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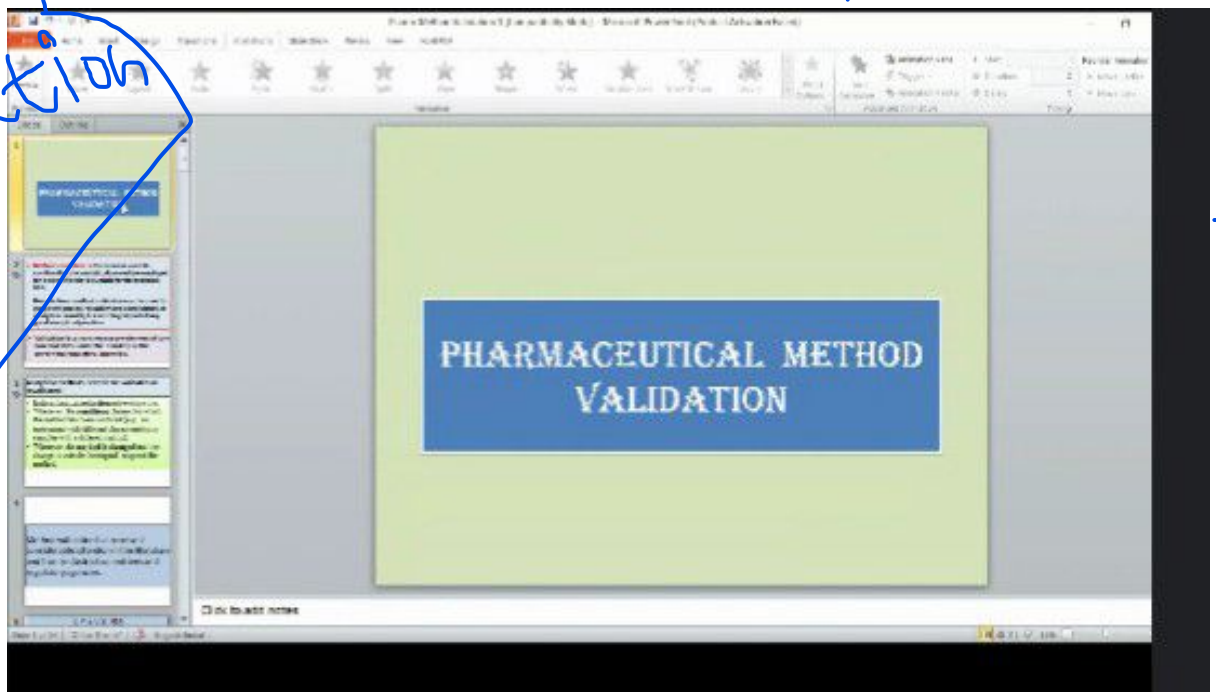
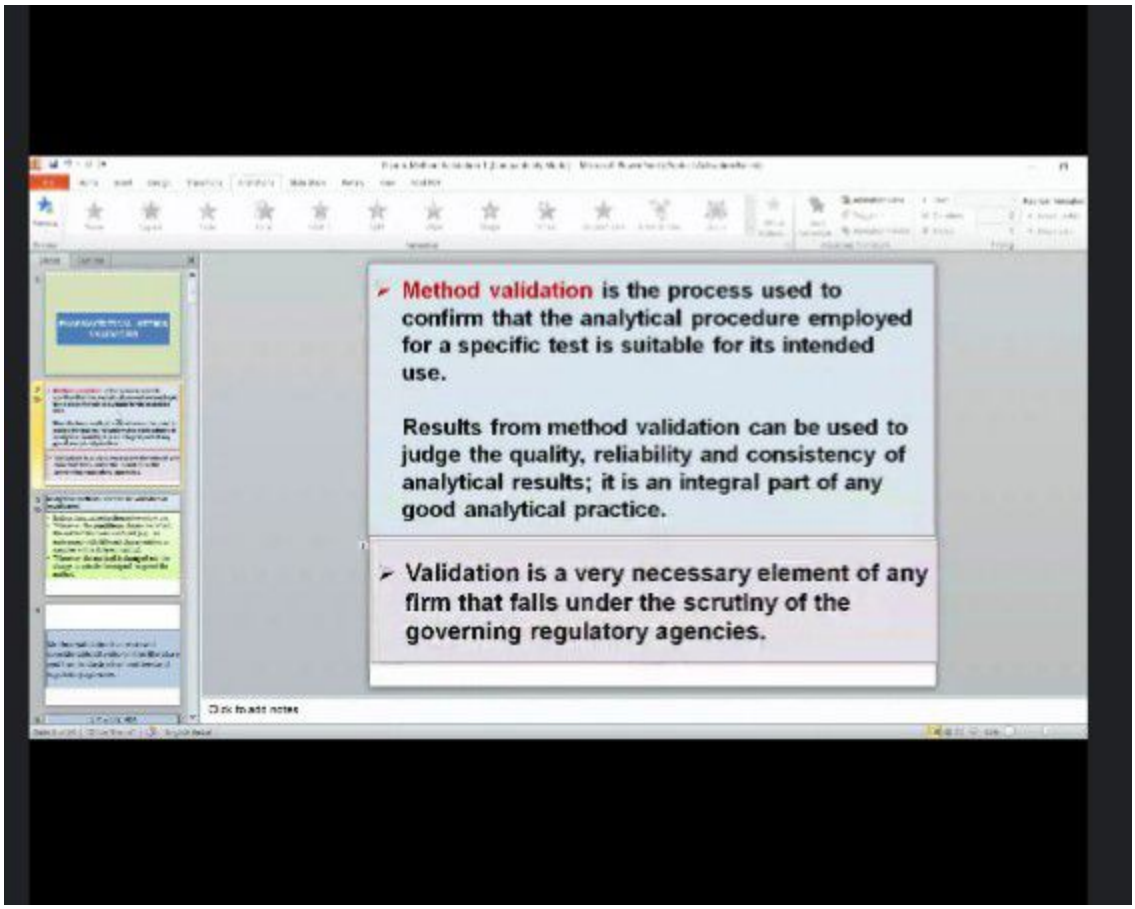
Selectivity





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Analytical methods need to be validated or revalidated:

- Before their **introduction** into routine use.
- Whenever the **conditions** change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix).
- Whenever the **method is changed** and the change is outside the original scope of the method.

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Method validation has received considerable attention in the literature and from industrial committees and regulatory agencies..

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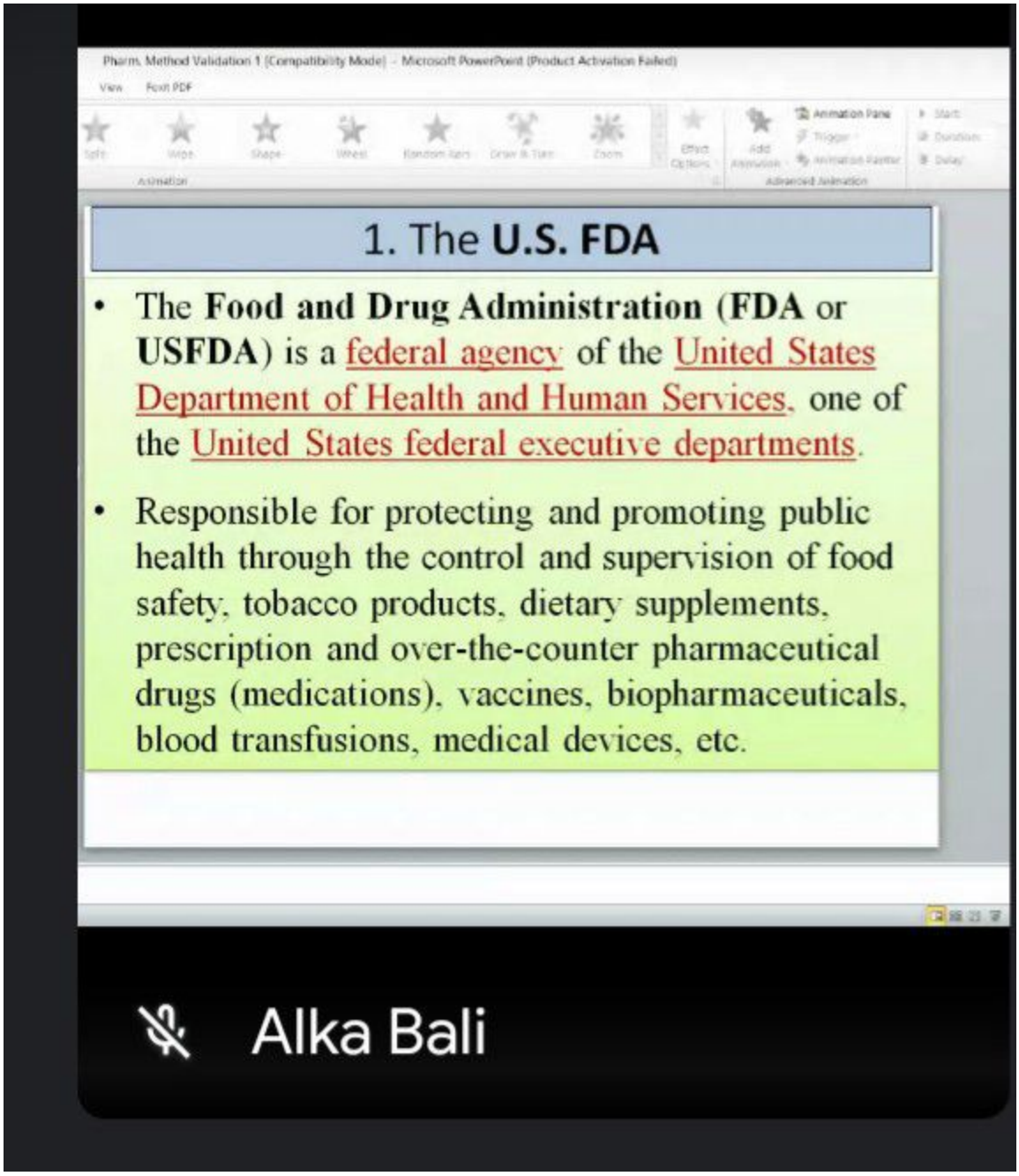

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The U.S. FDA

- The **Centre for Drug Evaluation and Research** (**CDER**, pronounced "see'-der") is a division of the U.S. Food and Drug Administration (FDA) that monitors most drugs as defined in the Food, Drug, and Cosmetic Act.
- Some biological products are also legally considered drugs, but they are covered by the **Centre for Biologics Evaluation and Research**.

