



# Impurities in drug substances and medicinal products

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# Outline of the presentation

- Principles of the assessment of impurities
- References
- Evaluation of the purity of synthetic drug substances (related substances, residual solvents, residual catalysts, genotoxic impurities)
- Evaluation of the purity of drug products



# Principles of the assessment of impurities

- **Quality supports efficacy and safety** of drug products
- Appropriate control of **impurities** primarily **supports safety** of the drug product
- The **limits** for impurities **are safety based**  
Other factors: **variability of a state-of-art manufacture** and **capabilities of the testing methods**
- Co-operation with toxicologists
- Adherence to the rules of **GMP** is assumed
- **Risk-based assessment**



# Impurities in the medicinal products

## SYNTHETIC API

SMs, intermediates, by-products, degradants, reagents, solvents, inorg. imp.-s, such as catalysts, HMs, microbiolog

## EXCIPIENTS

solvents, HMs, catalysts, monomers, microbiologic impurities

## CONTAINER

leachables, microbiol.

**Control of API, excipients, containers, their SMs and PCs**

degradants of the API, incl. adducts with excipients/contain.  
solvents used in DP manufacture, microbiological impurities

Degradation of excipients (development, performance tests)

Components of the packaging materials (development)

Equipment and site of manufacture (GMP)

# Impurities in the medicinal products

APIs of human, animal, microorganism, tissue culture, biotechnologic origin

Host cell DNA, HC protein, ovalbumine, related, (misfolded, aggregated protein, residual antibiotic solvents, TSE, viral, microbiologic impurities,

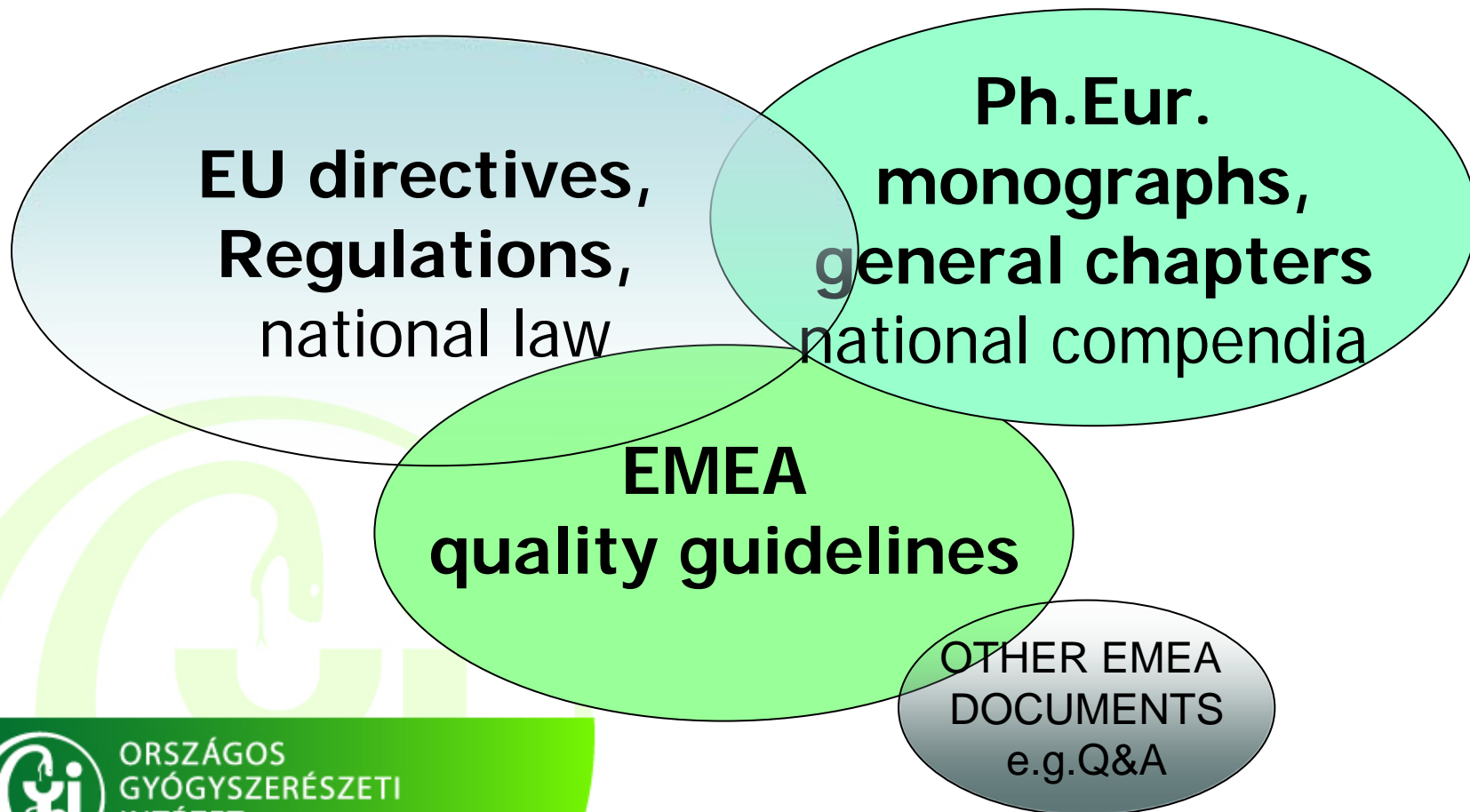
APIs of herbal origin  
solvents, HMs, pesticides, fumigants, mycotoxins, foreign matter, microbiologic impurities

