppm.

The main objectives for the trials were to (1) evaluate the efficacy of the equipment to withstand a 'semicontinuous' process, (2) assess the control over flow rate during the adsorption experiment, (3) determine the capacity of the system to perform metal removal, and finally (4) confirm the fate of the API intermediate.

As indicated in Figure 10, the kilo-lab experiments demonstrated the capability of the scavenging setup to run metal removal operations: experiment (a) was run applying a 500 mbar vacuum to the receiver vessel whilst experiment (b) was run pumping the solution through the fixed bed and in this case a pressure differential of 0.5−1.0 bar was observed across the scavenger cartridge.

In addition, both runs did show palladium attenuation, although the unoptimised conditions applied (e.g., ensuring adequate residence time for the scavenging process) were such that equilibration between stationery and mobile phases was certainly not achieved providing a suboptimal metal removal. No adsorption of the intermediate API was observed however, and good flow rates in terms of operational times were indicated as being readily achievable.

Previous trial and error and unstructured approaches to batch scavenging process development had sometimes resulted in nonrobust scale-up, inefficient use of relatively expensive metal removal adsorbent, repeated development work, handling issues, and facility decontamination difficulties at scale.

These problems have been addressed by developing a consistent and reliable laboratory methodology for the scavenging of metals from pharmaceutical process streams. It consists of a systematic workflow, providing the user with a scientific approach to impurity scavenging process development, and is based on a theoretical and predictive understanding of scavenging as a physicochemical adsorption process. The workflow comprises three main steps (a more detailed publication thoroughly exemplifying this process at AstraZeneca is in preparation): (1) scavenger screening to select the best performing scavenger in the system from a library in excess of 100;[10] (2) determination of the adsorption isotherm to assess the capacity of the scavenger to remove the impurity, and (3) measuring the system adsorption kinetics to ensure the process is operated optimally upon scale-up.

It is envisaged that this scavenger identification and early optimisation process will be run in a semicontinuous manner, where the solid scavenger is packed in a laboratory column.

Finally, the breakthrough point of a column is measured. This information may then be used to ensure that the column is not used for longer than it is effective. As reported by Girgis et al.[11] it is assumed that liquid-plug flow is present, that the thermodynamic equilibrium between the solid and liquid phase is established rapidly, and that the concentration of the impurity at the bed exit is essentially zero.

Once the loading and kinetics requirements and the breakthrough of the column have been identified, residence time and flow rates can be calculated.[12] However, it is recognised that these values can be dependent on the packing of a column.

Palladium Attenuation in Semicontinuous Mode Application. This process development was first applied to a kilo-lab GMP manufacture where Pd-113 was used to catalyse the α-arylation of an API intermediate (Figure 11).

The initial laboratory scavenger selection screen identified the most suitable scavenging agent as being a mercapto sulphide modified silica (Phosphonics SPM32): this scavenger provided an initial palladium attenuation of around 90% at 5 mL scale. Required scavenger loading was determined by running adsorption isotherms whilst adsorption kinetic experiments identified the minimum 'contact time' (also indicated as residence time) between the solution and the scavenger, necessary to reduce the metal content to the desired level.

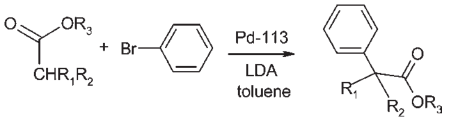

Figure 11. Reaction scheme for an α-arylation.

During the kilo-lab scale-up, two batches of the α-arylation chemistry were run at 4 kg scale (starting material); the crude reaction mixture containing the dissolved homogeneous catalyst and reaction products was passed through five SPM32 cartridges in series.

The scavenging process allowed a successful removal of the metal in both batches: the palladium concentration in solution went from an initial value of 600 ppm down to 15 ppm.

When the request for this particular API grew to 30 kg, a pilot plant campaign was organised. There was an opportunity to scale-out the scavenger step based on the results from the previously run kilo-lab campaign, using a 19 cartridge filter unit (Figure 9c).

No development work was required for the pilot plant campaign: a series of calculations from data extrapolated from the kilo-lab batches were carried out and adapted to the 19 cartridge filter unit, as the scavenger, the cartridges, the method, and process stream did not change.

The results for the two batches gave consistent values of palladium removal with virtually no palladium content at the bed exit throughout the batch. Figure 12 shows the particular equipment configuration used in this process.

Iridium Attenuation in Semicontinuous Mode Application. A further application of the scavenging as a linear, semicontinuous and also modular unit was the removal of leached iridium in a reaction mixture, where the substrate had gone through a reductive amination using iridium grafted onto calcium carbonate as catalyst and hydrogen.

One of the most efficient scavengers, identified during the laboratory screening trial, was again the Phosphonics SPM32 modified silica.