FDA Guidance Documents

- Represent FDA's current ***thinking*** on a topic.
- Do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.
- The FDA has also published a guidance for the validation of bioanalytical methods

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- The most comprehensive document is the **conference report of the 1990 Washington conference**: ***Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies***
- Was sponsored by, among others, the *American Association of Pharmaceutical Scientists (AAPS),* the AOAC and the U.S. FDA. The report presents guiding principles for validating studies of both human and animal subjects.

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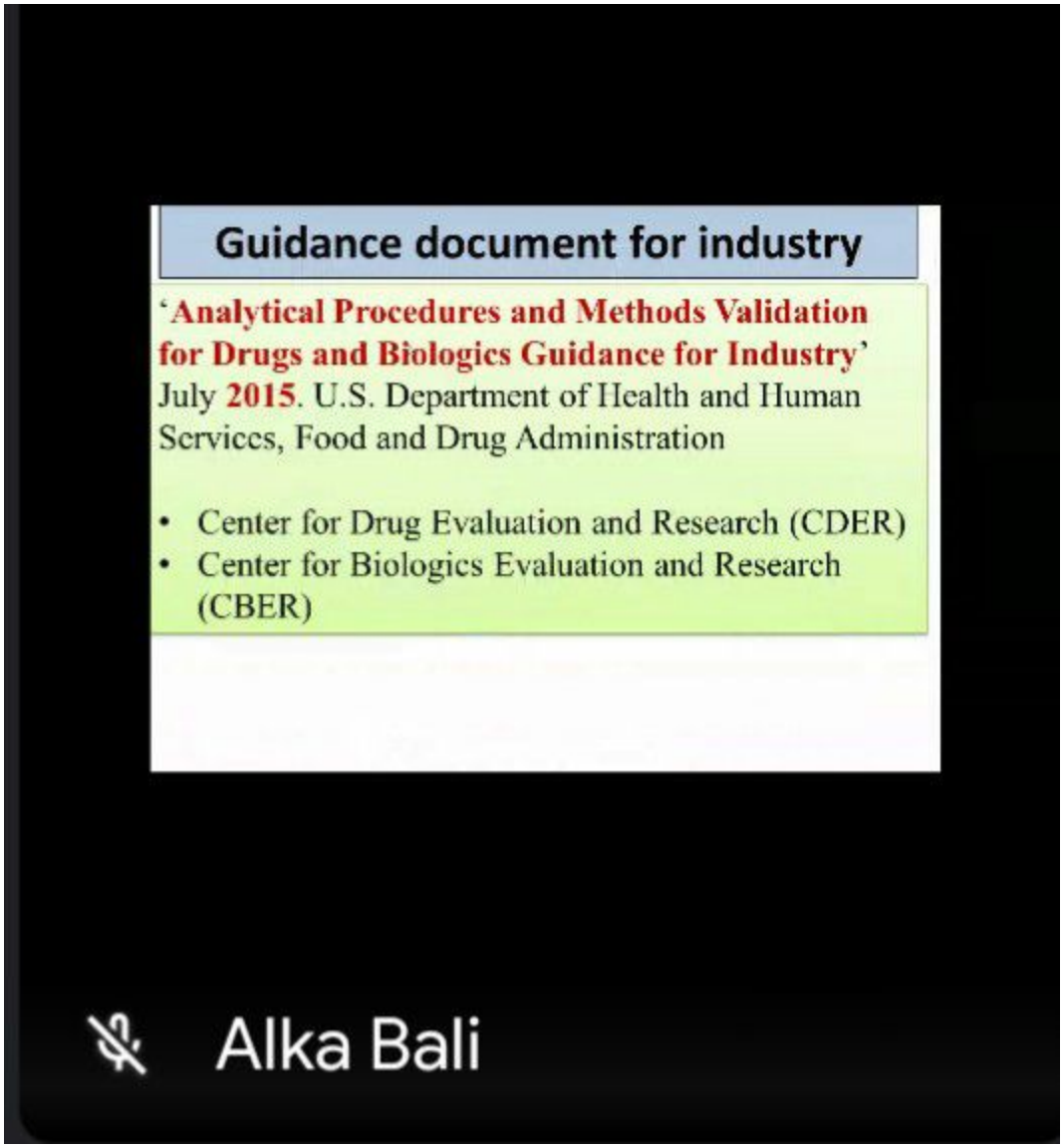

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Guidance document for industry

- The *accuracy, sensitivity, specificity, and reproducibility* of test methods employed by the firm shall be established and documented.
- Such validation and documentation may be accomplished in accordance with **Sec. 211.194(a).**
- *Statement*: These requirements include a statement of each method used in testing the sample to meet proper standards of accuracy and reliability, as applied to the tested product.
- The U.S. FDA has also proposed an industry guidance for Analytical Procedures and Methods Validation.

2. INTERNATIONAL CONFERENCE ON HARMONISATION ICH

- **ICH** has developed a consensus text on the validation of analytical procedures. The document includes definitions for eight validation characteristics. ICH also developed a guidance with detailed methodology.

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3. INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO)

- **ISO** is an independent, non-governmental international organization with a membership of 163 national standards bodies (including India) having its Central Secretariat in Geneva, Switzerland.
- These members are the foremost standards organizations in their countries and there is *only one member per country*.
- Each member represents ISO in its country. Individuals or companies cannot become ISO members.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO)

- **ISO/IEC 17025** includes a chapter on the *validation of methods* with a list of nine validation parameters.
- **ISO/IEC 17025:2005** specifies the general requirements for the competence to carry out tests and/or calibrations, including sampling.
- It covers *testing and calibration* performed using standard methods, non-standard methods, and laboratory-developed methods.
- Applicable to all organizations performing tests and/or calibrations, e.g., first-, second- and third-party laboratories, and laboratories where testing and/or calibration forms part of inspection and product certification.

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INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO)

ISO/IEC 17025:2005 is for use by:

- ***Laboratories*** in developing their management system for quality, administrative and technical operations.
- ***Laboratory customers, regulatory authorities and accreditation bodies*** may also use it in confirming or recognizing the competence of laboratories. ISO/IEC 17025:2005 is not intended to be used as the basis for certification of laboratories.

➢ Compliance with regulatory and safety requirements on the operation of laboratories is not covered by ISO/IEC 17025:2005.

4. U.S. ENVIRONMENTAL PROTECTION AGENCY EPA

- The U.S. EPA prepared a guidance for method development and validation for the Resource Conservation and Recovery Act (RCRA).

Meeting details

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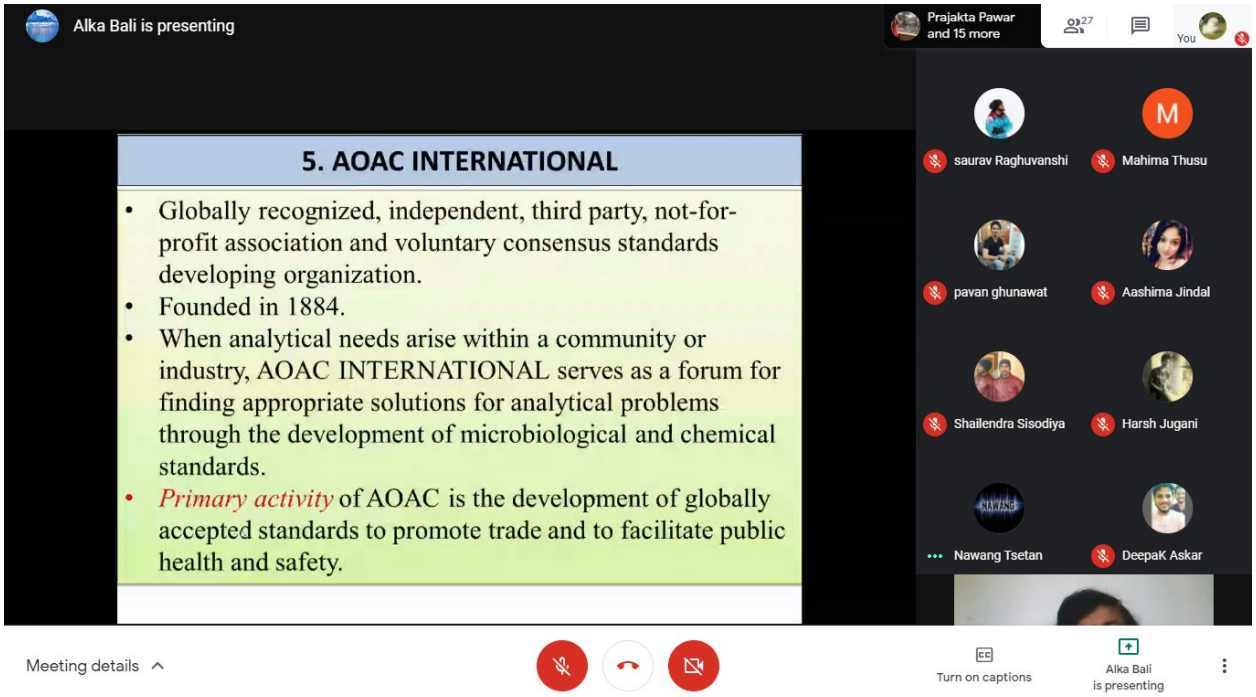

