

# Complying with Q3 or Not for Impurities from Excipients

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## Impurities from Excipients

### Overview of the Presentation

- Definitions: Impurities in New Drugs & Excipients
- Sources of Impurities
- Hypothetical Case.....
- Atypical Impurities in Drug Products (from Excipients)
- Control of Organic Impurities from Excipients
  - IPEC Position
  - USP Position
  - QbD based approach
- Summary

*Disclaimer: The messages and views presented are mine based on my own experience and interpretations of regulations and guidance documents.*

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## Impurities in New Drugs / Excipients

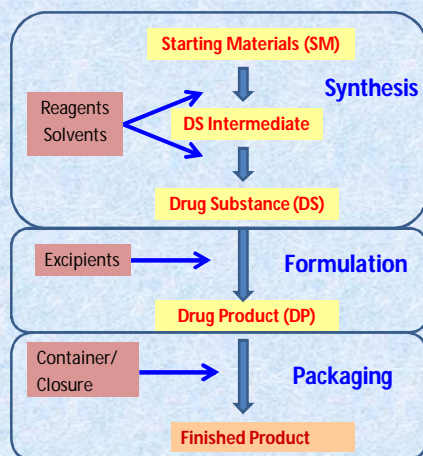
- Drug Substance Impurity (ICH Q3A): Any component of the drug substance that is not the chemical entity defined as the drug substance
- Drug Product Impurity (ICH Q3B): Any component of the drug product that is not the drug substance or an excipient in the drug product
- Impurity in an Excipient (IPEC): A component of an excipient that is not intended to be present but arises as a consequence of the manufacturing process
- Concomitant Component (IPEC): A material found in an excipient in addition to the major component(s) that is necessary for assuring the proper performance of the excipient in the drug formulation –  
– **Concomitant Component is NOT AN IMPURITY**

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## Impurities in New Drugs



### Potential Impurities in New Drugs

#### Drug Substance

- Residual Impurities in the SM
- Residual SM
- Residual intermediate
- Reaction by-products
- DS Degradation products
- Reagents / Solvents / Catalysts

#### Drug Product

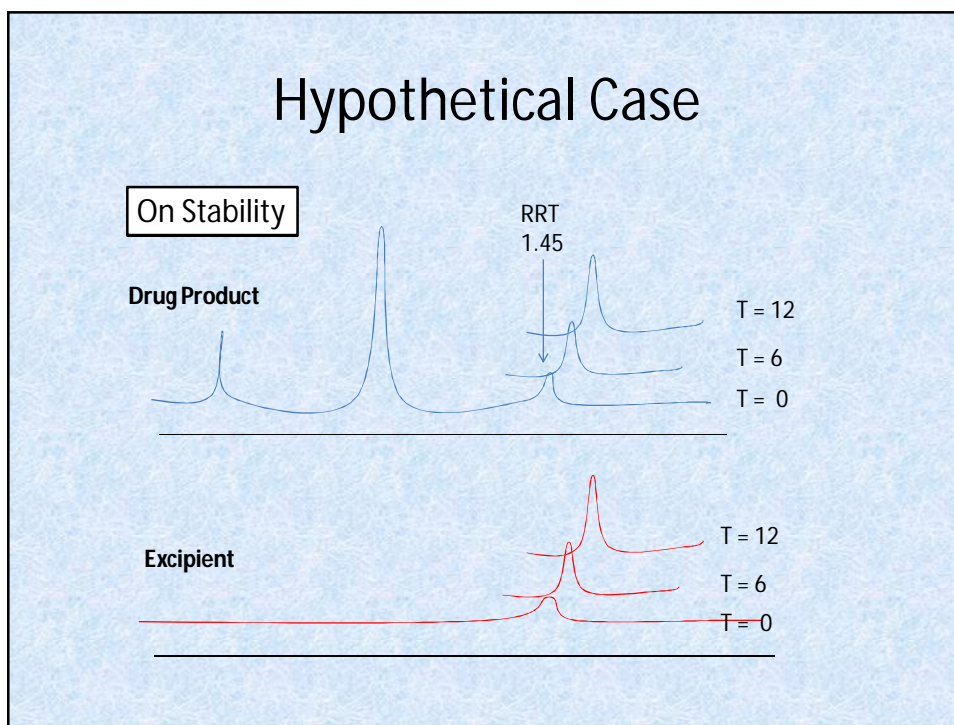
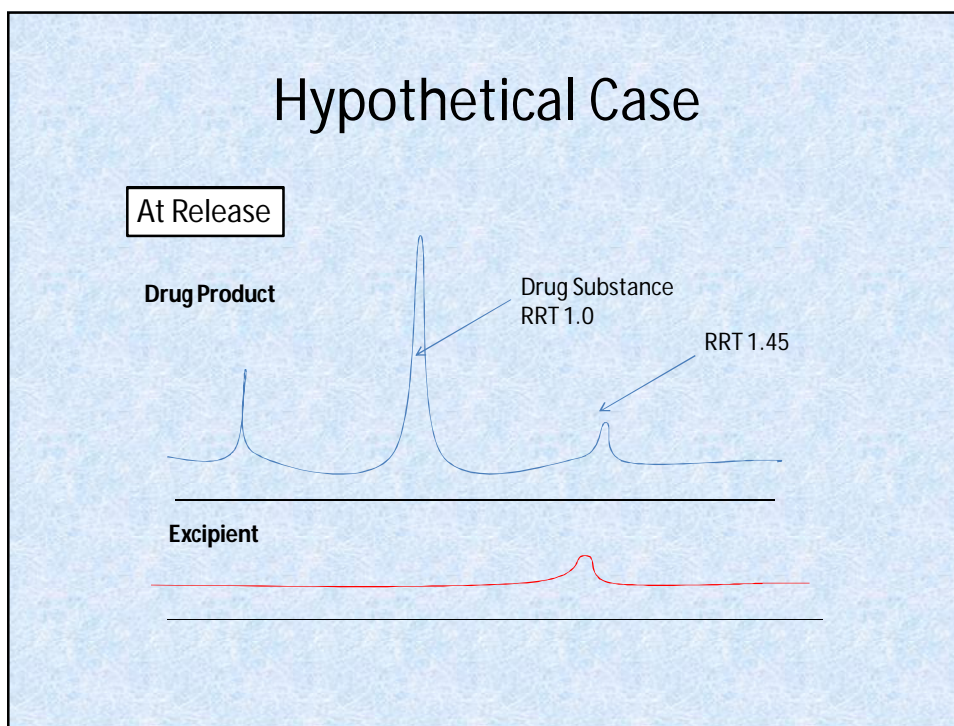
- Carry over of DS Impurities
- DS Degradation products
- DS-Excipient interactions
- DS-Container closure interactions