The process involved the filtration of the crude reaction mixture through a bed of scavenger at room temperature postcatalyst filtration. Scale-up of the method involved an initial assessment of the adsorption kinetics, an evaluation of the breakthrough curve, and the application of a mathematical relationship between the laboratory column used and the pilot plant cartridge system, based on the previous work carried out for the palladium removal.

In this instance though, only the equivalent of eight cartridges worth of scavenger material were calculated to be required to remove the iridium contamination down to the desired levels. The same 19 cartridge filter housing used for earlier processes, described above and shown in Figure 9c, was therefore fitted with 11 blanking cartridges for this process.

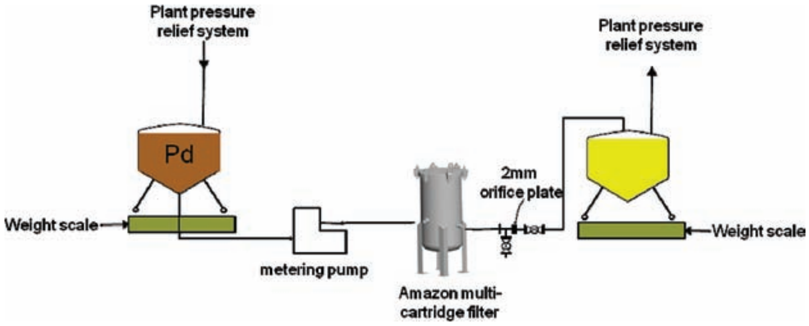

Figure 12. Plant configuration: one tank containing the reaction mixture, followed by a metering pump, the Amazon 19-cartridges filter, an orifice plate, and the receiving tank for the scavenged solution.

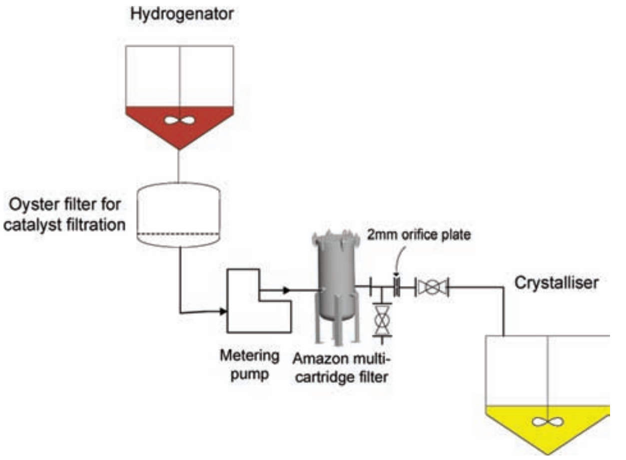

Figure 13. Plant equipment configuration for the scavenging of iridium from process stream.

Table 5. Comparison of the breakdown of the scavenger operation and timings for the three different methods used at scale

Operation	Batch mode (h)	Recirculation (average) (h)	Single Pass (average) (h)
solid scavenger addition to vessel	1	OFFline	OFFline
vessel make safe	1	Not required	Not required
scavenging	18	22	4
solid scavenger filtration	5	Not required	Not required
solid scavenger cake wash	2	2	2
filter unloading	1	OFFline	OFFline
filter cleaning; vessel cleaning	10	OFFline	OFFline
TOTAL	38	24	6

The general versatility and applicability of this methodology allowed for the scavenger equipment to be configured in series after the filtration unit, where the heterogeneous catalyst was filtered off, before being transferred to the final crystallisation vessel (Figure 13). The obvious and main advantage of this setup was that the two unit operations could be easily run in series, providing an advantageous saving in batch cycle time and in equipment cleaning.

The initial iridium concentration in solution was above 16 000 ppm (calculated vs concentration of API intermediate). Results over the two batches showed a consistent reduction of iridium content in solution at above 97% (average for the two batches); this was achieved in a processing/purification time of around 5 h, including a solvent wash of the cartridge system. The ratio of scavenger versus iridium metal (kg/kg) was 15 in Batch 1 and 18 in Batch 2.

Obviously the flow rate is a process dependent parameter.

By reviewing the batch documentation, one of the major benefits of this procedure appeared to be the time savings: the selected flow rate of the process stream through the cartridges was calculated to be 100 kg/h; with a batch of 400 kg, the iridium removal procedure took around 4 h, followed by a solvent rinse of the scavenger to displace the batch through the cartridges (2 h) (Table 5).

It has to be mentioned that to ensure homogeneous flow through the 19 cartridges (and so avoiding the risk of preferential flow) a flow restriction was introduced in the form of an orifice plate at the scavenger filter unit outlet. The orifice plate created an artificial back pressure against which the solution had to be pumped, with the pressure no higher than 3.5 bar at the inlet of the filter. As with the single cartridge run, operating back-pressures were not found to be restrictive in this multicartridge format, with only small operating pressure differentials of 0.5−1.0 bar observed.