APIs of radiopharmaceuticals  
chemical impurities  
radiochemical impurities  
radionuclidic impurities

**Control of API, excipients, containers, their SMs and PC**

Degradants of the API in the product  
solvents used in DP manufacture, microbiological impurities  
Degradants of excipients (development, performance tests)  
Components of the packaging materials (development)  
Equipment and site of manufacture (GMP)

# Regulation of the quality of medicines



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# How to identify the applicable rules?

„Guideline on the summary of requirements for active substances in the quality part of the dossier” (SRAS) provides guidance on the applicable rules for non-biologic APIs according to the categories of

- new active substances
- existing substances described in the EP(or MS compendium)
- existing substances not described in the EP (or MS compendium)



# **Guidelines for the impurities to be applied to the new active substances**

- **Summary of Requirements for Active Substances Chemistry of new active substances**
- **Chemistry of Active Substances**
- **Impurities Testing: Impurities in New Drug Substances (ICH Q3A R2)) CPMP/ICH/ 2737/99-ICH Q3A (R2)**
- **Impurities: Residual Solvents (ICH Q3C (R3)) CPMP/ICH/ 283/95-ICH Q3C (R3)**
- **GL on the limits of genotoxic impurities**
- **Nfg on specification limits for residues of metal catalysts or reagents**
- **Annex I. to CPMP/ICH/283/95 Guideline for Residual Solvents**
- **Other guidelines e.g. ICHQ6A and stability guidelines**





# **Guidelines for the impurities to be applied to the existing active substances not described in the EP**

SRAS: „In principle, the same requirements are as set out for new active substances”

Differences:

- qualification of impurities
- GTI exemption

if a valid product history is available for the substance in question and no specific cause of concern exists



# **Relevant requirements for the impurities of the existing active substances covered by the EP**

- **Compliance with the individual monograph**
- **Compliance with the relevant general monographs (Substances for pharmaceutical use, Fermentation products, Extracts, Herbal drugs etc.)**

## **Implications:**

**a) compliance with 5.4 residual solvents corresponding to ICH Q3C**

**b) application of the same thresholds for reporting, identification and qualification of the impurities as described in ICH Q3 A (5.10 Control of impurities in Substances for pharmaceutical use)**