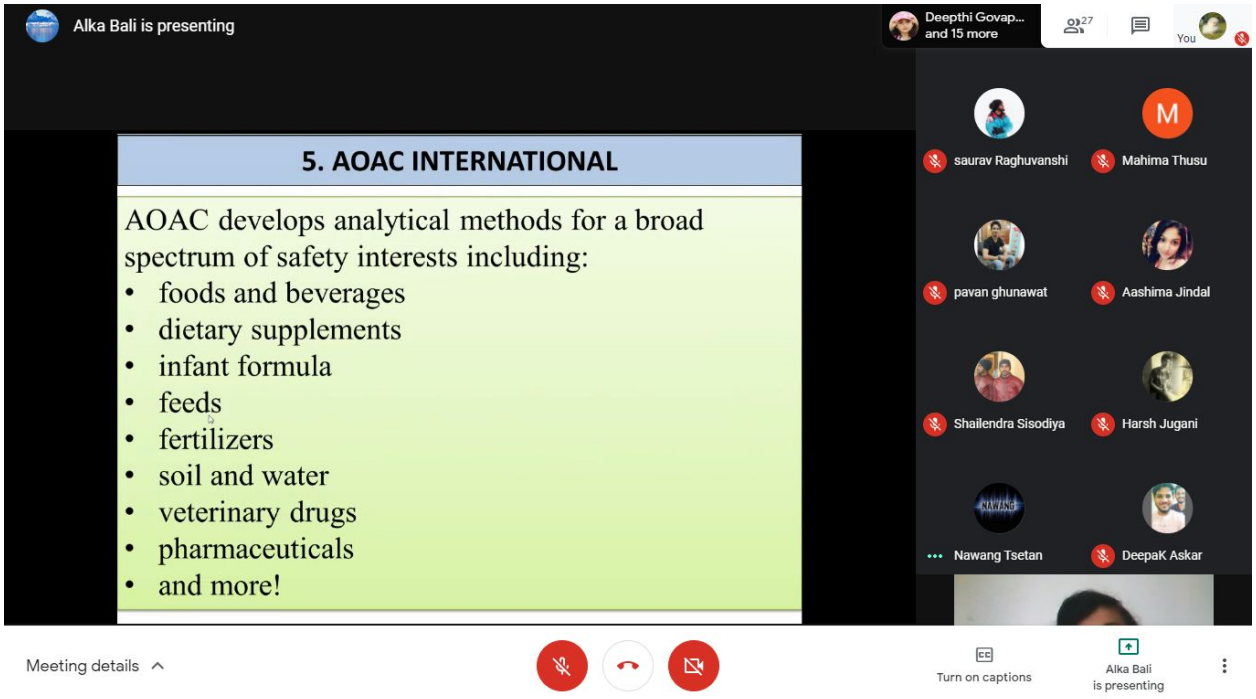

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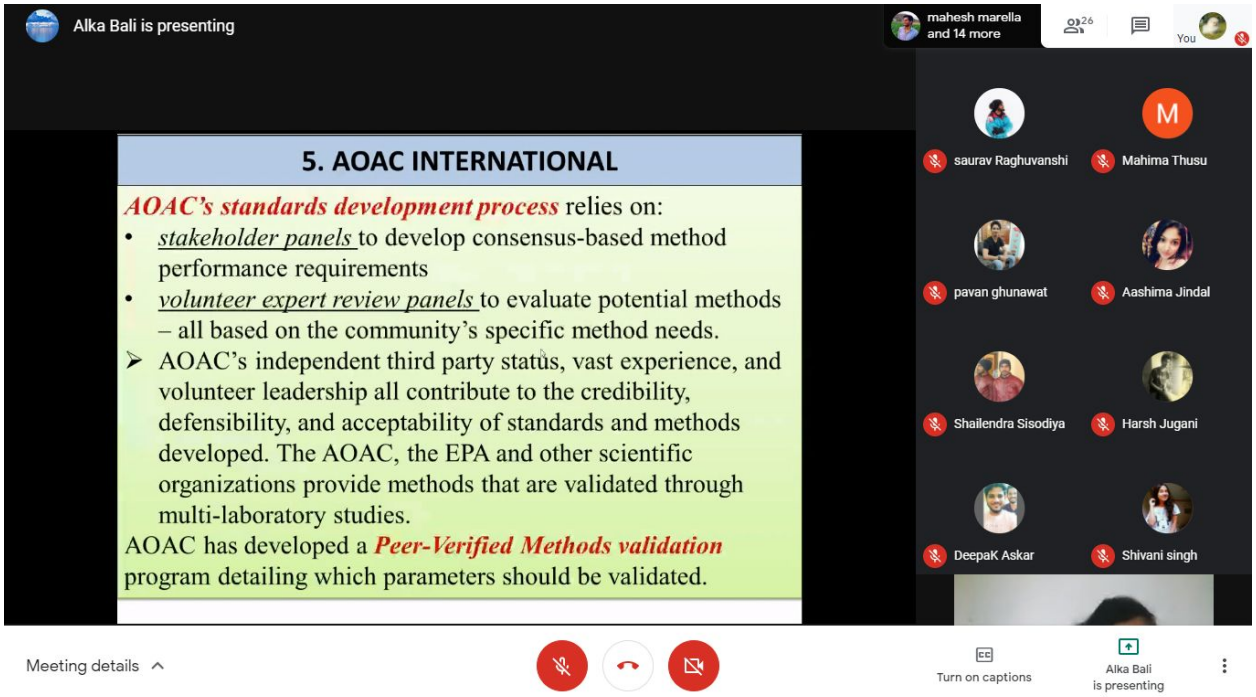

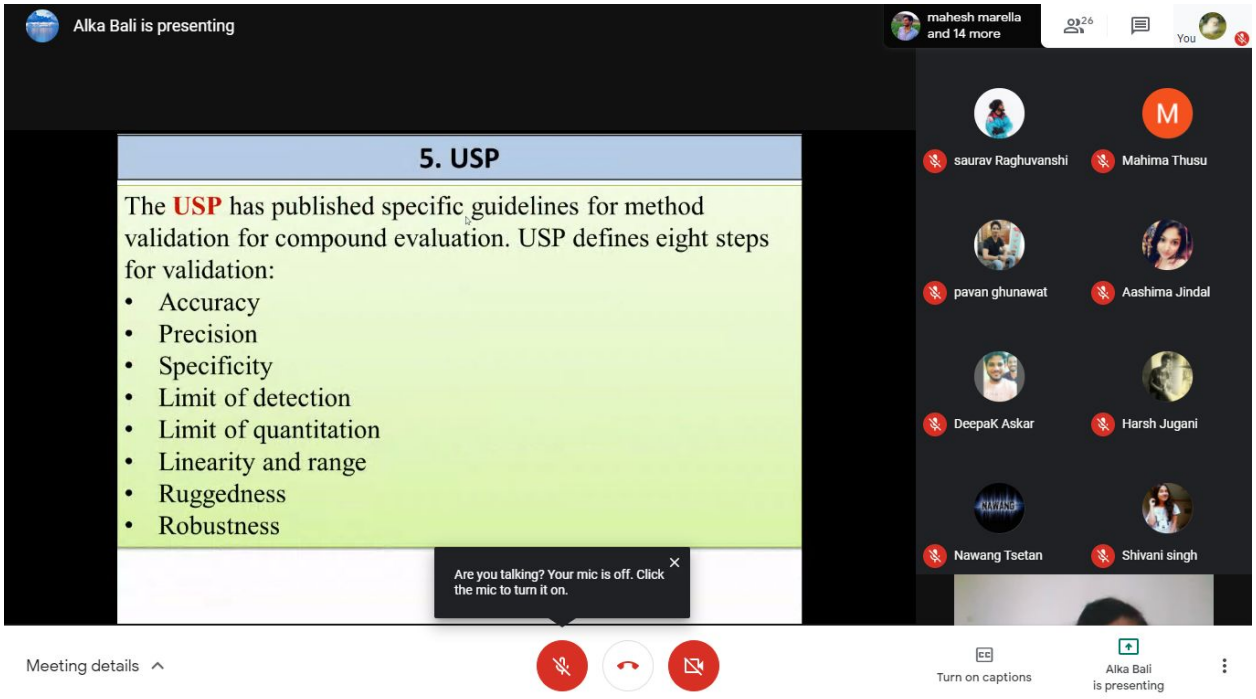

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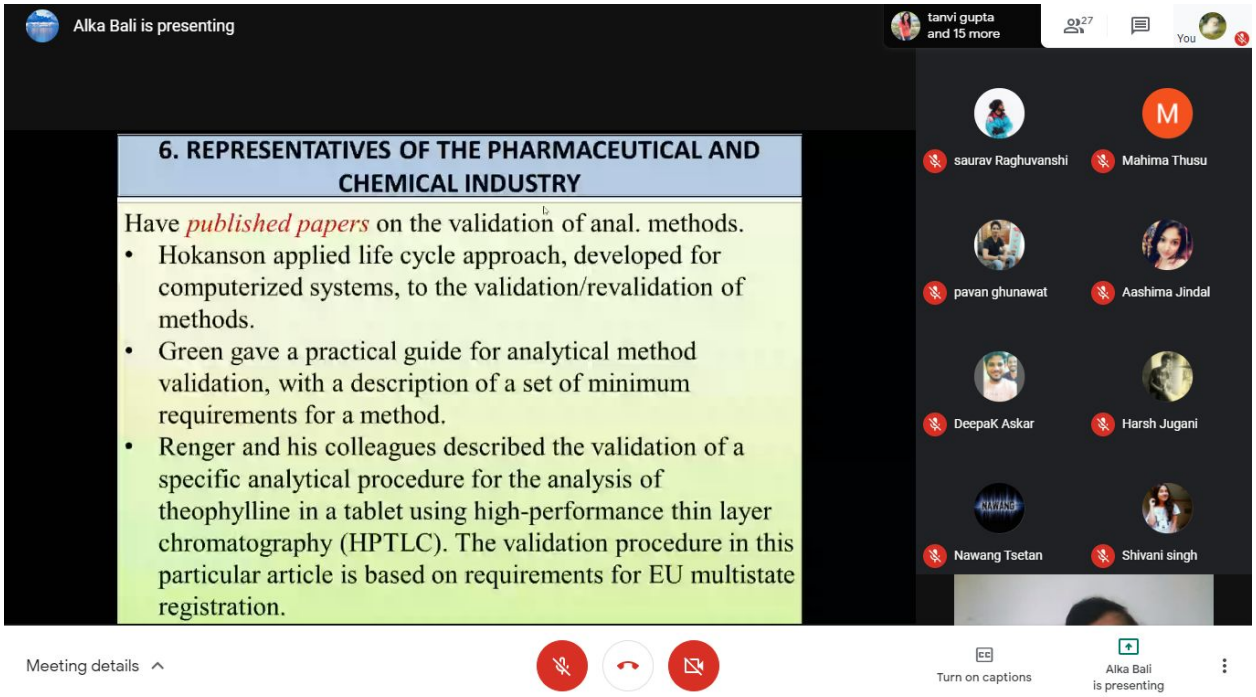