- **Impurities from Excipients**
- **Impurities from Container closure** 😊

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## Hypothetical Case

**Question:** Should the RRT 1.45 Impurity be controlled as an Impurity in Drug Product?

**NO, because:**

- It is not a drug related impurity
- It is from the excipient
- It is a PLACEBO peak

**YES, because:**

- It is an impurity, regardless of the source

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## Impurities in New Drugs

- Regulator's Position on Impurities
  - Impurities have **no therapeutic value**; they could be **potentially harmful (toxic)**. Therefore, they should be limited to the lowest level possible
    - Efficacy = Zero Benefit
    - Safety = Potentially high Risk

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# Impurities in New Drugs

## Classes of Impurities and Regulatory Status

<ul style="list-style-type: none"> <li>• <b><u>Inorganic/Metal Impurities</u></b> <ul style="list-style-type: none"> <li>➢ Fe, Mg, Mn, Cr, etc</li> </ul> </li> <li>• <b><u>Residual Solvents</u></b> <ul style="list-style-type: none"> <li>➢ EtOH, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, THF, etc</li> </ul> </li> </ul>	}	<p><b><u>Mostly predictable</u></b>  <b>Covered by existing guidances</b></p> <ul style="list-style-type: none"> <li>• ICH Q3D (Draft), USP &lt;232&gt;</li> <li>• ICH Q3C, USP &lt;467&gt;</li> <li>• USP &lt;281&gt; ROI</li> </ul>
<ul style="list-style-type: none"> <li>• <b><u>Organic Impurities</u></b></li> <li>• <b><u>Drug Related Organic Impurities</u></b></li> </ul> <ul style="list-style-type: none"> <li>• With good scientific knowledge, it can be predictable to a large extent.</li> <li>• Sponsor is expected to have thorough understanding of the origin, structure, toxicity, analytical behavior, process capability and establish controls/Specs</li> </ul>	}	<p><b><u>Highly Variable</u></b></p> <ul style="list-style-type: none"> <li>➢ Depends on the new drug</li> <li>➢ Most likely never seen before</li> <li>➢ Safety profile is unknown</li> </ul>
<ul style="list-style-type: none"> <li>• <b><u>Drug un-related Organic Impurities</u></b></li> </ul>	}	<ul style="list-style-type: none"> <li>➢ Low Predictability/High Variability</li> </ul>

