

Elemental Impurities in Pharmaceuticals: Sources, Toxicological Risk and ICH Q3D-Based Control Strategies

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Abstract

Elemental impurities are inorganic substances that may be present in pharmaceutical drug substances, excipients, and drug products, catalysts, processing materials, equipment and container-closure systems. Although some elements have valuable biological functions, several elements can produce toxic effects at relatively low exposure levels. Their presence in pharmaceutical products is therefore an important aspect of drug safety and quality assurance. The International Council for Harmonisation (ICH) developed the Q3D guideline to provide a harmonized, science- and risk-based framework for the assessment and control of elemental impurities in drug products. This review discusses the major sources of elemental impurities in pharmaceuticals, their toxicological significance, and classification according to ICH Q3D, permitted daily exposure (PDE), route-specific risk, analytical techniques and risk-based control strategies.

Keywords: Elemental impurities; ICH Q3D; PDE; toxicological risk; ICP-MS; ICP-OES; pharmaceutical quality; risk assessment; control strategy; heavy metals.

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Introduction

Elemental impurities are trace levels of metallic or non-metallic elements that may be present in pharmaceutical products.

The quality and safety of pharmaceutical products depend not only on the identity and potency of the active pharmaceutical ingredient (API), but also on the control of impurities that may be introduced during synthesis, formulation, manufacturing, storage, or packaging or they may originate from raw materials, active pharmaceutical ingredients (APIs), excipients, catalysts, manufacturing equipment, water, environmental sources or container-closure systems. Unlike organic process impurities,

elemental impurities cannot generally be destroyed by conventional chemical degradation processes. Consequently, their control requires identification of the source, understanding of the potential patient exposure and implementation of appropriate preventive or analytical controls.

To establish a harmonized approach to controlling these impurities, ICH developed Q3D, Guideline for Elemental Impurities. The guideline uses a risk-based approach and integrates toxicological information with pharmaceutical manufacturing knowledge. EMA describes Q3D as a process for assessing and controlling elemental impurities using

risk-management principles consistent with ICH Q9. The guideline combines toxicological evaluation, establishment of permitted daily exposures and risk-based control strategies. (European Medicines Agency (EMA)) The current effective version is ICH Q3D(R2), which became effective on 24 September 2022. (European Medicines Agency (EMA))

The FDA's guidance on elemental impurities in drug products is aligned with implementation of ICH Q3D. (U.S. Food and Drug Administration)

Sources of Elemental Impurities

Elemental impurities can enter pharmaceutical products from multiple sources.

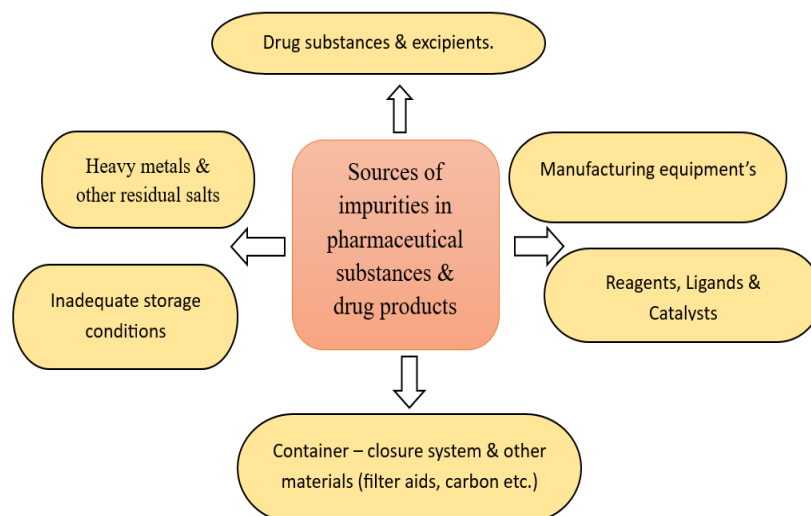


Fig 1: Sources of Elemental Impurities

Elemental Impurities in Pharmaceuticals

Elemental impurities are elements that may be present in pharmaceutical substances or products at potentially harmful concentrations.

Elemental impurities may occur as:

- Free elements
- Inorganic salts
- Organometallic compounds
- Metal complexes
- Residual catalysts
- Contaminants associated with raw materials or excipients.