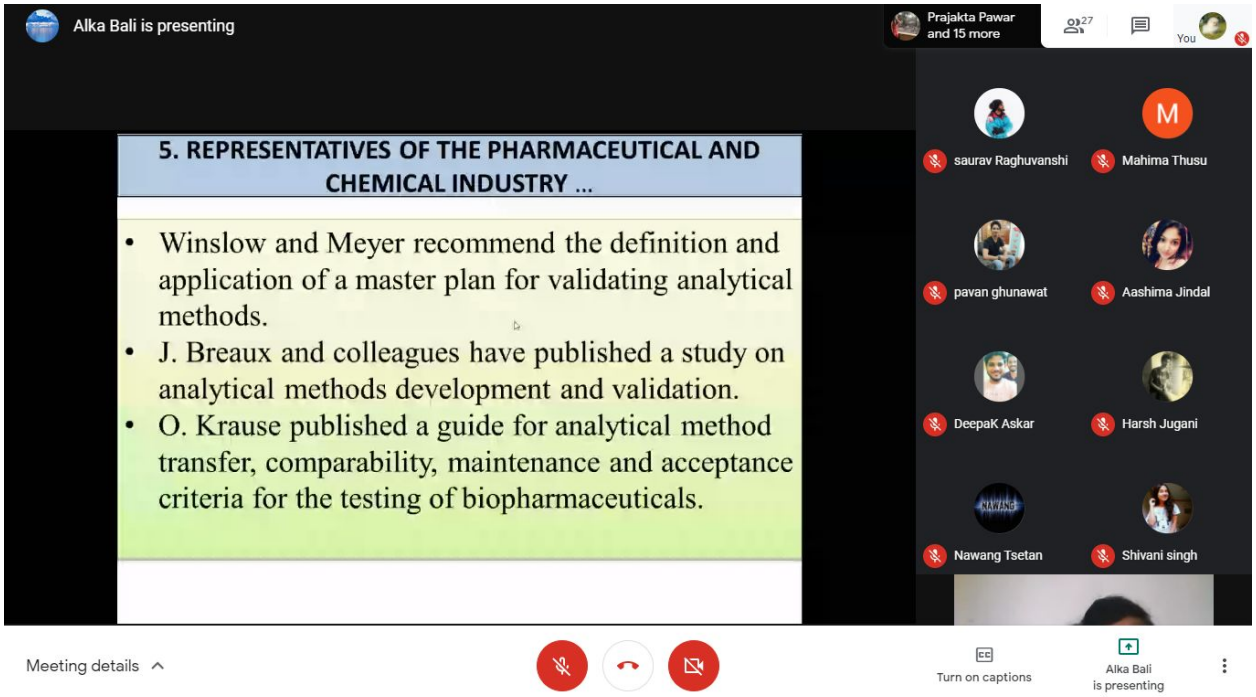

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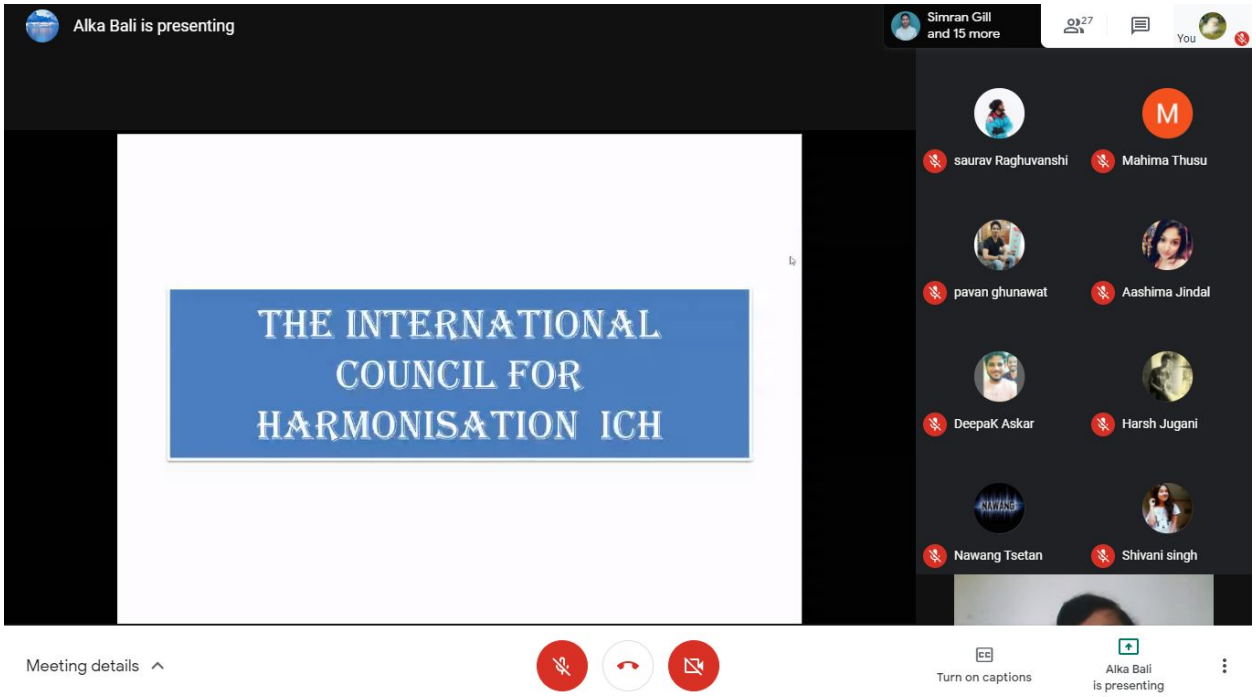

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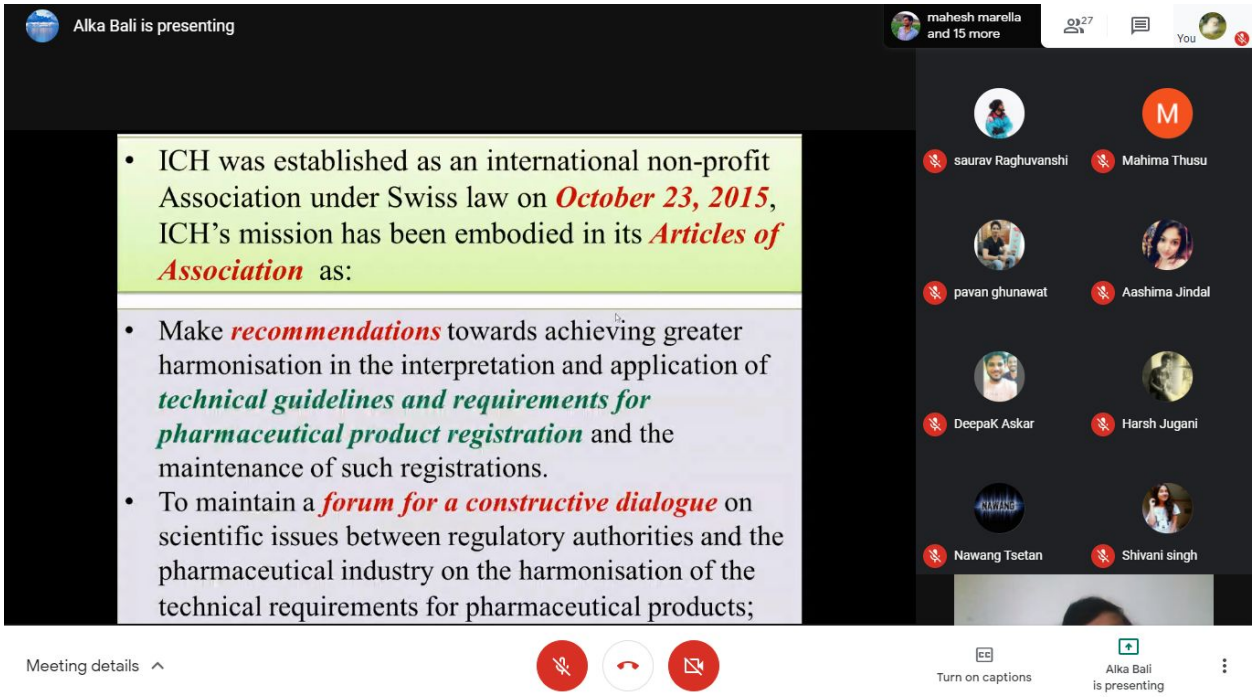