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# Organic Impurities in Drug Product

	Origin of Organic Impurities	How to Set Specs? (Guidance)
Drug Related	Carry over from Drug Substance (Starting materials, By-products, Intermediates etc.) *	ICH Q3A
	Degradation products of Drug Substance	ICH Q3B
	Reaction products of the drug substance with excipients or immediate container closure system	
Unrelated	<b>Excipients (and their Degradants)</b>	<b>???</b>
	<b>Leachables from the Container-Closure system (and their degradants)</b>	

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# Drug Related Organic Impurities

## Control of Drug Related Organic Impurities

Max. Daily Dose	Reporting Threshold	Identification Threshold*	Qualification Threshold*
<b>ICH Q3A – DRUG SUBSTANCE</b>			
≤ 2 g/day	0.05%	0.10% or 1.0 mg/day intake**	0.15% or 1.0 mg/day intake**
> 2 g/day	0.03%	0.05%	0.05%
<b>ICH Q3B – DRUG PRODUCT</b>			
< 1 mg	0.10%	1.0% or 5µg TDI**	1.0% or 50µg TDI**
1 mg – 10 mg	0.10%	0.5% or 20µg TDI**	1.0% or 50µg TDI**
> 10 mg – 100 mg	0.10%	0.2% or 2mg TDI**	0.5% or 200µg TDI**
> 100 mg – 1 g	0.10%	0.2% or 2mg TDI**	0.2% or 3mg TDI**
> 1 g – 2 g	0.05%	0.2% or 2mg TDI**	0.2% or 3mg TDI**
> 2 g	0.05%	0.10%	0.15%

\* = Lower threshold may be appropriate for toxic impurities

\*\* = Whichever is lower

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## Drug Unrelated Organic Impurities (From Excipients)

\$\$ Million Question: Should we control Organic Impurities arising from excipients?

- **“Yes, the impurities from the excipients shall be controlled ”**
- It is a statutory requirement: According to FD&C Act 21 U.S.C. 321 Section 201(g)(1) and 21.CFR.321.(g)(1), the term **“Drug”** means:
  - Articles recognized in the USP, US Homoeopathic Pharmacopoeia, or official National Formulary
  - Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man/animals
  - Articles (other than food) intended to affect the structure or any function of the body of man or other animals;
  - Articles intended for use as a component** of any article specified in clause (A), (B), or (C).

**How do we control Organic Imp. arising from excipients in DP?**

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## Evolution of Excipient Status

- Traditional thoughts on Excipients
  - Excipients are “inert” (i.e. pharmaceutically inactive)
    - Typically derived from food ingredients (Starch/Lactose/NaCl etc.)
    - Food grade is acceptable
- Current Status of Excipients – Highly “Complex”
  - No longer just food ingredients
  - Extensive synthetic modifications: Structurally and functionally modified to meet complex industry needs
  - Modern / Complex Manufacturing Processes
  - Increased Quality Focus due to Advancing Science and Technology
    - Toxicology – e.g. focus on Phthalates
    - Analytical testing – e.g. focus on ppm levels of Genotox Imps.

## Evolution of Excipient Status

- Current Status of Excipients – Highly “Complex”
  - Commercial / Financial factors
    - Multiple end users – Pharma/Food/Cosmetics/others
    - Commodity chemicals / Materials – Lower profit margin
  - Increasing criminal activities: Economically Motivated Adulteration by manufacturers
    - Heparin contamination with over-sulfated chondroitin
    - Melamine contamination in milk products
  - Complex global supply-chain
    - Challenges in tracking supply-chain integrity

## Control of Excipient Quality

- Consequently excipients have come under more rigorous Regulatory scrutiny for both Safety/Efficacy of the drug as well as for Quality/Compliance
- Sponsor is expected to control the Critical Quality Attributes (CQA) of excipients
  - **Safety related CQA: Impurities** ← Topic of Interest
    - Potential toxicological effects
  - **Efficacy related CQA: Physico-Chemical properties** (e.g Particle Size, Molecular Weight distribution)
    - Impact on functional aspects of the excipients (drug delivery etc)
- Sponsor is expected to manage the excipient Vendors / Supply Chain for QA/Compliance

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## Control of Organic Impurities (From Excipients)

- Control Organic Impurities from Excipients via Specifications
  - Test , Method, Acceptance limits
- What Guidance should I follow?
  - There is no formal regulatory guidance for control of organic impurities arising from excipients
    - ICH Q3A or ICH Q3B (Imp. in new DP) do not cover them
- There are some general guidelines (IPEC, PQRI, USP etc) which leave the responsibility of setting the impurity limits to sponsor
- Use of a QbD approach can offer a practical solution

