

## Metal Removal from Fine Chemical Products

### Introduction

Metal contamination in various injectable or even oral medicines is a serious concern. Certain metals are not only harmful for human health, but also contribute to poor synthetic processing of fine chemicals.

Most synthetic drug products utilize intermediates in processing. Intermediates can include active drug components, solvents or fine chemicals used in processing and as precursors to final drug formulation. Metal contamination of intermediates must be reduced to ppm or trace levels in final drug products. Sources of metal contamination can include catalysts used in synthesis, process components such as tanks, valves and piping, and the solvents used in synthesis. All fine chemical producers and consumers are highly interested in the improvement of product quality to differentiate themselves from the competition and to comply with GMP requirements.

This 3M Purification Inc. Application Brief reviews the various processing methods used to remove metal contamination from fine chemicals and presents the use of Zeta Plus™ filter media as an alternative metal removing step.

### The Process

Various processes are employed for the production of fine chemicals. Often the intermediate product is crystallized followed by resuspension in solvent to facilitate metal ion contamination. Various techniques can be used to remove metal contamination including: addition of chelating agents, ion exchange chromatography or adsorption, addition of acids to form metal precipitates and filtration. A process employing Zeta Plus depth filtration is illustrated in Figure 1.

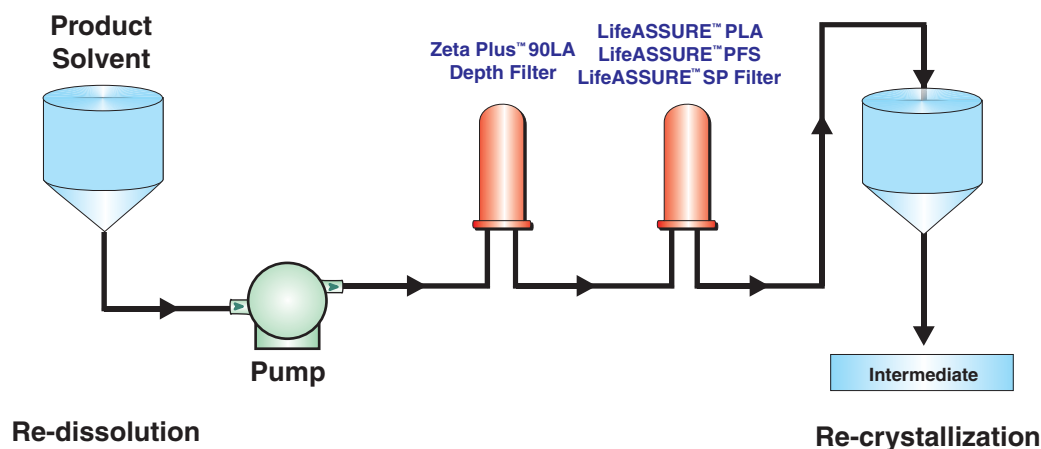


Figure 1 — Process Flow of Vaccine Production

## The Problem

As stated above, metal ion contamination of final drug products poses serious health hazards and can therefore lead to rejection of intermediate drug formulations. A number of different methods can be used to remove or reduce metal contamination, however, each of the different methods poses potential problems. One method of metal removal requires the addition of chelating agents, followed by sparkler filtration to remove metal precipitates. Addition of chelating agents results in a process additive, which then may not be completely removed from finished product. The use of sparkler filters is cumbersome and time consuming, in addition to introducing the possibility for bypass of unfiltered fluid containing the chelating agents and metal precipitates.

A second method for metal removal involves the use of ion exchange resin. This method can be performed using batch resin added to the solubilized intermediate product or by chromatography. Either method can be expensive due to resin costs and the resin may contaminate the process if shed from columns or not completely removed from batch processes.

Metal ion contamination can also be removed by adding acid to solubilized intermediate product. The acid can cause metal complex formations, which can form precipitates. The precipitate must then be removed by settling or filtration. As with chelating agents, acid addition is a process additive. All residual acid must be removed, often requiring the addition of alkali to form salts. While relatively inexpensive, acid addition can cause unwanted side effects.

## The 3M Purification Inc. Solution

An alternate method for metal ion removal involves the use of positively charged depth filtration. Zeta Plus™ depth filters consist of a cellulose matrix, inorganic filter aid and a cation resin. The resin component binds the cellulose and filter aid and imparts a positive charge to the filter medium. Metal ions are often complexed with particles having an overall negative charge. The negatively charged complexes can then be absorbed to the Zeta Plus medium by electrostatic attraction. In some instances, the metal ion complexes may be of sufficient size to be removed by mechanical entrapment within the Zeta Plus depth filter matrix. An example of particles adsorbed to the surfaces of Zeta Plus filter medium is shown in Figure 2.