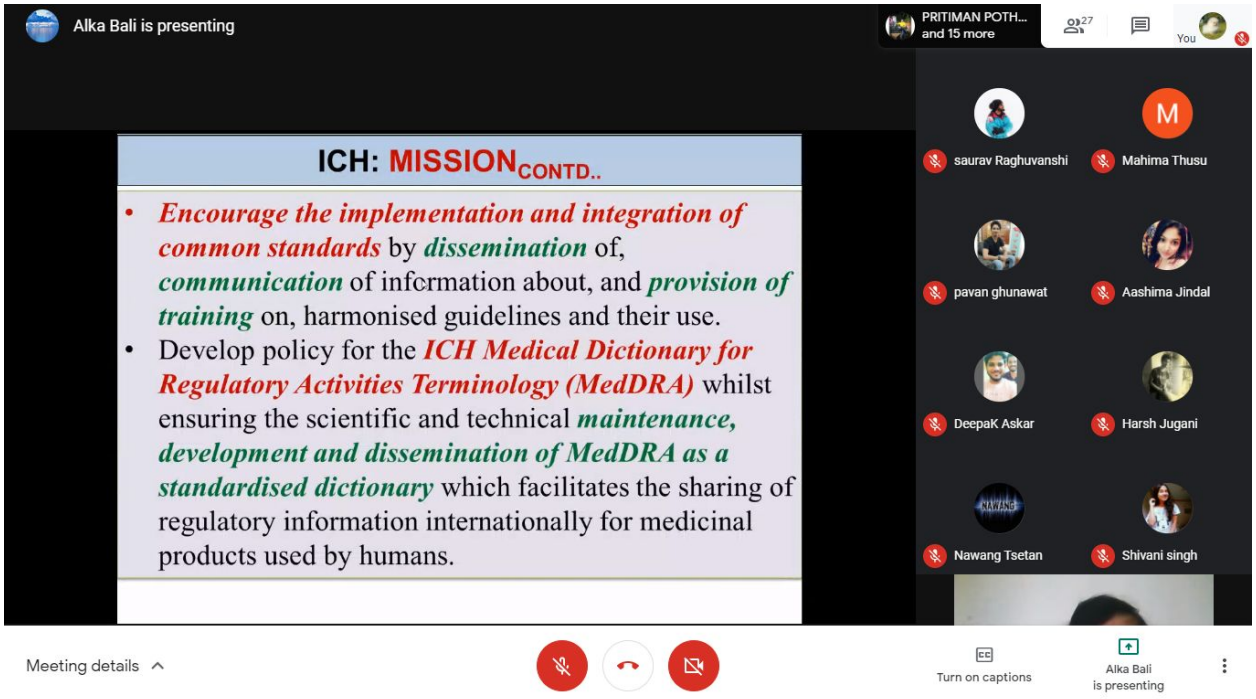

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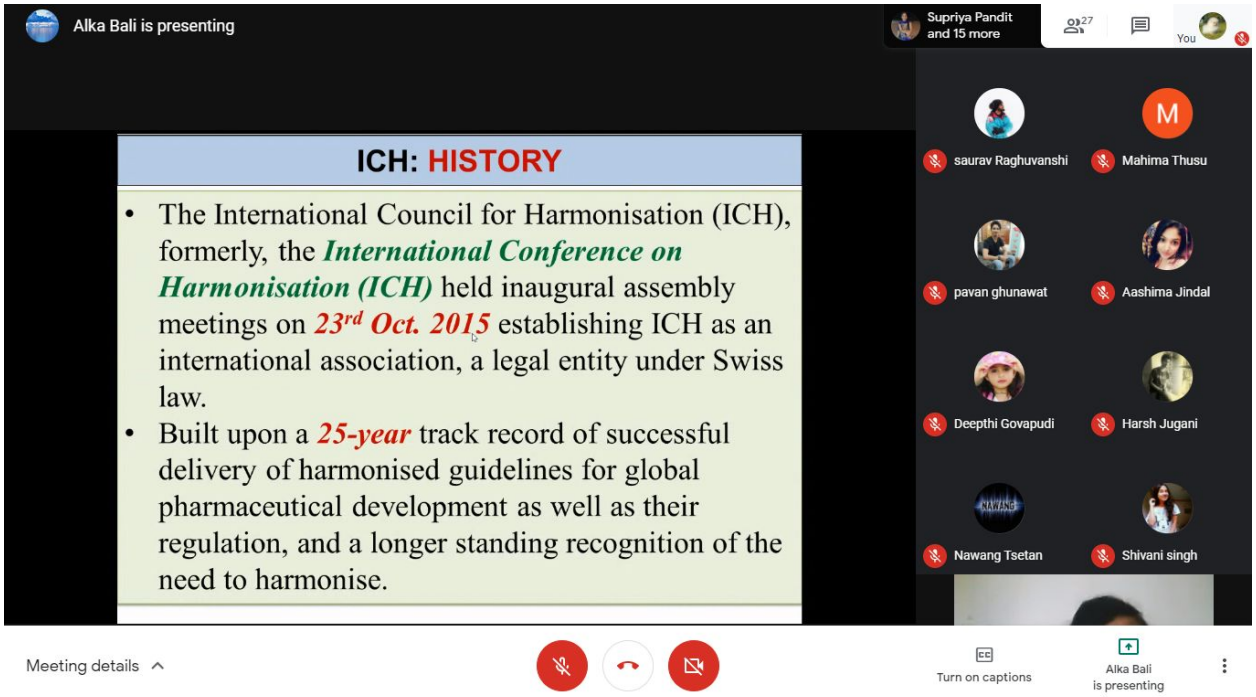

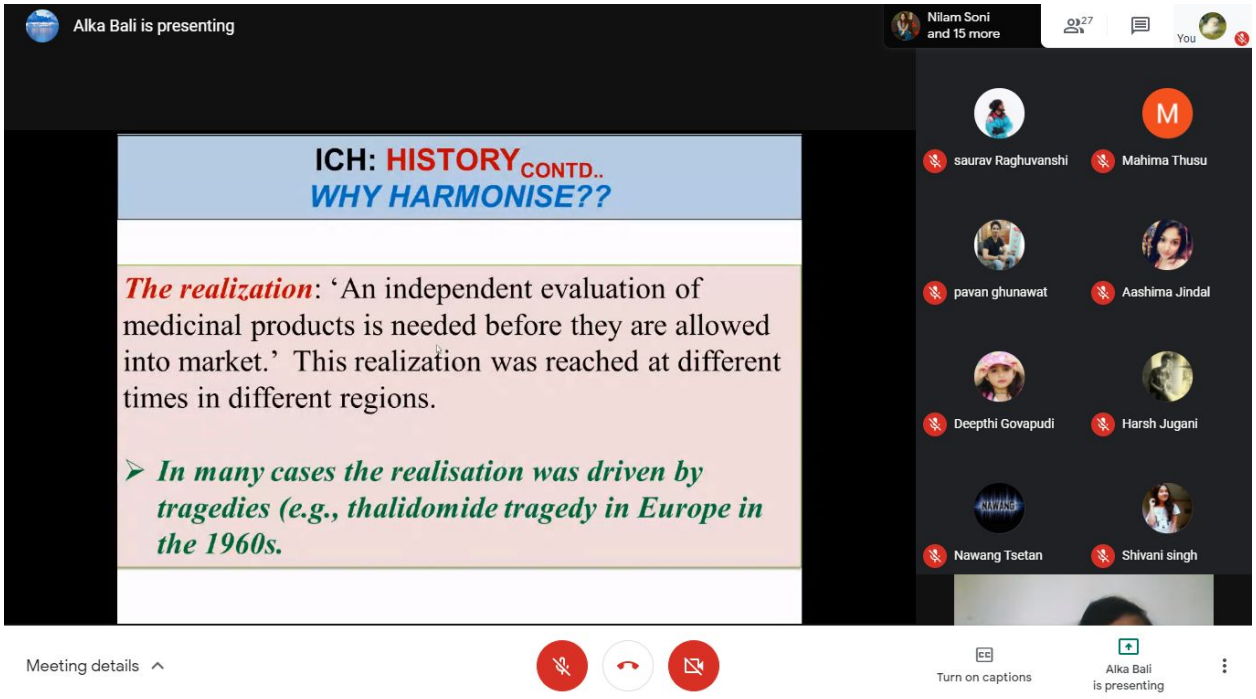

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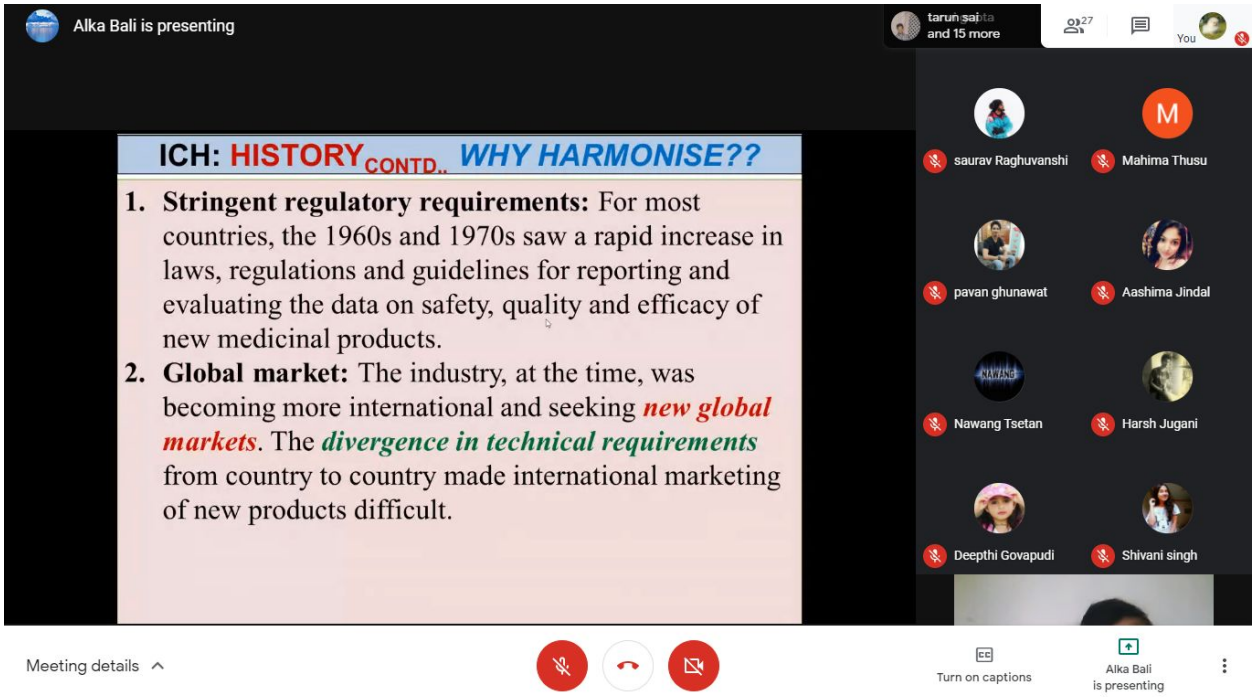