Significantly, the setting up of the scavenging equipment at scale was by far faster than the two previous procedures used, and from a manual handling perspective, the use of ready filled cartridges, with the desired scavenger, avoids requirements for the operator to get in contact with loose modified silica pre-scavenging and contaminated waste postscavenging (Table 5).

Behaviour of Packed Bed Adsorbers. Economics of Scavenger Cartridges. The adsorption process through the scavenger column is assumed to be plug flow, according to which infinitesimal layers of solution (plugs) with assumed perpendicular uniform composition travel axially along the column. Each layer has a slightly different composition from its predecessor and following layer, as the adsorbate (metal species to be removed) is being adsorbed onto the stationery phase (scavenger).

The adsorbent is gradually enriched with adsorbate, whilst the process stream has been deprived of it, during the longitudinal journey. The concentration of the adsorbate on the adsorbent is related to the concentration of adsorbate in the feed by a thermodynamic equilibrium. After the scavenging process, at the outlet of the bed, the adsorbate concentration should be close to zero, until each layer of adsorbent gets saturated, at which point the concentration of adsorbate in the effluent starts rising up to the concentration of adsorbate in the process stream at the feed point.

The empirical plotting of adsorbate concentration at the column exit versus time, the breakthrough curve, provides a powerful tool for understanding a particular scavenging process for a known packed bed.

Commercially available scavengers, when applied to GMP manufactures, and especially if considered against traditional techniques for metal removal, can be perceived to be an additional element to the overall materials costs, with subsequent impact on the total manufacture expenditure.

With an increasing pressure to drive the cost of raw materials down, a cost benefit analysis for the scavenging in cartridge format, in this particular case, should take into account of course the cost of raw materials; however the overall gain provided by introducing process intensification along with the long-term benefits of using new technologies should not be downplayed.

Introduction of optimised, efficient process scavenging steps is an important factor in such cost analysis when compared to less volume efficient metal extraction by phase separation or by time-consuming recrystallisation procedures.

Metal scavengers do vary in their cost however, with a wide range of suppliers offering competitive options, particularly for at scale application and to support their widespread usage.

Moreover, there are some considerations which can be extrapolated from the analysis of a breakthrough curve and which can

Figure 14. Breakthrough curve.

lead to a more targeted application of the scavenging step depending on when it is introduced in the synthetic sequence.

Essentially, the breakthrough curve gives an indication of the best compromise between efficient metal removal and 'value for money' scavenger usage (Figure 14), naturally being considered against the focus of a particular scavenging step, either being the removal of metal species effectively ahead of biological testing and use or ahead of further synthetic steps.

If the scavenger step is early in the synthetic sequence, a good economically viable compromise may be to undercharge the amount of scavenger to be used: the breakthrough point will be achieved before all the metal has been removed from the process stream: metal concentration at the outlet will rapidly increase to the inlet concentration. Whether downstream chemistry will be affected by the increased metal impurity or further downstream purification (extractions, isolation of intermediate by crystallisation) will lower the level of metal in the final API to acceptable levels must be evaluated. Additional scavenging steps might also be easily performed as necessary.

On the other hand, if the scavenging step is closer to the final API isolation stage, it is advisible to work with a slight overcharge of scavenger to allow a complete removal of the metal species; although the closer the scavenging step is to the final API formation step, the smaller the respective total amount of scavenger required will be.

The single pass mode of operation through scavenger cartridges accounts for a remarkable decrease in batch cycle time, as shown in Table 5, with less than a quarter of the time spent for this operation when compared to the all-in-one batch mode of operation. Time spent defining an appropriate residence time to enable the scavenging step to be effectively performed is particularly important to ensure performance is achieved.

In addition, the advantage of having a dedicated piece of equipment means that once the operation is completed, it can be removed from the equipment chain and cleaned offline; vessel fouling and staining due to prolonged stir-out is also more contained providing a substantial gain in time spent cleaning and a diminished usage of cleaning solvents.

Environmental Impact of the Scavenger Step. Environmental viability and long-term sustainability of a chemical process go hand in hand with its economical evaluation. Considerations such as treatment and/or disposal of waste streams, ecotoxicity and biodegradability of all components in aqueous waste streams, recovery and/or recycle of solvents and raw materials, and minimisation and/or elimination of discharge of APIs from waste streams are nowadays part of the environmental assessment required when a development project nears technology transfer for commercial manufacture (Figure 15).[13]

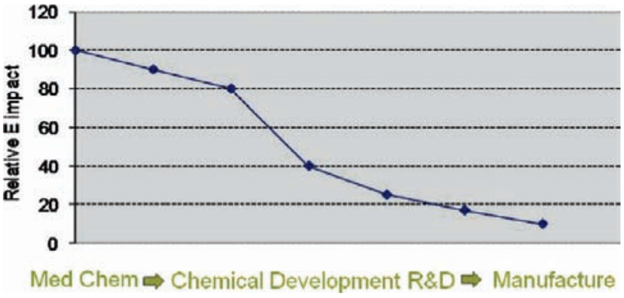

Figure 15. Model of environmental impact reduction in development projects.