These elements may be used as catalysts during chemical synthesis.

Although catalysts may be removed during purification, trace residues can remain in the API. The presence of an element does not

automatically mean that a pharmaceutical product is unsafe. Risk depends on the amount present and the expected patient exposure. Therefore, catalyst selection and removal are important parts of impurity control.

Raw Materials: Raw materials used in API synthesis may contain trace elemental contaminants. Potential sources include:

- Starting materials
- Intermediates
- Reagents & Solvents
- Process chemicals
- Inorganic salts

Variability in raw-material quality can contribute to variations in elemental-impurity levels. Supplier qualification and appropriate material specifications are therefore important components of the control strategy.

Excipients

Excipients can contribute substantially to the elemental impurity burden of a finished dosage form. Natural-origin excipients may be particularly variable because their elemental composition can depend on geographical origin, cultivation conditions and processing.

Potential contaminants may originate from:

- Natural mineral sources
- Agricultural materials
- Manufacturing processes
- Processing equipment
- Environmental contamination

For example, mineral-derived excipients may naturally contain trace amounts of elements.

Therefore, an elemental-impurity risk assessment should consider the contribution of each excipient to the final drug product.

Manufacturing Equipment

Equipment can contribute elemental impurities through:

- Corrosion
- Abrasion
- Metal wear
- Leaching
- Equipment surface interactions

Potentially relevant materials include:

- Stainless steel
- Nickel-containing alloys
- Chromium-containing alloys
- Copper-containing components

The risk depends on the equipment material, process conditions, temperature, pH and contact time.

Water and Utilities

Water used during manufacturing may contain trace elements.

Potential sources include:

- Purified water systems
- Water-treatment equipment
- Storage tanks
- Distribution pipelines
- Environmental contamination

Water quality therefore forms an important part of pharmaceutical manufacturing controls.

Container-Closure Systems

Elemental impurities may potentially originate from packaging materials through:

- Leaching & Corrosion
- Component degradation
- Interaction between formulation and packaging

The risk is particularly relevant when the formulation has characteristics that promote elemental migration.

Therefore, container-closure compatibility should be considered during product development and stability assessment.

Environmental Sources

Air, dust, soil, manufacturing environments & raw material production areas can provide additional sources of elemental contamination.

Appropriate environmental and facility controls therefore complement material and process controls.

Elements such as lead, arsenic, mercury and cadmium are particularly important from a toxicological perspective.

3. ICH Q3D Classification of Elemental Impurities

ICH Q3D uses a toxicological and risk-based classification system.

The elements are broadly categorized into Class 1, Class 2A, Class 2B and Class 3.

Class 1

Class 1 elements are considered to have significant toxicological potential and require particular attention.

Examples include:

- Cadmium (Cd), Lead (Pb), Arsenic (As), Mercury (Hg).

These elements generally require evaluation regardless of route because of their significant toxicological concerns.

Class 2A

Class 2A elements have relatively high probability of occurrence and therefore require assessment.

Examples include:

- Cobalt (Co), Nickel (Ni), Vanadium (V).

Class 2B

Class 2B elements have relatively low probability of occurrence because they are less commonly used or encountered in pharmaceutical manufacturing.

Examples include:

- Silver (Ag), Gold (Au), Iridium (Ir), Platinum (Pt), Rhodium (Rh), Selenium (Se).

Their inclusion in the risk assessment depends on the potential for introduction into the pharmaceutical product.

Class 3

Class 3 elements generally have relatively low oral toxicity compared with many Class 1 and Class 2 elements but can be important for parenteral or inhalation products.

Examples include:

- Barium (Ba), Chromium (Cr), Copper (Cu), Lithium (Li), Molybdenum (Mo), Antimony (Sb), Tin (Sn).

The route of administration is therefore an important factor in evaluating these elements.

Toxicological Risk of Elemental Impurities

The toxicity of an elemental impurity depends on:

- Element
- Chemical form
- Oxidation state
- Dose & Duration of exposure
- Route of administration
- Bioavailability
- Patient population

The ICH Q3D safety assessment establishes PDE values for elements of toxicological concern and considers oral, parenteral and inhalation routes. (European Medicines Agency (EMA))

Lead

Symbol: Pb

Lead is a highly toxic element with no established beneficial physiological role.

