PDA Training Course Extractables & Leachables

23-24 October 2025

AN INTRODUCTION TO: ICH HARMONISED GUIDELINE; GUIDELINE FOR EXTRACTABLES AND LEACHABLES - Q3E

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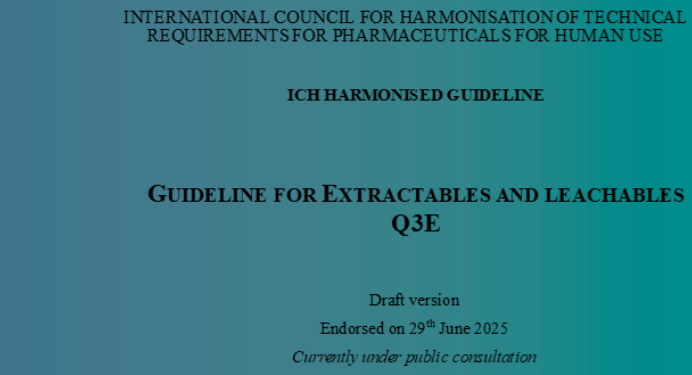
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR EXTRACTABLES AND LEACHABLES
Q3E

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Endorsed on 29th June 2025
Currently under public consultation

PDA Parenteral Drug Association

Nelson Labs
A Sotera Health company

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Presentation Outline

- Purpose and Scope
- Key Concepts and Definitions
- Leachables Risk
  - Factors Relevant to Leachables Risk
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- Dimensions of Chemical Characterization
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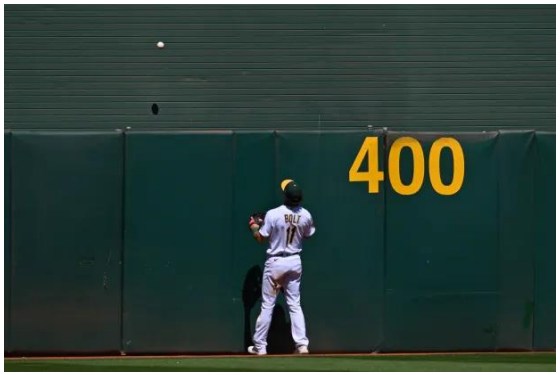
- Values for the SCT
- Potency Classes for Leachables
- Implementation Schedule

Were You Hoping for a Home Run?



Maybe a single is good enough!

Purpose

The purpose of the guideline is to provide a holistic framework whereby leachables-associated risk can be identified, assessed, and controlled to protect the safety, efficacy, and quality attributes of the finished drug product.

- **This guideline presents a holistic framework and process for the assessment and control of leachable impurities to further expand the existing ICH guidelines on impurities**
- **The framework of this guideline follows the principles of risk management as described in ICH Q9.**
- **Its primary purpose is to protect patient safety and product quality through assessment and control of leachables in the drug product**
- **The aim is to provide principles and concepts that are forward looking within the scientific and regulatory landscape**

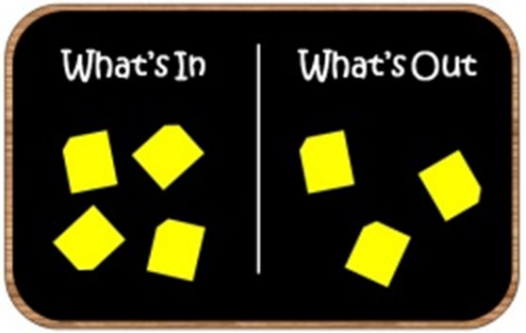
Strategic Versus Tactical

Q3E is more about what to do and less about how to do it.

Two Sides of the Same Coin

Chemical Testing **Safety Assessment**

Scope



In Scope:

- New drug products, including cell and gene therapy products.
- Drug-device combination products that … meet the definition of pharmaceutical or biological products.
- Changed approved products where the change is likely to impact the leachable profile or patient exposure.
- Organic leachables.

Out of Scope:

- Extrinsic, extraneous or foreign substances resulting from product contamination or adulteration.
- Herbal medicinal products and crude non-processed products of animal or plant origin
- Products used during clinical research stages of development.
- Radiopharmaceuticals.
- Systems used in the manufacture or storage of excipients.
- Extracted elements (see ICH Q3D).