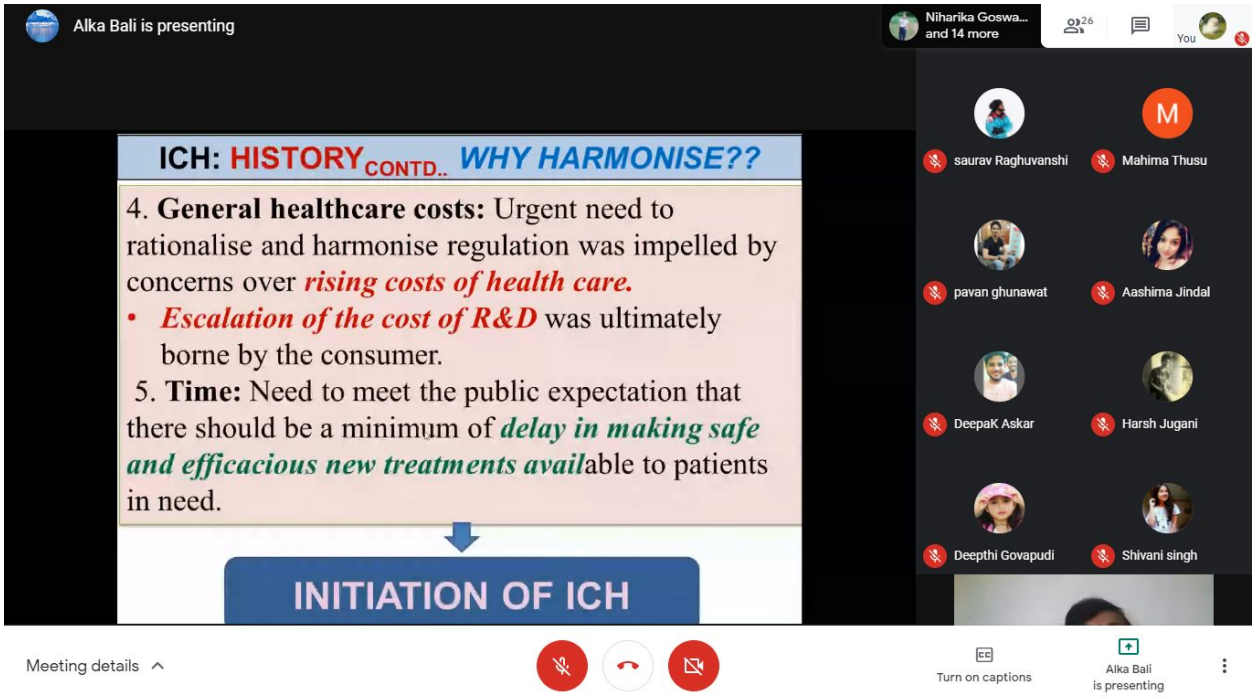

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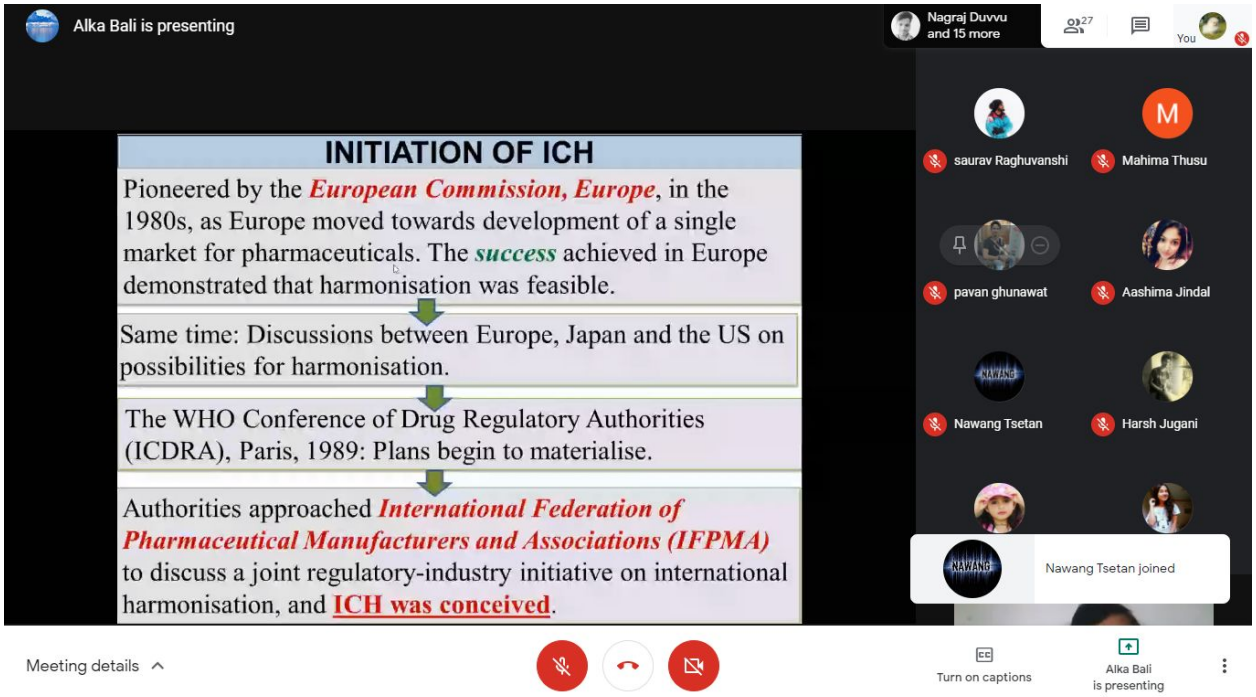

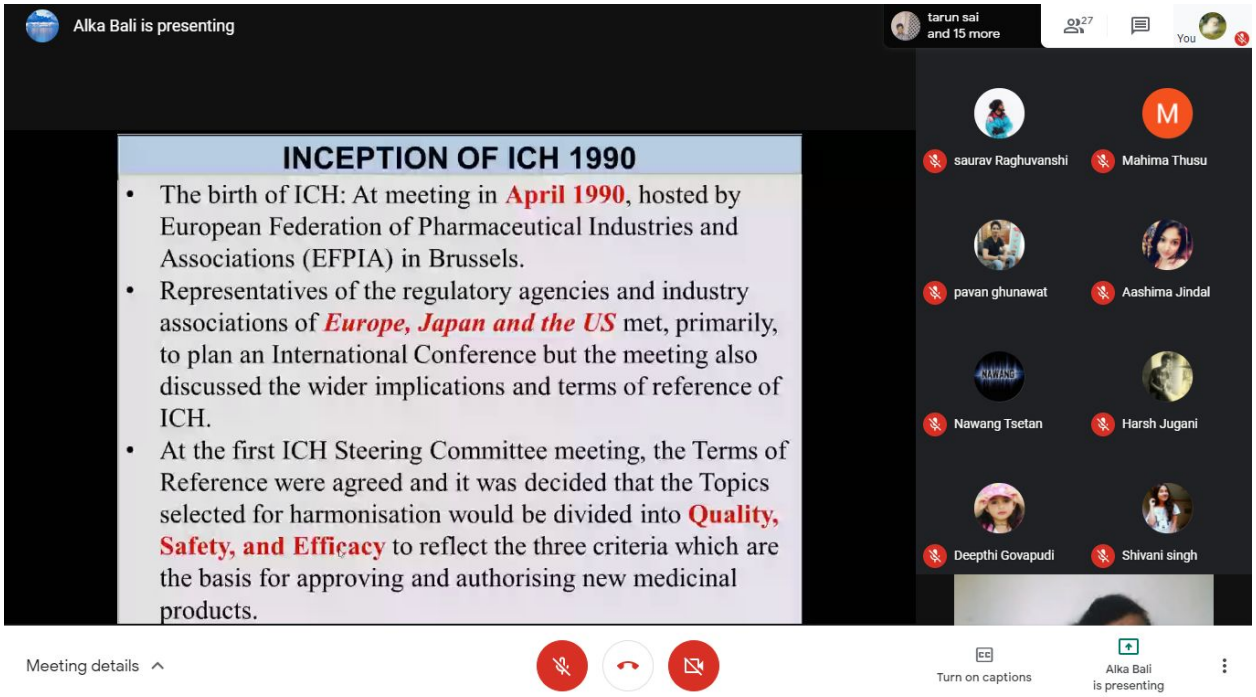

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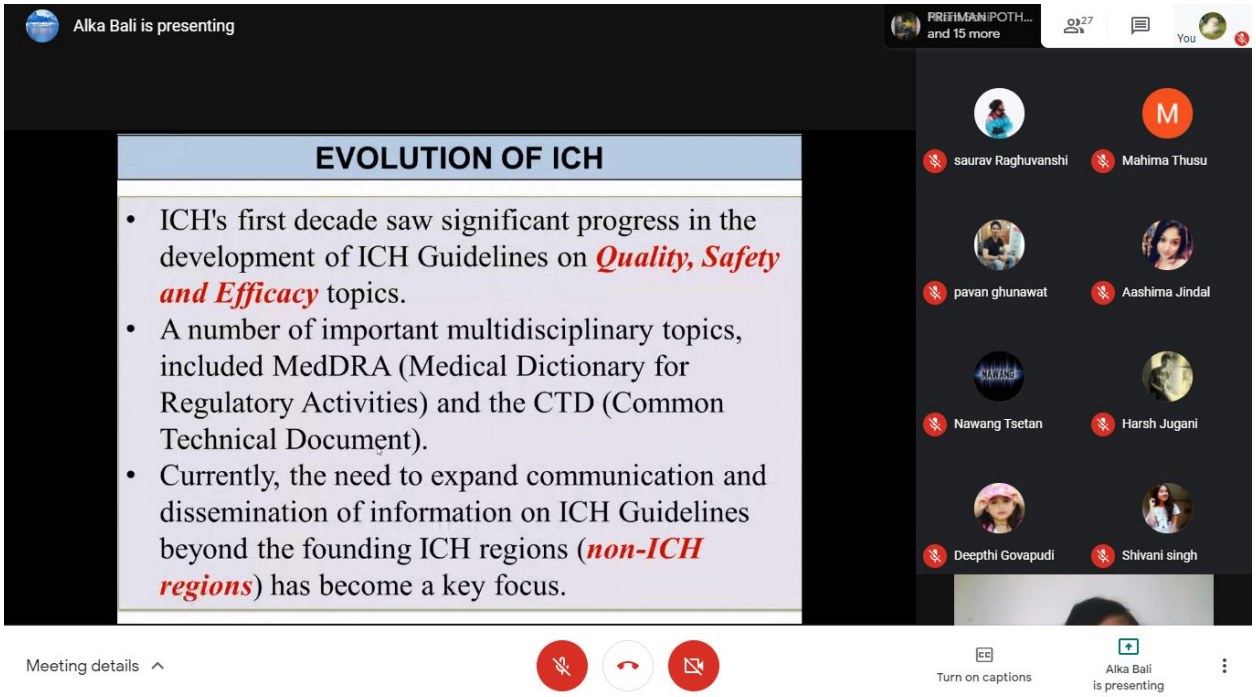