Potential effects include:

- Neurotoxicity
- Renal toxicity
- Haematological effects
- Reproductive toxicity
- Developmental toxicity

Chronic exposure is of particular concern.

Because of its toxicological significance, lead receives significant attention in pharmaceutical risk assessment.

Mercury

Symbol: Hg

Mercury toxicity depends strongly on its chemical form.

Potential effects include:

- Neurological toxicity
- Renal toxicity
- Developmental effects

The form and route of exposure must therefore be considered in toxicological assessment.

Toxicological Mechanisms

Elemental impurities may produce toxicity through several mechanisms.

Oxidative stress

Some elements can promote reactive oxygen species:

Element exposure → ROS generation → oxidative stress → cellular damage

Enzyme inhibition

Metal ions may interact with enzymes and interfere with normal biochemical processes.

Protein interaction

Elements may bind to proteins and alter their structure or function.

DNA damage

Certain elemental species can contribute to:

- DNA strand damage
- Oxidative DNA damage
- Chromosomal damage
- Mutagenic effects

Cellular dysfunction: Elemental toxicity can interfere with:

- Mitochondrial function
- Ion channels

- Cellular signalling
- Membrane integrity

Permitted Daily Exposure

A central concept of ICH Q3D is the Permitted Daily Exposure (PDE).

PDE represents the maximum acceptable daily exposure to an elemental impurity that is considered sufficiently protective for the relevant route of administration.

The guideline establishes PDE values for individual elements based on toxicological assessment. (European Medicines Agency (EMA))

A simplified conceptual relationship is:

$PDE = \text{Reference dose} \times \text{adjustment factors}$

The actual derivation involves toxicological considerations including:

- Point of departure
- Modifying factors
- Species differences
- Exposure duration
- Bioavailability
- Route-specific considerations

Route-Specific Toxicity

ICH Q3D recognizes that toxicity may vary according to route.

The major routes considered are:

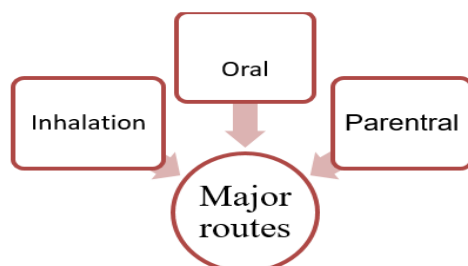


Fig 2:

The same elemental concentration does not necessarily represent the same risk for all routes. Therefore, route-specific PDE values are used.

Risk Assessment According to ICH Q3D: ICH Q3D uses a risk-based approach rather than requiring indiscriminate testing of every element in every product.

The basic workflow is:

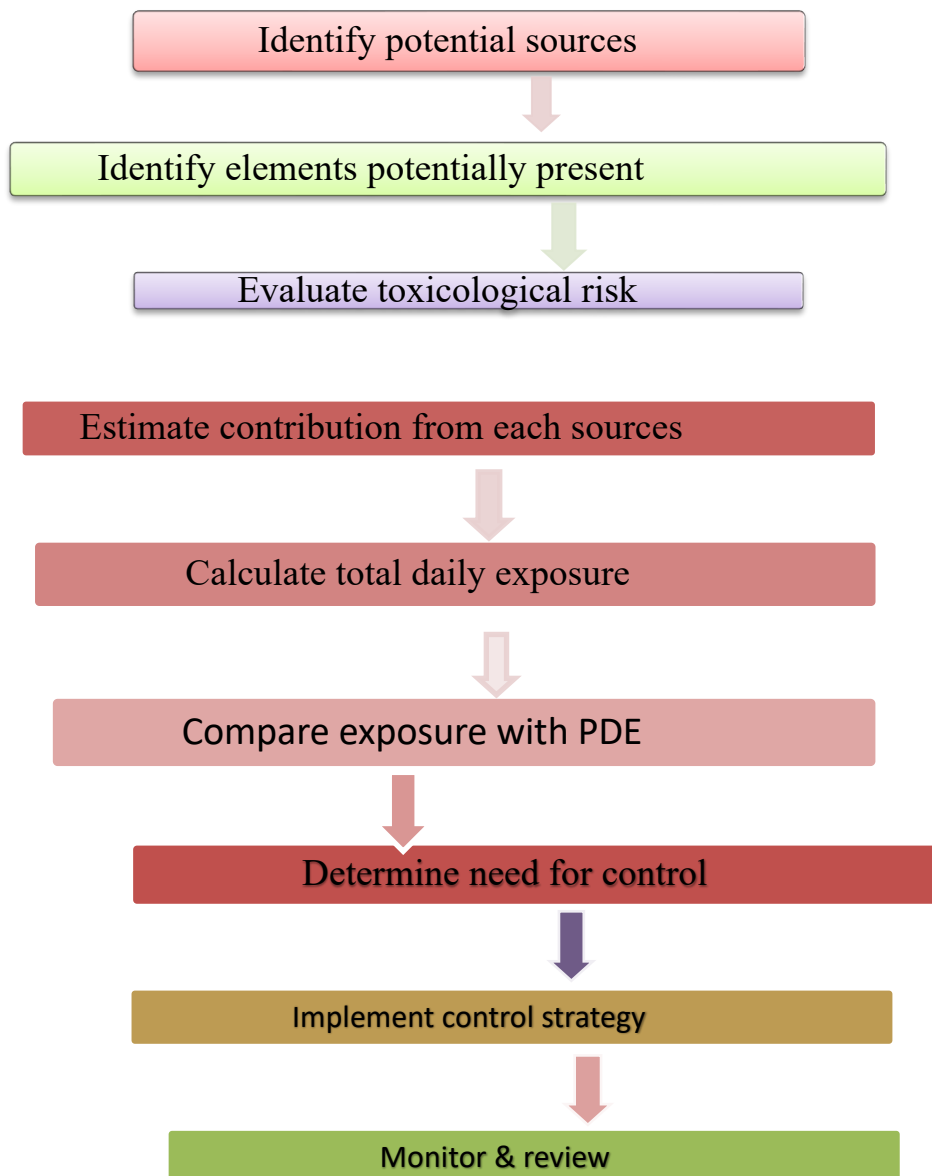


Fig 3:

The guideline explicitly uses principles of risk management consistent with ICH Q9. (European Medicines Agency (EMA))

Three Main Sources in ICH Q3D Risk Assessment: The risk assessment should consider three broad source categories.

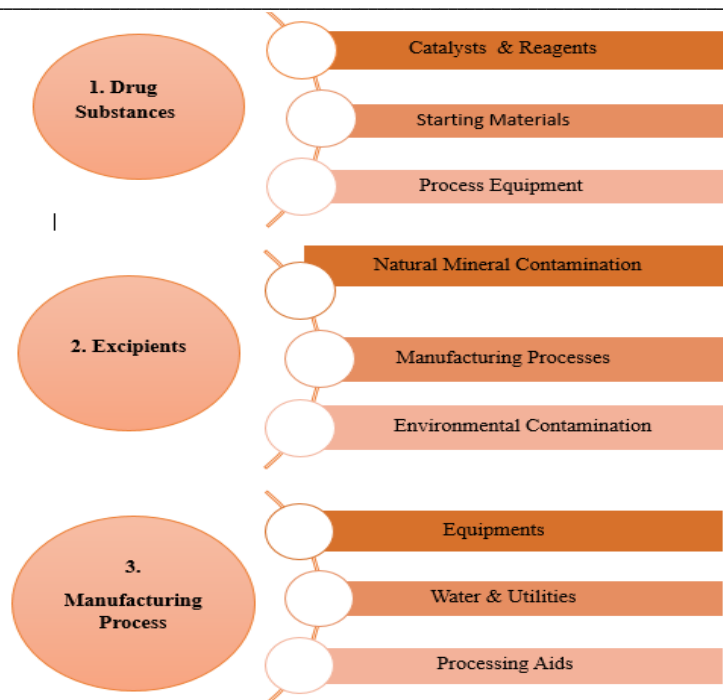


Fig 4:

The contributions from these sources can be combined to estimate the elemental impurity concentration in the final product.

Analytical Strategies

Analytical testing is used to confirm the presence and concentration of elemental impurities when required by the risk assessment.

ICP-MS

Inductively Coupled Plasma–Mass Spectrometry (ICP-MS) is one of the most powerful techniques for trace elemental analysis.