From the early studies and manufactures carried out in our laboratories and pilot plant, the optimisation of the scavenger process has led to a remarkable reduction of the scavenger loading and a reduction of solvent usage for cleaning purposes.

Another aspect exploited during these studies is the recovery of the metal species adsorbed onto the insoluble scavenging matrix via a metal refining process. Metal refining is an economical, sustainable, and morally responsible route for recovering precious metals: the metal value can so be used to offset the price of the scavenger or cover the cost of further catalysts, for example, in the rhodium project.

Around 70% of rhodium metal was recovered by the metal refining process, from one of our early processes, where rhodium had been adsorbed onto a modified silica scavenger.

Analytical Method for Metal Detection. An ideal metal detection method would quantitatively analyse metals in solution as it exits the scavenger setup, similarly to several process analytical technologies already integrated for larger scale manufactures, in the pharmaceutical industry.

Unfortunately such quantitative analytical methods are to date not yet available, first because the precious metal is usually present at such an extremely low concentration, challenging the level of detection of the metal analytical methodology, but also because most of the techniques normally used follow a lengthy sample preparation procedure.

In the work described in this paper the metals in solution were analysed using inductively coupled plasma optical emission spectroscopy (ICP-OES). The ICP-OES analyses were performed using a Perkin-Elmer ICO-OES 3300 radial view.

Sample preparation typically involved a dilution to a known volume of a solution sample using ashing, acid digestion, or simple sample dissolution. The solvent matrices used were dimethoxysulfoxide or 2 M nitric acid. Calibration graphs were created using standard solutions covering the range from 0.1 to 10 mg/L for most of the elements.

To assess the recovery of the method and to check for significant matrix interference affecting the analysis results, spiking experiments were run.

■ CONCLUSIONS

This paper describes the chronological, real-time application of functionalised silica scavengers for the removal of a variety of metals, including Pd, Rh, and Ir, from intermediates in a number of API projects at various stages of development passing through AstraZeneca's pilot plant at Charnwood, UK from 2007 to 2010. During this time, as part of an ongoing development of working processes, a versatile and scaleable cartridge format was developed. This paper does not focus on insights into the particular adsorption processes between a metal particle and the mercapto-sulfide appendages on the silica stationery phases used, but rather centres on the thought process followed to improve the scavenging process at scale, to make it of general applicability to development projects. The format for the scavenger cartridges described in this paper is still eligible for further improvements; in fact the multicartridge filter housing used at pilot plant scale is commonly referred to as a 'third generation scavenging concept', where first and second generation were respectively the all-in-one batch mode and the recirculation column. This 'third generation' format is currently in use for metal purification at commercial product scale.

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REFERENCES

(1) Hartwig, J. F. *Organotransition Metal Chemistry, from Bonding to Catalysis*; New York: University Science Books: 2010.

(2) Selected reviews include: Chincilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. *The Mizoroki—Heck Reaction*; Oestreich, M., Ed.; John Wiley & Sons, Ltd.: Chichester, U.K., 2009. Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. Beletskava, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(3) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253. Garrett, C. E.; Prasad, K *Adv. Synth. Catal.* **2004**, *346*, 889.

(4) Lakshman, M. K.; Gunda, P.; Pradhan, P. *J. Org. Chem.* **2005**, *70*, 10329. Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938. Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, D. P.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **2005**, *70*, 6034.

(5) "Guideline on the specification limits for residues of metals catalysts or metal reagents", EMEA/CHMP/SWP/4446/2000.

(6) Bien, J. T.; Lane, G. C.; Oberholzer, M. R. *Top. Organomet. Chem.* **2004**, *6*, 263.

(7) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, J. R. H. *Org. Process Res. Dev.* **2007**, *11*, 406.

(8) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 159. See also: Farard, J.; et al. *Tetrahedron Lett.* **2009**, *50*, 5729.

(9) Brock, S.; Hose, D. R. J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496.

(10) Screening approaches for residual metal removal have been described in the literature: Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198.

(11) Girgis, M. J.; Kucynzki, L. E.; Berberena, S. M.; Boyd, C. A.; Kubinski, P. L.; Scheholz, M. L.; Drinkwater, D. E.; Shen, X; Babiak, S; Lefebre, B. G. *Org. Process Res. Dev.* **2008**, *12*, 1209.

(12) Reginato, G.; Munday, R.; Horner, D. "On the development of a scalable metal removal process from an API process stream, using single pass disposable scavenging cartridges", in preparation.

(13) See also: Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273.