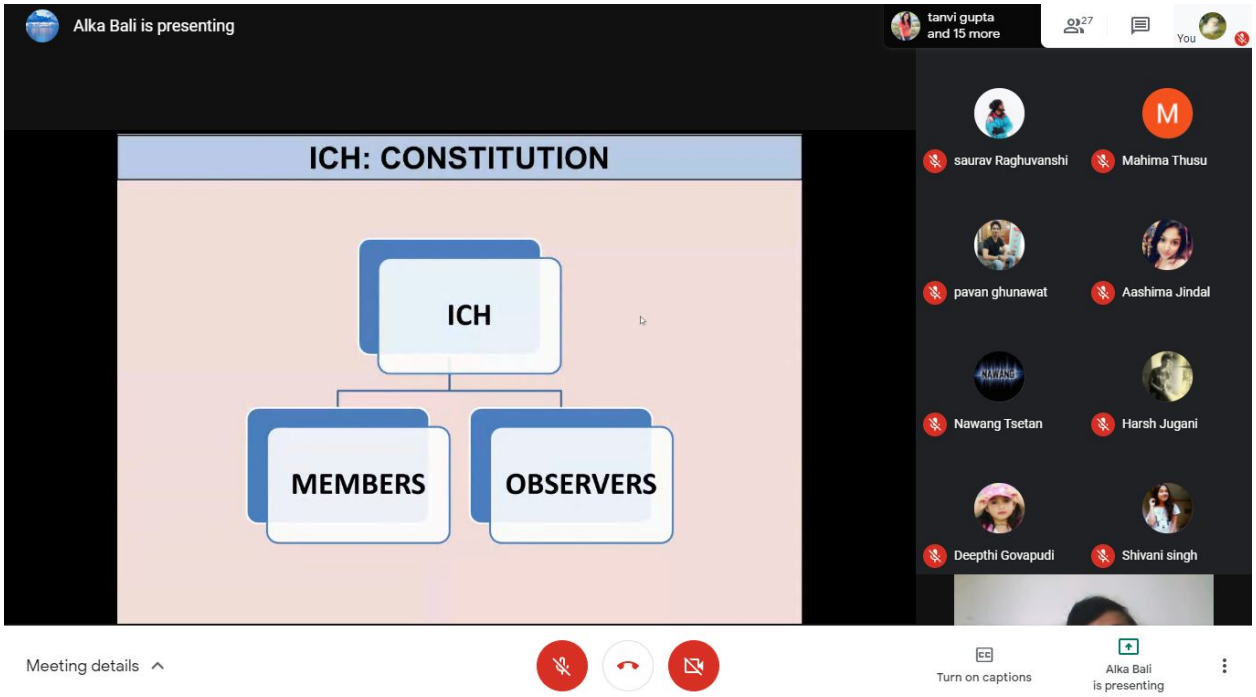

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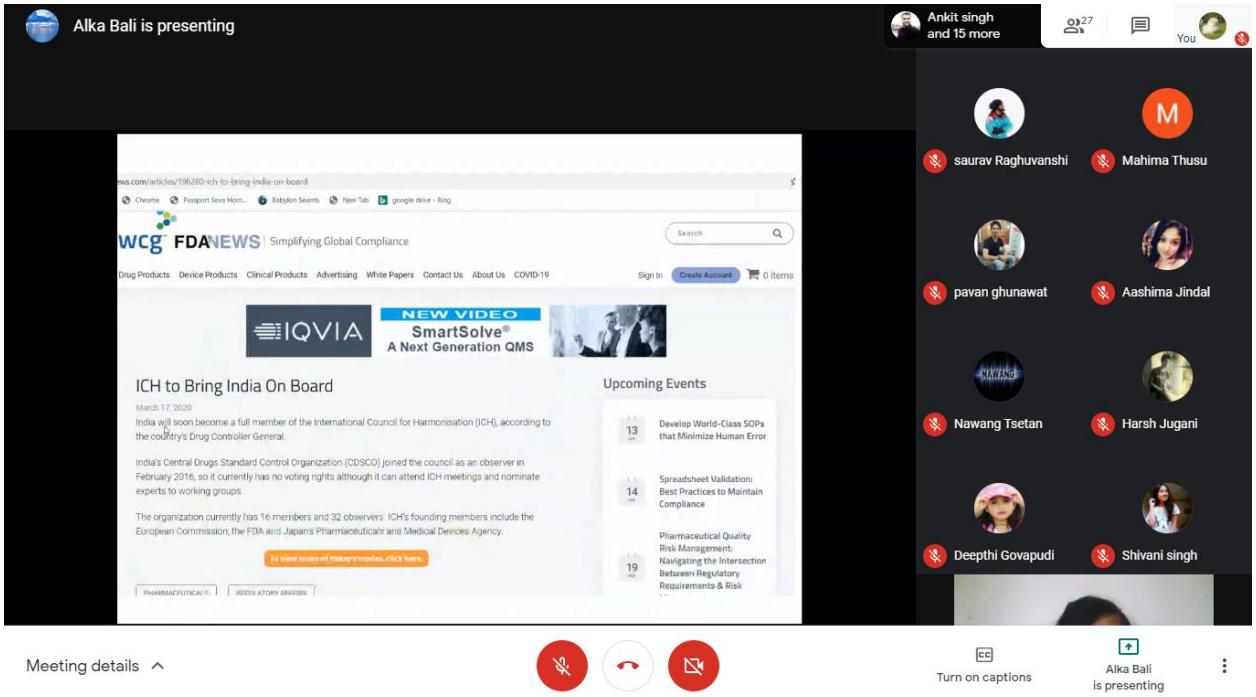

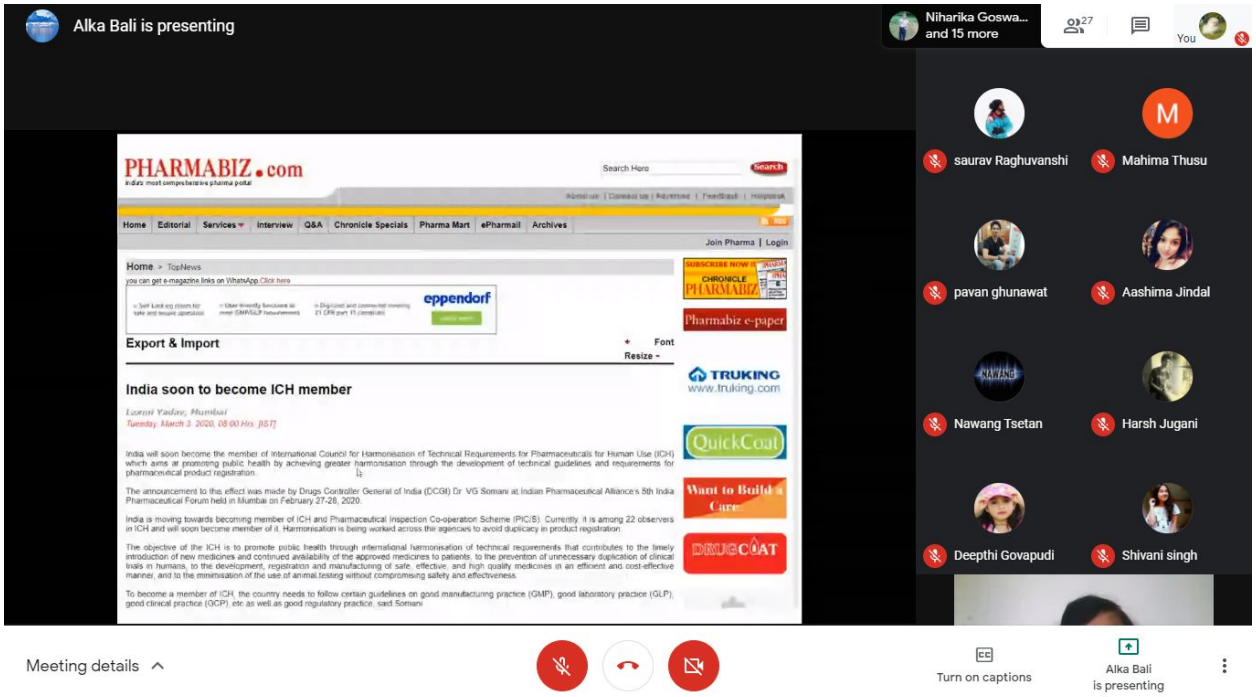

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PROCESS OF HARMONIZATION

Process of Harmonisation / Work Products /

ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure, depending on the activity to be undertaken (see below).

New topic for harmonisation of ICH?	Formal ICH Procedure	Concept Paper & Business Plan required
Clarification needed for an existing ICH Guideline?	Q&A Procedure	Concept Paper required (Business Plan may be required in certain cases)
Content of an existing ICH Guideline out of date or no longer valid? / New information to be added to an existing ICH Guideline?	Revision Procedure	Concept Paper required
Change to be made to either Q3C Guideline or M2 Recommendations?	Maintenance Procedure	Proposal/Concept Paper required for Q3C maintenance. No Concept Paper required for M2 Recommendations maintenance

Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required. The Business Plan outlines the costs and benefits of harmonising the topic proposed by the Concept Paper.

Meeting details

A. Formal ICH Procedure

- Step-wise procedure consisting of FIVE steps.
- Followed for harmonisation of all ***new ICH topics***.
- Initiated with the endorsement by the ICH Assembly of a ***Concept Paper*** and ***Business Plan***. An ***Expert Working Group*** (EWG) is subsequently established.

The EWG works to develop a draft Guideline and bring it through the various steps which culminate in *Step 5* and the implementation in the ICH regions of a ***Harmonised Guideline***.

Meeting details

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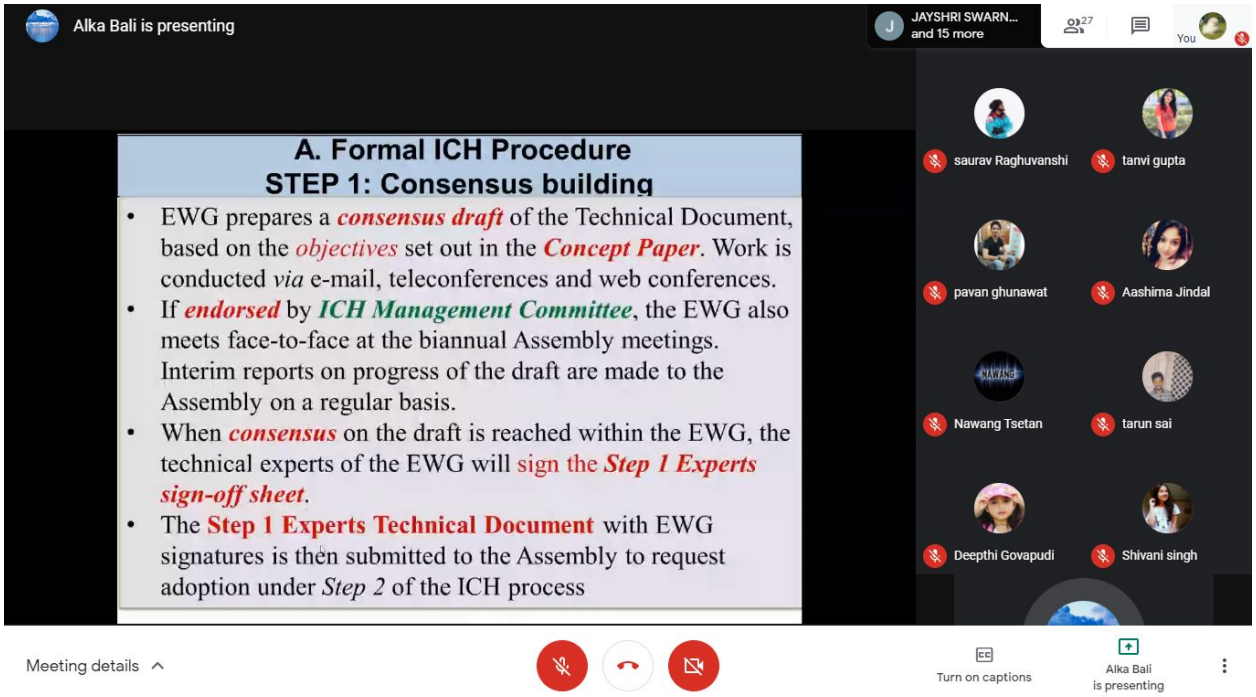