Advantages

- Very high sensitivity
- Multi-element analysis
- Wide dynamic range
- Low detection limits
- Suitable for trace and ultra-trace analysis

Applications

- API testing
- Excipient testing
- Finished-product analysis
- Investigation of contamination sources

ICP-OES

Inductively Coupled Plasma–Optical Emission Spectrometry (ICP-OES) determines elements based on characteristic optical emission.

Advantages include:

- Multi-element capability
- Good precision
- High throughput
- Lower operating complexity than some mass-spectrometric methods

ICP-OES may be suitable when elemental concentrations are sufficiently high for its detection capability.

Sample Preparation: Pharmaceutical samples often require digestion before elemental analysis. A common approach involves: Sample → acid digestion → dilution

→ filtration if appropriate → instrumental analysis

Microwave-assisted digestion can improve decomposition of complex pharmaceutical matrices.

The sample-preparation procedure should minimize:

- Contamination
- Analyte loss
- Volatilization
- Matrix effects

Analytical Method Validation

Analytical methods should be appropriately validated for their intended purpose.

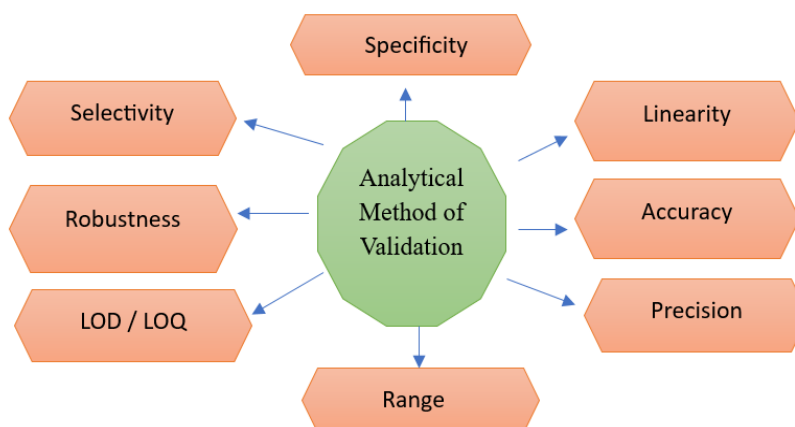


Fig 5:

Because elemental impurities may be present at very low concentrations, method sensitivity is particularly important.

ICH Q3D-Based Control Strategy

The control strategy should be designed based on the outcome of the risk assessment.

Potential controls include:

Raw-material controls

- Qualified suppliers
- Raw-material specifications
- Supplier certificates
- Periodic elemental testing
- Control of high-risk materials

API controls

- Catalyst selection & removal
- Purification
- Process optimisation
- Appropriate API specifications

Excipient controls

- Supplier qualification
- Elemental-impurity assessment
- Material specifications
- Periodic monitoring

Manufacturing controls

- Equipment qualification
- Corrosion control
- Process monitoring
- Appropriate water quality
- Prevention of cross-contamination

Finished-product controls

When justified by risk assessment:

- Elemental impurity specifications
- Routine testing & Periodic verification
- Stability monitoring

ICH Q3D emphasizes that control strategies should be equivalent to the identified risk rather than automatically applying identical

testing to all products. (European Medicines Agency (EMA))

Control Strategy Order

An effective strategy can be represented as:

Prevention → Source control → Process control → Material specification → Analytical testing → Finished-product specification

This approach prioritizes prevention and source reduction.

Example of Risk-Based Assessment

Consider an API manufactured using a palladium catalyst.

- **Step 1:** Identify palladium as a potential elemental impurity.
- **Step 2:** Evaluate catalyst quantity and process conditions.
- **Step 3:** Evaluate purification efficiency.
- **Step 4:** Determine residual palladium in the API.
- **Step 5:** Estimate contribution to the finished product.
- **Step 6:** Calculate patient exposure.
- **Step 7:** Compare exposure with the applicable PDE.

If necessary, introduce additional purification or a specification/control.

This demonstrates how Q3D transforms elemental-impurity management into a science- and risk-based process.

Pharmaceutical Quality by Design

Elemental impurity control can be integrated into the Quality-by-Design approach.

