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Lab & Production Materials

Technical Note

Impact of Trace Metal Impurities in API Synthesis and Drug Quality

Introduction

High-purity metal salts and precursors have gained increasing attention as a reliable solution for addressing the challenges posed by trace metal impurities in Active Pharmaceutical Ingredient (API) synthesis, enabling scientists and manufacturers to enhance drug quality and safety. Trace amounts of impurities can affect the quality, stability and efficacy of drug formulation leading to adverse chemical interactions, drug degradation and toxicity.[1] The ability to detect and quantify these impurities using advanced analytical techniques, such as Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES), plays a critical role ensuring consistent impurity control throughout pharmaceutical development.

Trace metal impurities can originate from multiple sources throughout the drug development process of both small molecule and large molecule drugs across the pharmaceutical and biotechnology fields. Control of all possible sources for the trace metal impurities from the initial steps of drug formulation is crucial to overcome these challenges. Usage of high-purity reactants, reagents, catalysts, solvents can be one of the potential strategies to minimize and avoid trace metal impurities.

This article emphasizes the primary sources of metal impurities, their impact on API synthesis, and the critical importance of stringent purity standards. It also outlines practical approaches for selecting high-purity materials to control trace metal impurities at the source, along with our proven expertise in providing the ultra-pure materials. Discover our high-purity salts/precursors and catalysts equivalent to pharma-grade expectations to enhance yield, ensure compliance, and elevate overall product quality.

Sources of Metal Impurities

Metal impurities can originate from different types of sources like raw materials, excipients, manufacturing equipment, process materials, packaging materials etc. However, quality and purity of raw materials such as reactants, catalysts, reagents, solvents used in the multi-step synthetic methods play a critical role in determining the overall quality of final drug product. For example, Pd used as catalyst in coupling reactions during the synthesis of Imatinib[2] & Asciminib[3] can persist as a residual metal impurity in the final product.

Our Expertise in Trace Metal Impurity Control

We offer a wide portfolio of high-quality, high-purity, and cost-effective products equivalent to pharma-grade purity essential for the synthesis of high-purity drug formulations. Our high-purity inorganic portfolio especially salts, metal alkoxides, metal acetylacetonates are designed for their effective consistency, quality and efficacy. Products like **AnhydroBeads™** salts feature ppm level water content and minimal volatility ensuring easier handling, enhanced storage stability, and greater process reproducibility. We produce these materials using controlled wet synthesis, solid-state reactions from high-purity raw materials resulting ultra-pure compounds of more than 99% up to 99.999% (3N–5N) purity and achieving trace metal purities. By combining advanced synthesis routes with rigorous purification and analysis, our products deliver strong reliability standards. This approach enables the production of both anhydrous and hydrated grades for novel applications and advanced research.

Each material is purified with an optimal purification route such as vacuum distillation, aqueous recrystallization, or sublimation based on its volatility and solubility profile. Purity is verified using advanced techniques such as ICP-MS and ICP-OES to quantify trace elements across a wide dynamic range (32–68 elements panel) as mentioned in **Table 1**.

This specialized approach removes metal, anionic, and volatile contaminants well beyond standard specifications, ensuring salts/precursors that perform consistently even in trace sensitive processes. Dedicated clean rooms, segregated production suites, and verified

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Table 1. Standard metal impurity panels and significance in purity assessment

Standard panel	List of elements	Significance
General "32-metals" panel	Ag, Al, As, B, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ir, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Pd, Pt, Sb, Sn, Sr, Ti, V, W, Zn, Zr.	Purity of each metal salt validated by assessing all corresponding metal impurities within the same panel, ensuring complete and reliable impurity control
"34-metals" panel (Specific for Alkali Metals)	Ag, Al, As, B, Ba, Be, Bi, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ir, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Pd, Pt, Rb, Sb, Sn, Sr, Ti, V, W, Zn, Zr.	
"16-metals" panel (Specific for Rare-earth Elements)	Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Nd, Pr, Sc, Sm, Tb, Tm, Y, Yb.	

line-clearance procedures minimize cross-contamination risk throughout manufacturing process. These robust, multistep analytical controls produce reliable purity profiles for every batch, ensuring consistent performance. As a result, our metal salts/precursors or any other inorganic materials provide a stable, well-characterized foundation for critical processes, reducing variability, simplifying qualification, and offering high-level of assurance in quality and purity.

Impact of Metal Impurities on Drug Formulations

Presence of metal impurities in pharmaceutical products is a major concern for manufacturers and consumers due to the inherent toxicity of metal contaminants and associated health risks.[4] Metal impurities may catalyze the degradation of APIs thereby reducing their shelf life and may also contribute to toxic or undesirable effects that result in poisoning the human body.[5] Many pharmaceuticals undergo degradation through oxidative cleavage, known as auto-oxidation, a process that can be catalyzed by trace levels of metal ions such as Fe, Zn, Mn, and Cu leading to incompatibility issues.[6] These issues further result in change in physical and chemical properties of the pharmaceuticals.