# **Relevant requirements for the impurities of the existing active substances covered by the EP**

- **Control of Impurities of Pharmacopoeial Substances**
- **SRAS: need of demonstration that impurities from the actual manufacturing process can be controlled by the monograph**
- **GI on the limits of genotoxic impurities (the same exemption as for non-compendial existing substances)**
- **Nfg on specification limits for residues of metal catalysts or reagents**
- **Annex 1 to CPMP/ICH/283/95 Guideline for Residual Solvents**



# Evaluation of the list of potential impurities in active substances proposed by the applicant I.

**The assessor should evaluate that the applicant gives sufficiently detailed information in the section of impurities(S.3.2) on the potential impurities of the API in terms of their origin, fate and nature.**

The assessor evaluates if adequate discussion is provided on:

- possible side reactions
- possible isomerisation,
- possible reactions with the impurities of the SMs,
- for possible residues of solvents, impurities of solvents, catalysts, reagents,
- for potential highly potent or toxic incl. genotoxic impurities (if applicable)



# Evaluation of the list of potential impurities in active substances proposed by the applicant II.

(cont.)

- possible degradation pathways
- the testing methods and experiments used for impurity profiling (e.g. for selectivity, sensitivity for early or late eluting, low RF impurities)

***knowledge in chemistry , scientific literature, compendia, other DMFs, other dossiers, other parts of the dossier (synthesis, method validation, stress, accelerated and long term stability studies of the API and the product!***



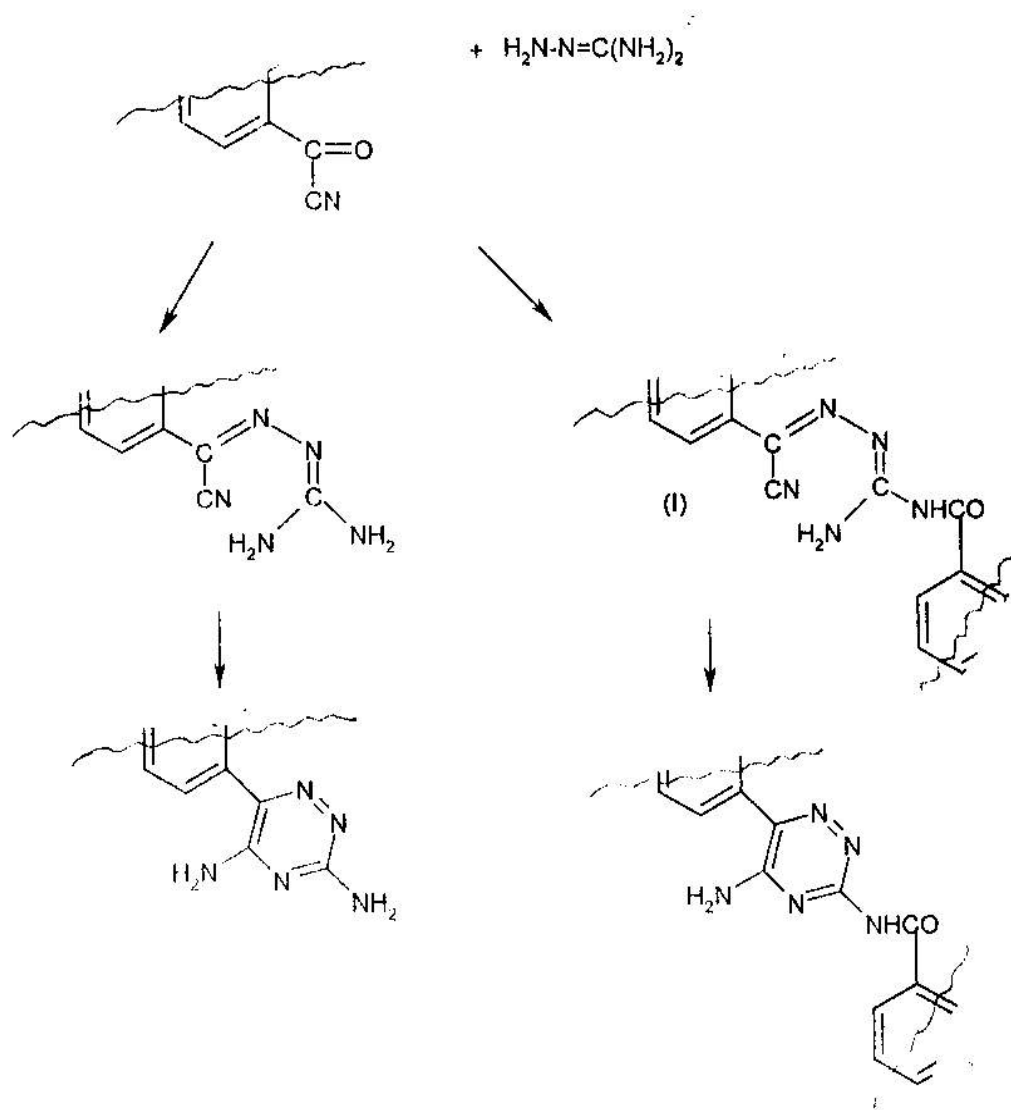
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# An example of losing an impurity