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## Control of Organic Impurities (From Excipients)

- Guidelines from The International Pharmaceutical Excipients Council (IPEC) Europe are very helpful (<http://www.ipec-europe.org/>)
  - Qualification of Excipient for Pharmaceutical Use, 2008
  - The IPEC Excipient Composition Guide, 2009
- Guidelines are intended to provide *excipient manufacturers* with strategies for assessment of the overall composition of their excipients, and also provide *excipient users* with a means of understanding what affects the composition of an excipient and how this could impact their medicinal products.
- Guidelines are general; **does not consider functionality or route of administration of excipients which must be evaluated on a case-by-case basis for each application.**

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## Control of Organic Impurities (From Excipients)

### **IPEC's Position:**

- **Excipient:** Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.
- Excipients often have uses other than pharmaceutical applications
- Pharma excipient is often used with a broad range of APIs and in a diverse range of finished dosage forms
- **Application of GMP is relevant once it has been determined that a chemical is intended for use as a component of a drug product**
- **Impurity in Excipient:** A component of an excipient that is not intended to be present but arises as a consequence of the manufacturing process
- Excipients frequently function because they contain substances in addition to the main components (concomitant components). These components should be considered as part of the composition profile, and not construed as being undesirable, nor confused with the presence of added substances

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## Control of Organic Impurities (From Excipients)

### **IPEC's Position:**

- The impurity situation for excipients is more complex than drug substances; they are frequently multi-component, and may be less well defined
- Guidelines like ICH Q3A/Q3B do not apply to excipients. They are inactive ingredients and should not be subjected to those standards
- The ICH definition of the term "impurity" can be misleading when applied to excipients. To distinguish these components from true impurities the appropriate term when discussing excipients is "minor component" or "concomitant component"
- Where possible, excipient manufacturers should identify and set appropriate limits for any components having exposure concerns (toxicity)
- If genotoxic impurities are detected, their toxicological potential should be assessed and acceptable limits determined for their levels; EMA (or FDA) guidelines on Genotoxicity may be of assistance in setting limits

## Control of Organic Impurities (From Excipients)

- For existing Excipients
  - Is there a compendial monograph
  - Is there impurity specifications and acceptance limits
  - If yes, complying with the Compendial limits may be sufficient
  - Note that additional impurity control may be required; This needs to be decided on a case by case basis
    - E.g. impurity limits for an excipient to be used in pediatric product may require tighter control

## Control of Organic Impurities (From Excipients)

### Organic Impurities in New/Novel Excipients

- This requires a more thoughtful & systematic approach
  - Safety is the primary focus (toxicology)
- For a New/Novel Excipient\*, FDA & EMA require tox qualification to the same level as a new drug substance
  - FDA Guidance (2005): Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
  - EMA Guidance (2007): Guideline on Excipients in The Dossier for Application for Marketing Authorization of a Medicinal Product (EMEA/CHMP/QWP/396951/2006)

\* **Novel excipient**: A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration (ICH).

## Control of Organic Impurities (From Excipients)

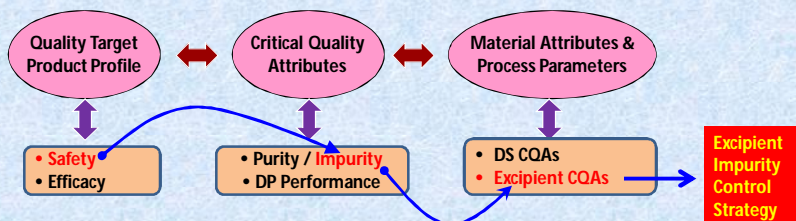
### • USP's position on Organic Impurities in New Excipients

The Impurity test of an excipient monograph is intended to limit all specified impurities, with a further limit of 0.10 % for all unspecified impurities. For **new monographs** USP will follow nomenclature and approaches shown in Table below. (Organic Impurities shown)

Impurity Type	Traditional USP Test(s)	New USP Tests	Q3A Impurity Classes
Organic	<ul style="list-style-type: none"> <li>• Ordinary Impurities</li> <li>• Chromatographic Purity</li> <li>• Related Compounds</li> <li>• Limit of _____</li> </ul>	Specified Impurities	Starting Material
			By-Products
			Intermediates
		Specified and Unspecified Impurities	Degradation Products
		Specified Impurities	Reagents, Ligands, and Catalysts

## Control of Organic Impurities (From Excipients)

- QbD approaches for setting Specifications for Organic Impurities from Excipients
  - Science-based / Risk-based
  - More likely acceptable for regulators



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## Control of Organic Impurities (From Excipients)

### Knowledge/information required to define Excipient-Impurity control strategy and specifications

- What are potential impurities?
- What are the sources for the potential impurities
- Is it an impurity or a concomitant component
- Is the structure of the impurity known
- Could the impurity have unusual toxicity (structural alert)
- Could the impurity levels be lowered or eliminated by process enhancements
- Is the excipient stable during its manufacture/Storage?
- Is the excipient stable during DP manufacturing process and storage?