Metal impurities such as Pb, Hg, Cd, and As are toxic at much lower levels and can also induce undesirable metal-catalyzed reactions affecting the quality and stability of drug formulation. The major toxicity concerns due to metal impurities include neurotoxicity, nephrotoxicity, hepatotoxicity, cardiovascular effects, reproductive/developmental toxicity, neuro developmental toxicity, immune toxicity and carcinogenicity.[5] For example, Fluocinonide Topical Solution USP, 0.05% (Teva Pharmaceuticals USA, Inc., Sellersville, Pennsylvania) was recalled in the United States after impurities and product degradation led to sub potency.[7]

Significance of Purity Standards & Compliance

Pharma-grade chemicals typically contain a minimum of 99.0% to 99.9% active salt content (e.g., NaCl) with extremely low levels of contaminants, including calcium, magnesium, sulphate, heavy metals, and insoluble matter. Such high-purity is essential to prevent adverse chemical interactions or potential toxicity in sensitive pharmaceutical and biotechnological products. Rigorous analytical characterization using advanced techniques like ICP-MS, ICP-OES, and atomic absorption spectroscopy ensures that trace metals and other impurities remain within pharmacopeia limits (e.g., IP, BP, USP).

Globally, the ICH Q3D and USP <232>/<233> elemental impurity guidelines play a critical role in minimizing impurities and ensuring the production of high-quality pharmaceutical products. Compliance with these guidelines is essential to maintain the required purity standards in drug products. ICH Q3D impurity guidelines provide the classification of elemental impurities for safety assessment, risk assessment and control of potential elemental impurities as presented in **Table 2**.[8]

A Case Study: From Process Failures to Reliability with Ultra-Pure Salts

For high-stakes pharmaceutical programs, having a trusted partner is essential during the most critical stages of formulation development. A recent collaboration with a leading pharmaceutical innovator clearly demonstrated the value of ultra-low trace metal levels for density gradient applications using Cesium chloride (CsCl).

The customer approached us after experiencing repeated process failures due to unacceptable levels of trace metals in their existing CsCl supply. Elevated levels of trace metals such as K, Mg, Na, Ni, Rb, and Pb were causing unexpected interruptions, leading to in-process shutdowns and delays in key project timelines. Additionally, the project required exceptionally tight impurity control, with lead levels maintained below 0.1 ppm and stringent biochemical quality criteria, including DNase, RNase, exonuclease, NICKase, endonuclease, and protease activities kept below the limit of detection. This

Table 2. ICH Classification of elemental impurities

ICH Class	Elemental impurities
1	As, Cd, Hg and Pb
2A	Co, Ni and V
2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl
3	Ba, Cr, Cu, Li, Mo, Sb and Sn

challenge underscored the need for a more reliable, ultra-high purity CsCl source to ensure consistent performance.

Over the course of a few months, we developed a tailored, high-purity CsCl that exceeded the client's target specifications for both trace metal levels and nuclease/protease activities. This collaboration ensured that the required conditions were fully established, enabling the customer to execute their density gradient step with exceptional reliability and reproducibility. Through this partnership, we successfully transformed significant process risks into a robust, scalable solution, further reinforcing its position as a long-term strategic partner in the customer's innovation journey.

Metal Impurities: Key Effects on Catalytic Efficiency

High-activity salts/precursors used as catalysts or reagents demand uncompromising purity, as even trace levels of metallic impurities particularly Fe, Ni, Cu, Pb, and certain rare-earth elements can severely impact reaction performance. This level of purity is more important in synthesis of API through the reactions like cross-coupling, hydrogenation, oxidation, etc. The following are compelling examples of widely used reactions that highlight the importance of minimizing metal impurities.

Cross-Coupling Reactions

Palladium precursors/salts such as palladium acetate ($Pd(OAc)_2$) and palladium chloride ($PdCl_2$) serve as versatile pre-catalysts for key C–C coupling reactions, including Suzuki, Heck, Negishi, and Stille. They are readily reduced to active Pd(0) *in-situ* in the presence of phosphines or bases.[9,10] The purity of the catalyst is paramount for optimal performance and reaction efficiency. Even at ppm-levels, metal impurities like Fe, Co, Ni, Cu, or Pb can poison Pd(0)/Pd(II) intermediates, trigger aggregation, and derail the catalytic cycle. Such interferences depress reaction yields and promote unwanted pathways, including protodeboronation and homocoupling, ultimately compromising product quality and overall process efficiency.[11, 12] Our rigorously purified palladium salts and precursors provide reliable, high-yield performance in complex pharmaceutical scale processes while ensuring compliance with stringent regulatory standards.