In the synthesis of the API  
condensation of benzoyl-  
nitrile and aminoguanidin  
is carried out, followed by  
a cyclisation step (left)

If anhydride is present  
in the SM, another type of  
condensation product is  
also formed. (right)

HPLC of the applicant can  
not detect this, late eluting  
impurity



# Other examples of disregarding impurities

- impurity profile of gabapentin without paying attention to the late eluting dimeric/oligomeric impurities (USP PF)
- In the synthesis of a DS a primary amine is methylated to form a dimethylamino group. SST of peak to valley ratio between the main peak (dimethylamino compound) and the peak of the primary amine impurity. No discussion on the possible presence of monomethyl amine.
- In the synthesis of bicalutamid the starting material is an epoxy compound. A limit of 0.10% was proposed for it by the applicant. Based on the structural alert genotoxicity was raised by the assessor and a limit of 30 ppm was approved.



# Evaluation of the proposed list of actual impurities in active substances

The assessor should assure that **all actual impurities are selected and controlled**

Means: assessment of batch data (pilot, production), stability data and the testing method and validation data





# Evaluation of the proposed specification for related substances in active substances

Does it reflect the impurity profile of the production batches?

Does it comply with the relevant guidelines ?

- limits for each specified (identified and not identified), any unspecified and the total
- application of the reporting, identification and qualification thresholds corresponding to the maximum daily dose of the substance
- appropriate limits for unusually potent or toxic impurities
- suitability of the testing methods



# Thresholds (active substance)

	MDD $\leq$ 2g	MDD > 2g	
Reporting	> 0.05%	> 0.03%	Only imp.s above RT should be reported in the total RT > LOQ
Identificat.	> 0.10% or 1.0 mg per day intake, whichever is lower	> 0.05%	IT is the limit for any unspecified imp. (RFs of unspecified?) Imp.s above IT should be specified and identified if possible
Qualificat.	> 0.15% 1.0 mg per day intake, whichever is lower	> 0.05%	Impurities above the QT should also be qualified



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*thresholds for substances which are out of scope of the ICHQ3A?*

# Qualification of impurities

- 1) **New substances** :pre-clinical, clinical studies, metabolites
- 2) **Existing, non Ph.Eur**: literature, information on the length of time that the active substance from the same source has been on sale in the EU, comparison of the impurity profile with marketed products
- 3) **Existing covered by Ph.Eur**: impurities in the transparency list of under subheading „specified impurities” are regarded as qualified

New impurities of 2) and 3) where no conclusion can be drawn from licenced products possibilities for 1) can be applied



# Evaluation of the residual Class1solvents in the API

## **The use of a class1 solvent is only acceptable:**

- **if it is used as starting material:** it should be routinely controlled at API or intermediate level (Annex1)
- **if it is an contaminant of a solvent:** a routine test is not required when e.g.a level of NMT30% of the limit is demonstrated on the API or intermediate level (Annex1)
- **if it is used as an unavoidable solvent:** no information in Annex1 and „should be tested if it is likely to be present” in Ph.Eur.5.4