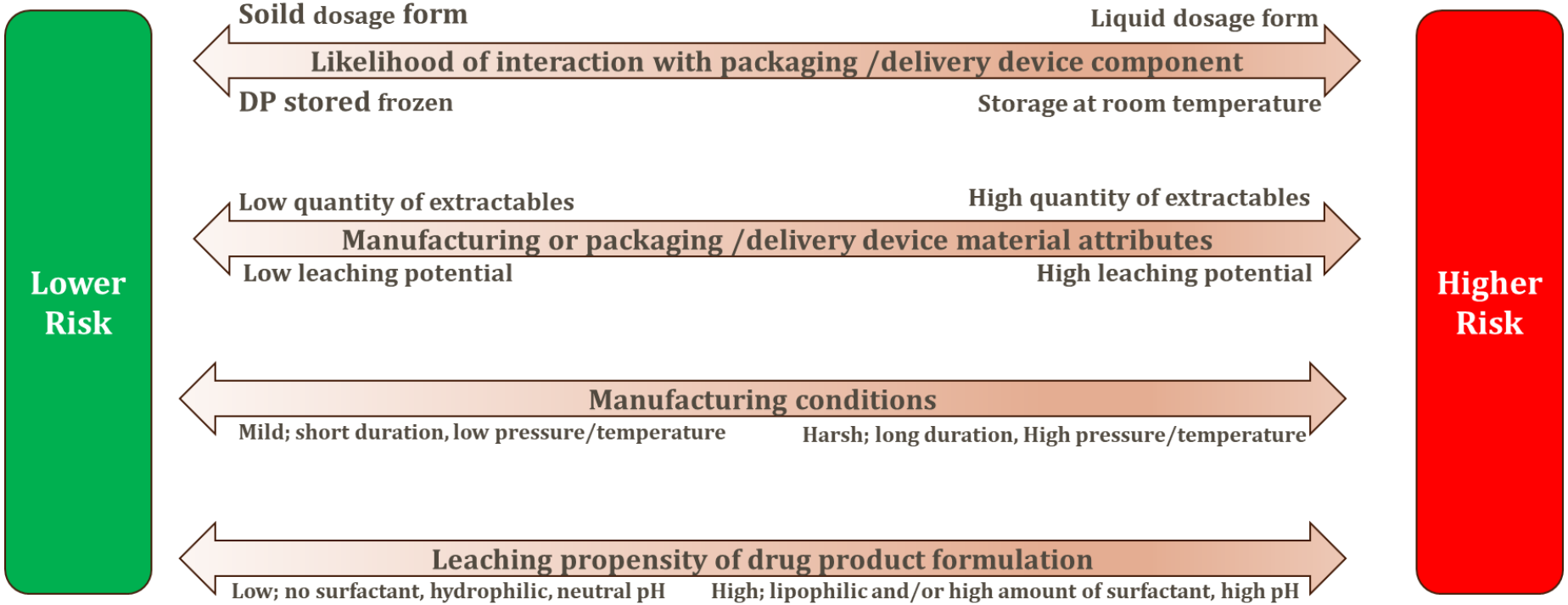
Key Concepts & Definition

- **Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions.**
- **Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions and are potential leachables.**
- **The Analytical Evaluation Threshold, AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified, quantitated, and reported for safety assessment.**
- **When an AET is used in semi-quantitative analytical methods, an appropriate uncertainty factor, UF, should be applied to account for potential underestimation of analyte concentrations.**

Additional Key Concepts

- ***Depending on*** **the anticipated** ***risk*** **and leveraging prior knowledge,** ***various approaches can be adopted*** **ranging from compliance with relevant food-contact safety or pharmacopeial standards/regulations to more extensive E&L characterization and safety risk assessment.**
- **For biological and biotechnology-derived products … interactions between** ***reactive leachables*** **and formulation components that may lead to potentially adverse impact on product quality, safety, and/or efficacy. If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered (such as denaturation, aggregation or degradation).**
- **For manufacturing of drug substance,** ***leachables may be removed during the last purification step.*** **Therefore, the quality risk assessment will typically focus on subsequent manufacturing processes.**
- ***Close collaboration between the analytical chemist(s) and safety expert(s) is essential*** **for knowledge sharing and development of the E&L quality risk management process.**

Dimensions of Leachables Risk



Low Risk Scenarios for Packaging

Risk Scenario	Potential Outcome
Scenario 1: Container closure system components for oral drug products compliant with regional food contact regulations including composition, fabrication, specification, testing results, and in-use limitations specified therein.	**An abbreviated data package may be adequate with justification.**
Scenario 2: Frozen, non-lyophilized drug product stored in well-characterized packaging system (i.e., prior knowledge provided by the applicant). DP thawed and administered within a short time-period and the duration between initiation of filling and freezing is also short (e.g., < 24 hours).	
Scenario 3: Delivery device components with very short/transient contact with oral drug products (e.g., oral syringes, oral dosing cups) are compliant with regional food contact regulations.	