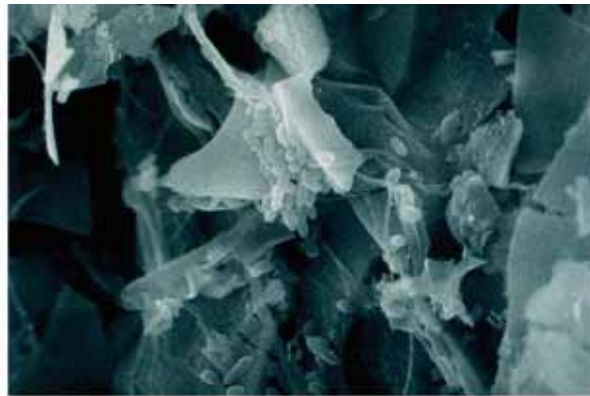


Figure 2 — Zeta Plus filtration

Zeta Plus depth filters are available in a variety of configurations including filter sheets and cartridges. Zeta Plus filter cartridges are the most convenient form for efficient filtration. Examples of Zeta Plus cartridges are shown in Figure 3.

The Zeta Plus depth media reduces metal ions such as Sn, Fe and Cr to be low ppm level and removes negatively charged small particles by electrokinetic adsorption. Zeta Plus cartridge systems are totally enclosed and reduce operator exposure and system downtime. In addition to these benefits, Zeta Plus cartridge systems are scalable from bench-top to full production.



Figure 3 — Zeta Plus filtration

Table 1 shows metal reduction by Zeta Plus 90LA and 50LA. According to test results, Zeta Plus™ 90LA filter reduced Sn from 50 ppm to be low ppm and Fe from 20 ppm to 1.2 ppm. Zeta Plus 50LA filter reduced Cr content from 10 ppm to less than 1 ppm.

**Table 1 — Metal Ion Removal by Zeta Plus Depth Filter Medium**

<b>Metal</b>	<b>Upstream</b>	<b>Downstream</b>	<b>Base solvent</b>	<b>LA grade</b>
Sn	50 ppm	Less than 1 ppm	Methanol	90LA
Fe	20 ppm	1.2 ppm	NMP	90LA
Cr	10 ppm	Less than 1 ppm	Ethyl lactate	50LA

## Conclusion and Summary

Metal ion contamination of drug intermediates and fine chemicals is a serious problem in final product formulations. A number of methods can be used to remove metal contamination, however, several of these methods may produce undesirable effects. This 3M Purification Inc. Application Brief describes the use of a positively charged depth filtration medium to remove unwanted metal ion contaminants. This innovative technology can provide significant benefits compared with conventional technology for metal ion removal. These benefits include:

- Eliminate product contamination by chelating agent.
- Reduction of washing time of production facility.
- Eliminate contamination of working environment caused by solvent exposure
- Reduction of production time.
- No industrial waste of chelating agent or acid solution.
- Both metal removal and fine filtration are available by one system.

## Additional 3M Purification Inc. Literature:

<b>Title</b>	<b>Old Literature Identification</b>	<b>New Literature Identification</b>
3M Purification Inc. Filter Systems for Bioprocess and Biological Separations	LITCATBP	70-0201-8680-8
Zeta Plus LA Series Filter Media	LITZPLA2	70-0201-8860-6
Zeta Plus EXT Series Filter Cartridges	LITZPMEXT	70-0201-8862-2
LifeASSURE™ PLA Capsule and Cartridge Filters	LITCLAPB1	70-0201-8713-7
LifeASSURE SP Membrane Filters	LITCZR020SP	70-0201-8738-4
LifeASSURE PFS Filter Cartridges	LITMRFP1	70-0201-8776-4
ZPB Model Zeta Plus Filter Housings	LITHSZPBC	70-0201-8762-4

## Scientific Applications Support Services

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- Validation And Regulatory Support
- Extractable And Compatibility Analysis
- Filter System Optimization Studies
- CUNOCheck™ 2 Integrity Tester Validation.

For more information regarding our Validation Support Services, please contact 3M Purification Inc. Technical Services or your local Distributor.

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