Quality Target Product Profile → Identify elemental-impurity risks → Identify Critical Material Attributes → Identify Critical Process Parameters → Develop control strategy → Analytical verification → Continuous monitoring

This approach supports proactive rather than reactive impurity management.

Advantages of the ICH Q3D Framework

The ICH Q3D approach provides several important advantages:

- Science-based limits
- Toxicology-driven assessment
- Route-specific PDE values
- Risk-based testing
- Global harmonization
- Greater focus on prevention
- Flexibility in control strategies
- Integration with pharmaceutical quality systems

EMA describes Q3D as a process for assessing and controlling elemental impurities using risk-management principles. (European Medicines Agency (EMA))

Challenges in Elemental-Impurity Control: Despite advances in regulatory science, several challenges remain.

Multiple sources

An impurity may originate from several components simultaneously.

Very low limits

Some PDE values require highly sensitive analytical methods.

Supplier variability

Elemental concentrations may vary between batches of raw materials and excipients.

Complex formulations

Matrix effects can complicate analytical measurement.

Global regulatory differences

Although ICH Q3D provides harmonization, implementation and regulatory expectations may vary between jurisdictions.

Lifecycle changes

Changes in suppliers, equipment, process or formulation may alter elemental-impurity risk.

Emerging Technologies

Future elemental-impurity control may increasingly involve:

- High-resolution ICP-MS
- Collision/reaction-cell ICP-MS
- Automated sample preparation
- Chemometric data analysis
- Real-time process monitoring
- Artificial intelligence-assisted risk prediction
- Advanced supplier-risk models

AI and machine learning could potentially assist in predicting elemental contamination based on:

- Chemical process data
- Raw-material characteristics
- Equipment materials
- Historical analytical results

However, computational tools should complement rather than replace validated analytical and toxicological assessment.

Future Perspectives

Future developments in elemental-impurity control are likely to focus on:

1. More sensitive analytical technologies.
2. Improved prediction of contamination sources.
3. Greater use of continuous manufacturing.
4. Automated analytical monitoring.
5. Better control of excipient variability.
6. Improved supplier qualification.
7. Integration of Q3D with Quality-by-Design.

8. AI-assisted risk assessment.
9. Greater lifecycle monitoring.
10. Continued international regulatory harmonization.

Conclusion

Elemental impurities are an important pharmaceutical quality and patient-safety concern because certain elements can cause significant toxicity even at relatively low exposure levels. These impurities may originate from catalysts, raw materials, excipients, manufacturing equipment, water, environmental sources and container-closure systems.

ICH Q3D(R2) provides a systematic framework based on toxicological assessment, permitted daily exposures and risk management. The guideline recognizes that the risk of an elemental impurity depends on the element, exposure level and route of administration. (European Medicines Agency (EMA)) Modern analytical techniques, particularly ICP-MS and ICP-OES, provide the sensitivity required for elemental-impurity determination. However, analytical testing should be integrated with preventive controls rather than used as the sole method of risk management. An effective elemental-impurity strategy therefore involves source identification, toxicological assessment, exposure estimation, analytical verification, preventive process controls and lifecycle monitoring. The implementation of ICH Q3D has significantly strengthened the scientific and risk-based management of elemental impurities in pharmaceutical products.

Table 1. ICH Q3D Element Classes

Class	General significance	Examples
Class 1	High toxicological concern	As, Cd, Hg, Pb
Class 2A	Higher probability of occurrence	Co, Ni, V
Class 2B	Lower probability of occurrence	Ag, Au, Pd, Pt, Rh, Ru

Class 3	Generally lower oral toxicity; route-dependent concern	Ba, Cr, Cu, Li, Mo, Sb, Sn
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Table 2. Analytical Techniques

Technique	Principle	Major advantage	Major limitation
ICP-MS	Mass spectrometric detection of ions	Very high sensitivity	High instrument cost
ICP-OES	Optical emission	Multi-element analysis	Higher detection limits than ICP-MS for some elements
AAS	Atomic absorption	Simple and established	Limited multi-element capability
XRF	X-ray fluorescence	Minimal sample preparation in some applications	Less sensitive for some trace levels

Recommended Graphical Abstract**Elemental impurities in pharmaceuticals**

Sources → Toxicological Risk → Analytical Detection → ICH Q3D Risk Assessment → Control Strategy → Patient Safety

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