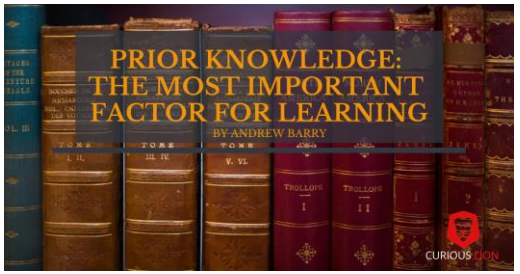
Low Risk Scenarios for Manufacturing Components

Risk Scenario	Potential Outcome
Scenario 1: Solid oral drug product manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements.	**Components considered qualified without additional extractables or leachables testing.**
Scenario 2: Liquid oral drug product using polymeric manufacturing equipment/systems compliant with relevant regional food-contact safety regulations, use of these materials is consistent with the relevant regulations, and the leaching propensity of the drug product is not greater than identified in the relevant regulation.	
Scenario 3: No manufacturing components/systems extractables above the applicable AET in a semi-quantitative extractables study.	
Scenario 4: All manufacturing equipment extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE).	

Dimensions of Chemical Characterization

Prior knowledge	• Collect and leverage existing information relevant to drug products or processes
Component selection	• Leverage prior knowledge and possibility generated general extraction study data to make justified decisions concerning material and component selection
Extractable study	• Semi-quantitative • Quantitative
Leachable study	• Testing of the to-be-marketed drug product over shelf-life and in-use stability; Data may be supplemented using accelerated stability storage conditions if relevant.
Simulated leachable study	• Augment or replace a leachables study when a leachables study is not technically feasible to conduct
E&L Correlation	• Correlating leachables with extractables may support a justification for the use of routine extractables testing of components as an alternative to routine leachables testing during stability studies when appropriate for high-risk drug products, change control, and ongoing quality control.

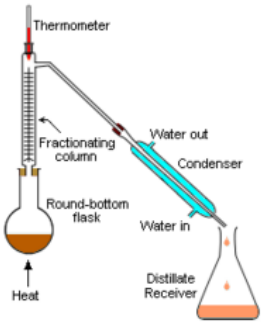
Prior Knowledge



Types of Prior Knowledge:

- composition (e.g., base polymer and copolymer, any known additives such as plasticizers, processing aids, catalysts, antioxidants)
- food contact compliance
- statements indicating particular (e.g., non-authorized) compounds have not been intentionally added
- compendial testing
- any available extractables studies
- biological reactivity testing
- processing or pretreatment steps (e.g., sterilization, cleaning, flushing, siliconization, surface treatments)
- prior use history, including any historical use with other similar drug products, process and/or contact conditions

Extraction Studies



Key characteristics of an adequate extraction study include:

- Establishment and **application of a drug product-specific AET** to indicate extractable chemical entities to be identified and treated as potential leachables.

- **Testing is performed on components** or an assembled system including any processing and treatment (e.g., sterilization, molding and fabrication conditions, cleaning, siliconization) that would be **representative of the final, finished component or system as intended for use**.

- Proper extraction media selection, including **appropriate solvents of varying pH and polarity relevant to and representative of the drug product formulation** (e.g. excipients, surfactants).

Extraction Studies

Key characteristics of an adequate extraction study include:

- Represents the drug product specific **worst-case scenario for leachables occurring during manufacturing or** arising from packaging components/systems **during shelf life** (e.g., contact area, temperature, duration).
- The **analytical procedures used are adequately qualified** at a level commensurate with the purpose of the extraction study.
- Includes appropriate analytical procedures for **volatile, semi-volatile, and non-volatile organic extractables and elemental extractables**.
- Specific **targeted tests for potential Class 1 leachables** should be performed based on the understanding of the material of construction.

Semi-quantitative Extraction Studies

A semi-quantitative extractables study may be appropriate in scenarios where a leachables study will subsequently be conducted to establish the acceptability of materials for intended use. **The purpose** of a semi-quantitative extractables study **is to understand which extractables can be present as leachables in the drug product.**

Key characteristics include:

- **Analytical procedures that are qualified** using several relevant standard compounds typically observed as extractables or leachables.
- **Use of analytical uncertainty factor (UF)** in the calculation of the drug product-specific AET.
- **Quantification** of observed extractables **against relevant standard compounds**.
- **Semi-quantitative extractables observed above the AET can subsequently be used as targets** for a quantitative extractables study or a leachables study.