Hydrogenation Reactions

Hydrogenation is essential for API synthesis and industrial manufacturing, enabling key conversions such as saturating double bonds, reducing nitro groups to anilines, transforming ketones into alcohols, and facilitating selective deprotection steps. These conversions are essential for building stable, active, and high-quality drug molecules. For example, Ruthenium(III) chloride hydrate ($RuCl_3 \cdot xH_2O$) excels in hydrogenating *N*/O-heterocycles using $H_3N–BH_3$, delivering alicyclic products but this homogeneous protocol also supports undesirable pharmaceutical intermediates like donepezil and flumequine under mild conditions.[13] Additionally, it enables Ru(II)-catalyzed C–H arylation/alkylation via cathodic reduction.[14] The impurities like Fe, Ni, Cu, Co, Pb, Pd, Pt poison Ru sites and disrupt selectivity leading to undesirable reactions. Hence, it is important to control this trace metal contamination from the catalyst. Our ultra-pure Ru catalysts (>99.9% trace metals basis) ensure reliable performance and high yields in pharma-scale processes.

Few of our top leading homogeneous metal salts widely used as catalysts in various reactions are available with boarder impurity panel with the desired activity and stability as shown in **Table 3.**

Table 3. High-purity homogeneous metal salts with expanded trace metal impurity control (3N-5N purity)

Product name	Specification	Total metal impurities	Applicable reactions
Palladium(II) chloride (921033)	≥99.99% trace metals basis	≤100 ppm	• C-C coupling • Hydrogenation • Wacker-type oxidation • Carbonylation
Ruthenium(III) chloride hydrate (931578)	≥99.9% trace metals basis	≤ 1000 ppm	• Hydrogenation
Palladium(II) acetate (379875)	99.98% trace metals basis	≤ 250 ppm	• C-C coupling • Hydrogenation
Potassium tetrachloroplatinate(II) (925098)	≥99.9% trace metals basis	≤ 1000 ppm	• Hydrosillylation • Isomerization • C–H activation
Rhodium(III) chloride hydrate (450286)	99.95% trace metals basis	≤550 ppm	• Hydrogenation • C–H activation • Electrochemical C-H/C-H coupling

Note: View product-specific Certificates of Analysis (CoAs) directly on the respective product pages.

Conclusion

Trace metal impurities remain a significant challenge and threat to pharmaceutical innovation and development, causing API degradation, reducing shelf life, and increasing toxicity risks. They further contribute to process failures and regulatory hurdles under ICH Q3D and USP <232>/<233> guidelines. Collectively, these challenges not only compromise drug quality and safety but also cause delays in timelines and escalate costs across high-stakes in API synthesis and formulation programs.

We stand as your trusted partner and provide a robust solution through its portfolio of ultra-high purity salts, precursors, and catalysts (3N–5N purity). By eliminating trace metal risks at their source, we help to ensure consistent performance in critical reactions and synthesis of high-quality drug formulations. By integrating advanced synthesis, multistage purification strategies, and lot-specific ICP-MS and ICP-OES testing against comprehensive metal panels, we assure and deliver the reproducibility, reliability, and quality required for modern pharmaceutical processes.

To view the complete list of product offerings, visit

SigmaAldrich.com/highpuritysalts

Related Products

Product No.	Product Name	Product Description
516961	Ammonium formate	≥99.995% trace metals basis
229873	Sodium acetate	99.995% trace metals basis
372331	Ammonium acetate	99.999% trace metals basis
328650	Potassium *tert*-butoxide solution	1.0 M in THF
216593	Ammonium hexafluorophosphate	99.98% trace metals basis
345865	Ammonium trifluoromethanesulfonate	99%
703516	Zinc chloride solution	1.9 M in 2-methyltetrahydrofuran
229806	Potassium phosphate monobasic	99.999% trace metals basis
204501	Ammonium sulfate	99.999% trace metals basis
277908	Ammonium molybdate	99.98% trace metals basis
562599	Cesium chloride	99.99% trace metals basis
409286	Sodium iodide	99.999% trace metals basis
215120	Silicon tetrachloride	99%
377996	Titanium(IV) isopropoxide	99.999% trace metals basis
342920	Barium chloride	99.9% trace metals basis
931950	Sodium perchlorate	≥99.9% trace metals basis
930903	Lithium hydroxide monohydrate	≥99.9% trace metals basis
920320	Lithium acetate	99.9% trace metals basis
935484	Ruthenium(III) chloride	anhydrous, powder, 99.99% trace metals basis
923060	Copper(I) bromide	99.9% trace metals basis

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