### Helpful Information

Knowledge of excipient manufacturing process, starting materials, intermediates, reagents, solvents etc.

Stability information from excipient Vendor

Drug Product Preformulation/Stability studies

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## Control of Organic Impurities (From Excipients)

- Many times, the manufacturing info and other information needed to assess the impurities in excipients are confidential
- Sponsor needs to work closely with the excipient manufacturer to define the impurity control strategy
  - Process/Material Controls
    - Is it possible to reduce impurity levels or entirely eliminate the impurity by process changes / improvements / Controlling quality of starting materials etc
  - Specifications (Test / Method / Acceptance limit)
    - What to test / How to test
    - Who will do the test
    - At which point will the test be done (Ideally at the incoming stage unless the excipient impurity is also a degradant)
    - What is the acceptance limit
  - Use of PAT / RTRT during continuous manufacturing

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## Control of Organic Impurities (From Excipients)

- Consider the following while setting the acceptance criteria
  - Typical levels in the batches
  - Stability of the excipient (on storage, DP manufacturing and DP storage)
  - Toxicology qualification levels
  - Structural alerts / Genotox potential
  - Maximum daily intake
  - Route of administration
  - Patient population (pediatric)
  - Benefit/Risk ratio (unmet medical need vs Life style drugs)
  - What thresholds to use? ICH Q3B can be a helpful reference
  - Should use validated analytical methods

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## Hypothetical Case

**Question:** Should the RRT 1.45 Impurity be controlled as an Impurity in Drug Product?

**NO, because:**

- It is not a drug related impurity
- It is from the excipient
- It is a PLACEBO peak

**YES, because:**

- It is an impurity, regardless of the source
- Impurities have no therapeutic value and could have harmful toxic effects
- You may not need a specification or control limits if justified appropriately

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## Control of Organic Impurities (From Excipients)

**Summary:**

- Impurities, regardless of their source, have no therapeutic value and potentially could have unwanted adverse effects
- Therefore, it is imperative that impurities arising from excipients, should be evaluated and controlled; it is also statutory requirement
- Control of impurities present in drug products, arising from excipients, can be challenging due to many factors including multiple end-users and global supply chain
- Sponsor is ultimately responsible for defining control strategy to ensure drug product quality
- There are no direct regulatory guidelines for control of excipient impurities; ICH Q3A/Q3B are for active drug substances and drug products but the scientific principles can be utilized
- Position papers from Professional Associations (IPEC) and Pharmacopeias (e.g. USP) are also sources of valuable guidance
- For new excipients, use of sound Science-based and Risk-based approaches to set specifications and control strategy for impurities under a QbD model can lead to favorable regulatory outcome

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## References

- **FDA Guidance: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005**
  - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf>
- **EMA Guideline: Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product, 2007**
  - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003382.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003382.pdf)
- **IPEC: Qualification of Excipient for Pharmaceutical Use, 2008**
  - [http://www.ipec-europe.org/UPLOADS/2008\\_Qualification\\_of\\_Exciprt\\_for\\_Pharma\\_Use\\_-\\_PDF\\_final\(1\).pdf](http://www.ipec-europe.org/UPLOADS/2008_Qualification_of_Exciprt_for_Pharma_Use_-_PDF_final(1).pdf)
- **IPEC: The IPEC Excipient Composition Guide, 2009**
  - <http://www.ipec-europe.org/UPLOADS/IPECCompositionGuidefinal.pdf>
- **PQRI Joint Position Paper: Pharmaceutical Excipient Testing And Control Strategies**
  - [http://pqri.org/pdfs/Excipient\\_Position\\_Paper\\_Final\\_06212007.pdf](http://pqri.org/pdfs/Excipient_Position_Paper_Final_06212007.pdf)
- **USP Guideline for Submitting Requests for Revision to USP-NF (2007): EXCIPIENTS**
  - [http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/chapter3.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/chapter3.pdf)

# Thank You



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