Quantitative Extraction Studies

A quantitative extractables study supports the qualification of manufacturing components/systems and certain low-risk packaging components/systems scenarios for which extractables were observed at a level above the AET during the semi-quantitative extractables study.

Key Characteristics include:

- **Confirmed identification** of extractables above the AET.
- **Quantification** of the identified extractables above the AET **using standards** with identical or similar analytical response.
- The **analytical procedure** used for quantifying the identified extractables above the AET **should be qualified** for the specific standard compound.

Important Points:

- If the amount of an adequately identified and quantified extractable exceeds its qualification limit a leachables study is warranted.
- Leachables study can also be used to assess the quality risk for extractables above the AET when those extractables cannot be identified with confirmed identities.

Leachables Studies – Key Points

- **Leachables studies** are designed to **represent the actual** manufacturing **conditions** and intended storage conditions throughout the proposed shelf-life and in-use period.

- During the shelf life and in-use period, **multiple time points** should be **evaluated** to characterize **trending** of leachables to **estimate maximal occurrence**.

- The **leachables** assessment … **may include accelerated storage conditions**.

- The study should involve **multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product.** If multiple batches are not available, alternative approaches may be proposed with justification.

Leachables Studies – Key Points

- **Use** of **the same lots of components used in extractables assessments** potentially enables a more meaningful correlation between extractables and leachables.

- **Analytical procedures for specific, targeted leachables should be** appropriately **validated** to establish that they are sensitive, selective, accurate, and precise.

- **Non-targeted screening procedures** should also be used and employ appropriate analytical techniques **to** facilitate **detection of any unanticipated degradation of leachables, leachables from secondary packaging, and/or interaction products**.

Simulated Leachables Studies - Concept

Circumstances may exist when performing a drug product leachables study is not technically feasible ***despite thorough due diligence*** which may include systematic investigation of multiple diverse sample preparation techniques coupled with highly sensitive and selective analytical methods, techniques and instrumentation. In such situations, **use of a simulation study to support** actual drug product **leachables** evaluation **may be justifiable**.

- A simulation study could be performed to **augment a leachables study** to accomplish the **objectives that cannot be obtained by leachables testing**.
- A simulation study could be used to **replace a leachables** study when, through ***thorough due diligence***, it is established that **performing the leachables study is impractical**.
- The goal of a simulation study is to obtain **a simulated leachables profile that closely mimics the actual leachables profile** generated by the drug product over its shelf-life.
- **When properly justified, use of a simulation study is an alternative to the recommended practice of performing leachables studies.**

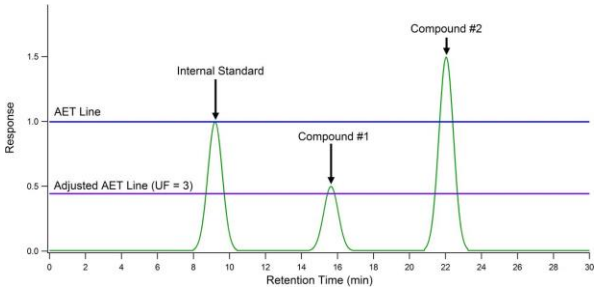
Simulated Leachables Studies – Key Points

- It is important to recognize that, regardless of how well the simulation study is designed and executed, its outcome will likely only approximate the results of a drug product leachable study and cannot fully replicate a true leachable profile of the drug product.
- The simulation conditions and process used in the simulation study should closely match the drug product manufacturing/storage conditions used in a leachables study.
- The simulation solvent should be chosen so that is has a similar propensity to leach as the drug product.
- The simulated manufacturing process should be performed using worst-case conditions.

Simulated Leachables Studies – Key Points

- A simulation study can be accelerated versus drug product shelf storage conditions.
- The intended application, justification, and qualification of a simulated leaching study for a particular drug product should be based on a scientifically sound rationale with demonstration of due diligence supported by appropriate testing and experimentation.
- ***When considering the use of a simulation study, consultation with the relevant regional Regulatory Agency prior to implementation may be warranted.***

The AET - Key Points



- An **extraction study should include the** establishment and application of an **AET** to indicate extractable chemical entities to be detected, identified and reported as potential leachables for the drug product.
- For a leachable study, the AET is established at **a concentration above which compounds should be identified and quantitated** to enable appropriate safety assessment.
- This guideline recommends incorporation of **a Safety Concern Threshold (SCT) to establish** a study-specific **AET**.
- For Class 1 leachables, the compound-specific safety limit, instead of a product-specific SCT, should be used for quantification.