**„In each case the final substance should comply if tested” (Annex1)**

Due to divergency in the interpretation (should or need not be specified at API level?) a harmonised approach is discussed by QWP



# Evaluation of the residual Class 2 solvents in the API

1. Class 2 solvents used in the last step of the synthesis should be routinely controlled in API (Annex1)
2. The routine testing of a class 2 solvent used prior to the last step is not required if its content is demonstrated to be NMT 10% of the limit in an intermediate or the final substance. (Annex1)

The substance should comply if tested (Annex1)

Divergency in interpretation of case 2. (whether to include in the specs or not)

**Q&A on limits of class 2** :no tightening ICH limits based on batch data



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# Evaluation of the residual Class 3 solvents in the API

## Up to 0.5%

- Class 3 solvents can be tested by a LOD test
- If LOD test is not suitable, a validated (GC) method should be used

*In practice, conditions of exemption from routine testing allowed for class 2 solvents are also applied for class 3 solvents*

## Above 0.5%

a validated (GC) method should be used



# Evaluation of the metal catalysts and reagents

- The guideline is applicable for active substances and excipients
- Concentration limits are derived from PDEs and MDDs
- A higher limit is acceptable if the medical product is used for a short period
- Higher limits should be justified case-by-case on safety or risk-benefit ground
- All test methods should be validated. It should be taken into account that a residual catalyst may occur in a variable form in the final substance



# Evaluation of the metal catalysts and reagents

Control strategy for class 1 and class 2 metals  
(as it described by the NfG):

If the synthetic or manufacturing processes have shown to result in the removal of a potential metal residue, routine testing of that metal residue may be replaced by non-routine (skip) testing. **A change from routine to non-routine testing does not mean that the test may also be deleted from the specification.**

Control strategy for class 3 metals:

**the test may be deleted from the specification of the drug substance if removal of the metal is demonstrated**





# Evaluation of GTIs

## Scope of the guideline

- New active substances
- New applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of GTIs are introduced as compared to products currently authorised in the EU containing the same AS
- No need for retrospective application to authorised products, unless there is a specific cause for concern



# Evaluation of GTIs

**„Cause for concern:** If a manufacturing procedure for API remains essentially unchanged, a **re-evaluation** with respect to the presence of potentially genotoxic impurities is generally not needed. However, new knowledge may indicate a previously unknown “cause for concern”.(Q&A)

***Interpretation of “cause for concern” is still different.  
Is an impurity with a structural alert a „cause for concern”?***

***Should „re-evaluation” be interpreted that there was an initial one?***

**Interpretation and clarification of the scope is under discussion by QWP and SWP**



# Evaluation of GTIs

A specific discussion should be provided for potential GTIs highlighting:

- potentially genotoxic (e.g. showing alerting structure) reagents, intermediates used and/or side products formed during the synthesis,
- technical efforts (alternative synthetic steps, purification) made to eliminate or reduce the levels
- experiments demonstrating elimination of GTIs
- the proposed control strategy
- limits and testing methods (rationale)



# Evaluation of GTIs

Limits for GTIs are set

- for impurities with evidence of a threshold related mechanism, based on PDEs obtained from NOEL/LOEL/UF
- for impurities without a threshold related mechanism the ALARP principle and the TTC (Threshold of toxicological Concern) approach with an daily exposure of  $1.5\mu\text{g}$  per day should be applied. If more than one GTIs having the same mechanism of the action are present, the limit applies to the sum of such impurities.(Q & A )
- A higher limit than TTC limit may be set in justified cases

**No control strategy is described by the guideline**



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# An approach under discussion for the control strategy of GTIs

1. If a potential genotoxic impurity is just a theoretical impurity i.e. based on theoretical considerations but not found in practice as demonstrated by studies during development of the manufacture, the impurity does not need to be included in the drug substance specification.