The AET - Key Points

$$AET = \frac{\text{DBT x A x CF}}{\text{B x C x S x UF}}$$

- Calculation of the AET should **clearly indicate what the units are and how the calculation was performed**.

- An **uncertainty factor (UF) should be employed** in the AET calculation.

  - Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of **no greater than 0.5.**
  - Alternatively, **an uncertainty factor can be derived from statistical analysis of appropriately constituted response factor database** of relevant reference compounds.
  - **Justification of UF** applied **should be included** in the extractable/leachable study report.

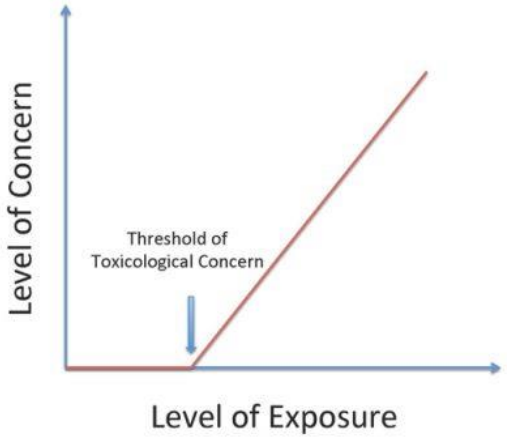
Values for the SCT – Table 1

Systemic Toxicity Thresholds				
Exposure Duration	Oral		Parenteral, Dermal/Transdermal, Inhalation	
	TTC	QT	TTC	QT
> 10 years	1.5 µg/day	48 µg/day	1.5 µg/day	12 µg/day
> 1 to 10 Years	10 µg/day		10 µg/day	
> 1 Month to 1 Year	20 µg/day		20 µg/day	
≤ 1 Month	120 µg/day	136 µg/day	120 µg/day	26 µg/day

Local Toxicity Thresholds				
Topical Ophthalmic	Subcutaneous and Intradermal	Dermal and Transdermal	Intracerebral, Intrathecal, Epidural and Intraocular	Inhalation
20 ppm	50 ppm	500 ppm	Compound-specific evaluation	5 µg/day

Interpreting Table 1

The SCT is the lowest value of either the TTC or QT for a specific drug product, considering route and potential duration of exposure (shown in yellow in Table 1).



Potency Classes for Leachables

Class 1 – Leachables to be avoided

ICH Q3E Class 1 leachables should be avoided when practically feasible and exposure should not exceed a scientifically justified compound-specific acceptable exposure level.

Mutagens/Predicted Mutagens

- Leachables that are part of the ICH M7 cohort of concern (aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds).
- Leachables meeting criteria for ICH M7 Class 1 impurities and an AI < 1.5 µg/day.

Non-mutagens/Predicted Non-Mutagens

- Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety (e.g., Benzo(a)pyrene, Bisphenol A).

Potency Classes for Leachables

Class 2 – Leachables to be limited

ICH Q3E Class 2 non-mutagenic (or predicted non-mutagenic) leachables are considered qualified up to the QT pertinent to the drug product without further safety justification.

Mutagens/Predicted Mutagens

- Leachables meeting criteria for ICH M7 Class 1 impurities and an AI ≥ 1.5 µg/day.
- Leachables meeting criteria for ICH M7 Class 2 or 3 impurities.

ICH Q3E Class 2 mutagenic (or predicted mutagenic) leachables should not exceed (1) the TTC or less-than-lifetime TTC as appropriate or (2) the QT pertinent to the drug product.

Non-mutagens/Predicted Non-Mutagens

Leachables considered to have a parenteral PDE > QT (excluding those established as Class 3) following the methodology described in Appendix 5.

Potency Classes for Leachables

Class 3 – Leachables with relatively low toxic potential

ICH Q3E Class 3 leachables are considered qualified up to 1.0 mg/day or the compound specific PDE (see Table below and Supporting Document) without further safety justification.

Non-mutagenic leachables established to have a chronic parenteral PDE in excess of the levels at which leachables are typically observed.

Examples: 2,6-Di-tert-butyl-4-methylphenol (BHT), Erucamide, 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid, Rubber oligomer C21H40, fatty acids (C8 – C22, palmtic acid, stearic acid)

Implementation Schedule

Expected Completion date	Deliverable
Mar. 2025	Begin PWP consultation (Health Canada)
Jun. 2025	Step 1 sign-off, Step 2a/b endorsed
Nov. 2025	End of Public consultation period
Jun. 2027	Step 3 sign-off and Step 4 adoption of final guidance

Questions about ICH Q3E?

Thank you!

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