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# An approach under discussion for the control strategy of GTIs

2. If a potentially genotoxic impurity is formed or introduced in a step before the final synthesis step, it is possible to not include this impurity in the drug substance specification if it is controlled by
- a suitable limit in a synthesis intermediate
  - and if it is unambiguously demonstrated by analysis result (use of spiking experiments is encouraged) that presence of this impurity does not exceed 30 % of the limit, derived either from TTC or LOEL etc, in the drug substance.

If these conditions are not fulfilled, this impurity has to be included in the drug substance specification and the test has to be carried out on a routine basis.



# An approach under discussion for the control strategy of GTIs

3.If a potentially genotoxic impurity is formed or introduced in the final synthesis step, it should be included in the specifications.

- However, it is considered possible to apply skip testing if the level of the impurity does not exceed 30 % of the limit, derived from either TTC or LOEL etc, in the drug substance.
- Data should be presented for at least 6 consecutive pilot scale or 3 consecutive production scale batches.

If this condition is not fulfilled, a routine test in the drug substance specification is needed.

*A harmonised way of evaluation for three types of highly toxic impurities would be reasonable*



# Evaluation of impurities in drug products

- Note for Guidance on Impurities in **New Drug Products**
- Annex II: Residues of Solvents used in the Manufacture of Finished Products
- Dosage form monographs of the EP (do not have too much information on impurities)
- General monographs of the EP ( e.g.on vaccines, allergen products)
- Individual monographs of the EP on radiopharmaceuticals, vaccines etc.





# Evaluation of impurities in drug products

- Degradation products of the substance including reaction products of the active with excipients or container closure system should be considered
- Non-degradant impurities of the active substance (e.g. by-products) are not controlled at drug product level



# Evaluation of impurities in drug products

The assessor should evaluate

- the potential degradation pathways and potential interactions of the API with the excipients or containers
- Batch data (development and commercial)
- Stability data (stress, accelerated, long term)  
mass balance!!, API stability data
- Testing methods used for detection degradants  
(discussion of selectivity, detector response etc.)
- The applicable thresholds based on the MDD



# Evaluation of impurities in drug products

Specification (shelf-life and release, if applicable)

- Each specified, identified degradation product with a qualified limit
- Each specified unidentified degradation product (if any): with a nominal limit at which the degradant is qualified
- a limit equal to the identification threshold for any unspecified degradation product
- a limit for the total degradants (measured above the reporting threshold)
- Special attention to and limit for the toxic degradants
- In-use specification should also comply with the thresholds



# Evaluation of impurities in drug products

## Some problems in practice

- Specification for each unspecified and total in case of combination products (assignment to the 2 APIs)
- Different degradation pathways in the original and generic, e.g. ramipril diketo-piperazin in original and ramipril diacid in the generic product. (qualification by metabolite concept)
- Use of amorphous API. Each degradant is identified and qualified as per ICHQ3B but the total is much higher than in the reference product
- What thresholds to apply for DPs out of scope of the guideline (semi synthetic, fermentation, peptides)



# Residual solvents (medicinal products) (1)

Organic solvents can be used in the manufacture of medicinal products:

- As a granulation solvent
- As part of a tablet coating solution
- As a solvent for adhesives (transdermal patches)
- As a solvent for polymers (implants)



# Residual solvents (medicinal products) (2)

- Class 1 solvents are not acceptable.
- Justification of the choice of solvents should be provided in the pharmaceutical development part.
- A test for residues of solvents should be included in the product specification.
- For class 3 solvents a loss on drying testing is acceptable.



# Conclusion

- The section on impurities is one of the most important section in an application file.
- Thorough preparation and presentation of this section is most helpful for the assessor but other parts of the dossier can also be consulted.
- Limits and thresholds included in guidelines should be followed but it should also be kept in mind that in justified cases, on a benefit/risk ground higher limits/thresholds might be appropriate.
- Discussion/collaboration with safety experts and inspectors is important.

Thanks

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# Thank you for your attention!



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