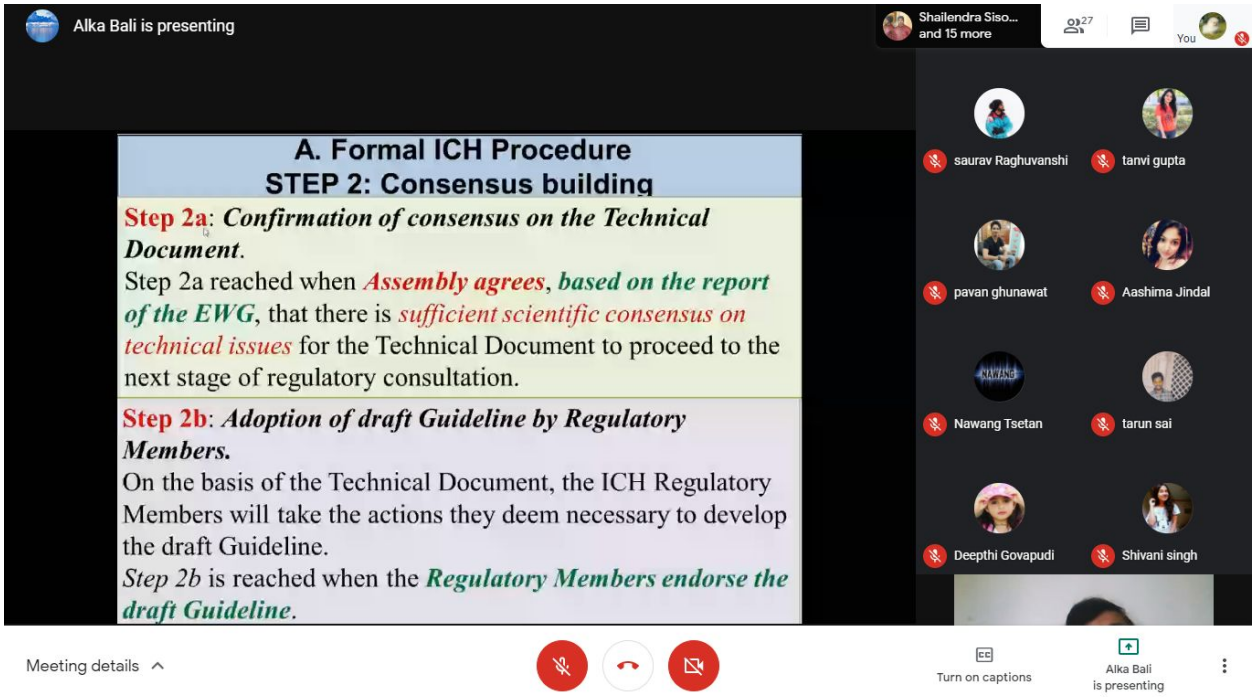

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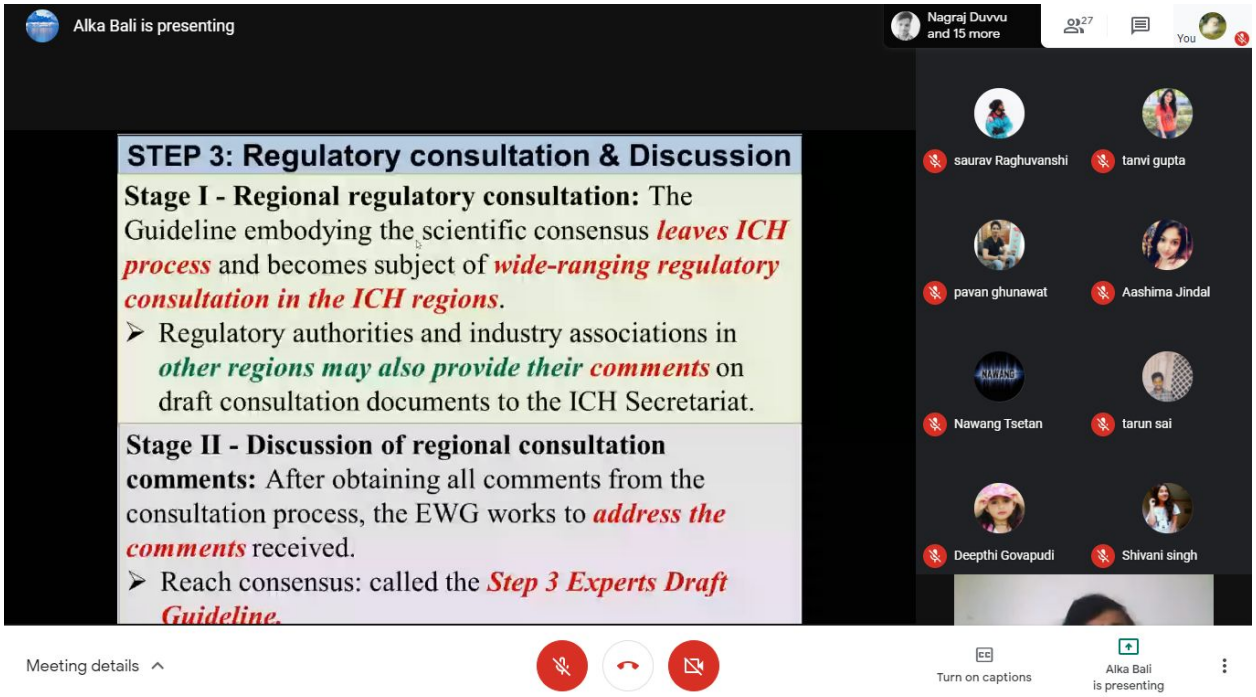

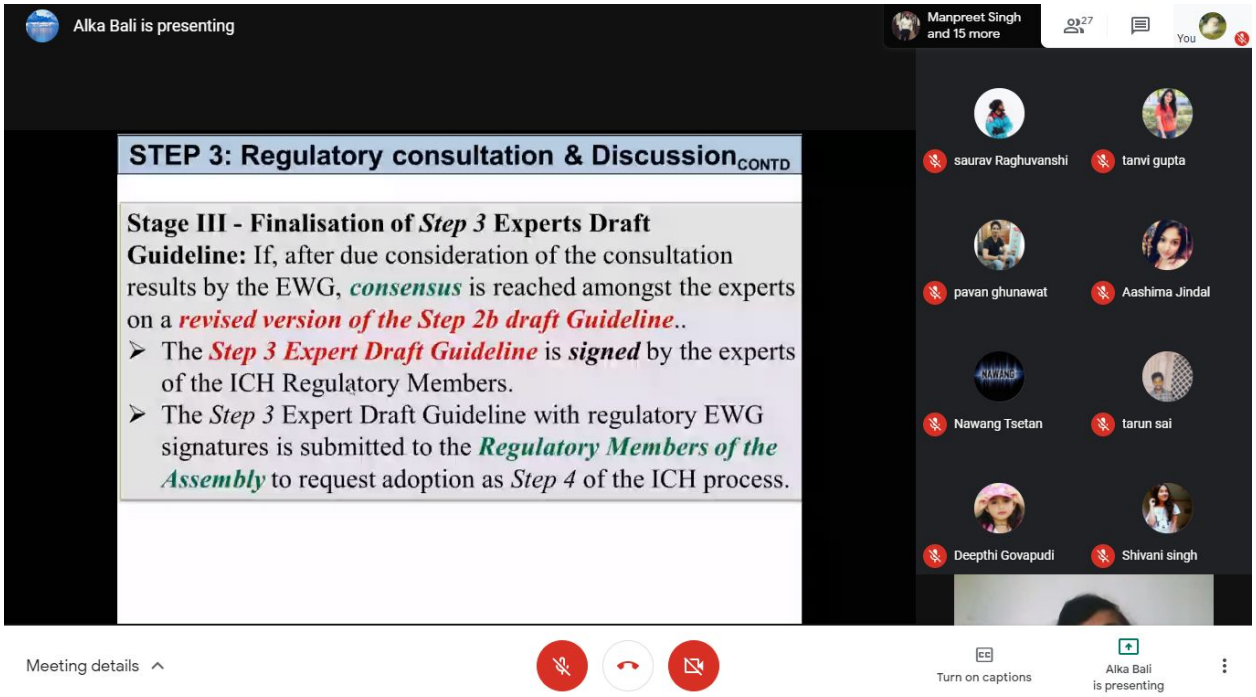

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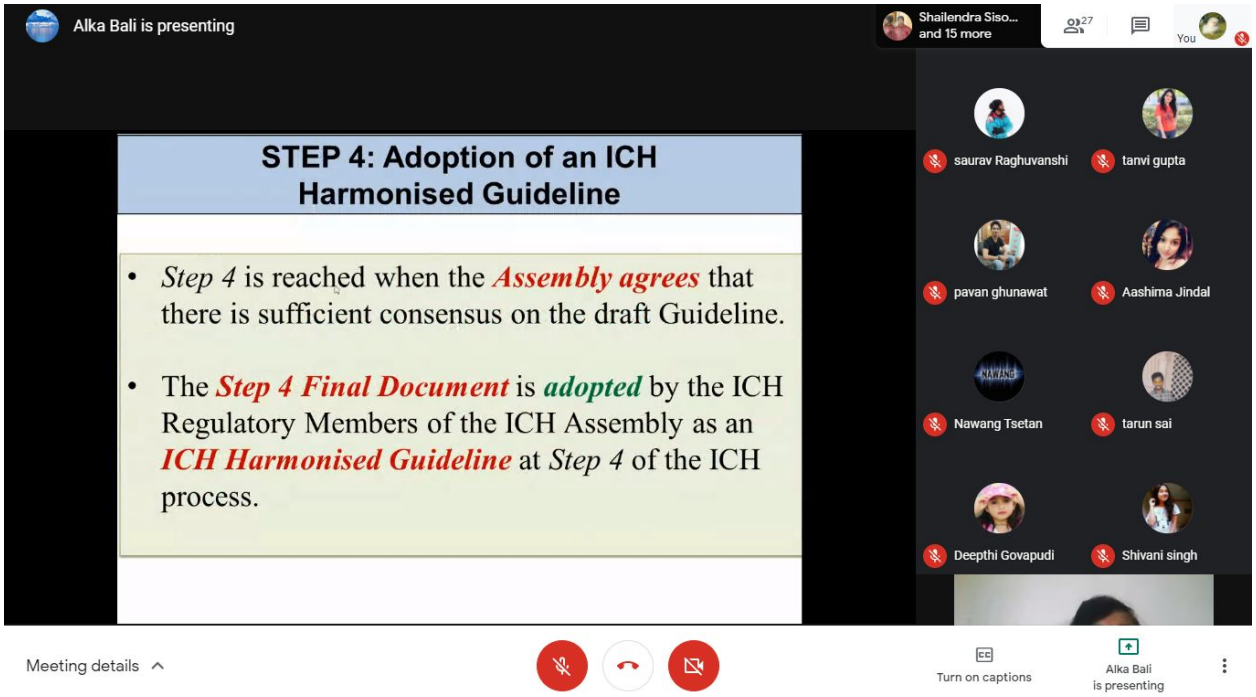

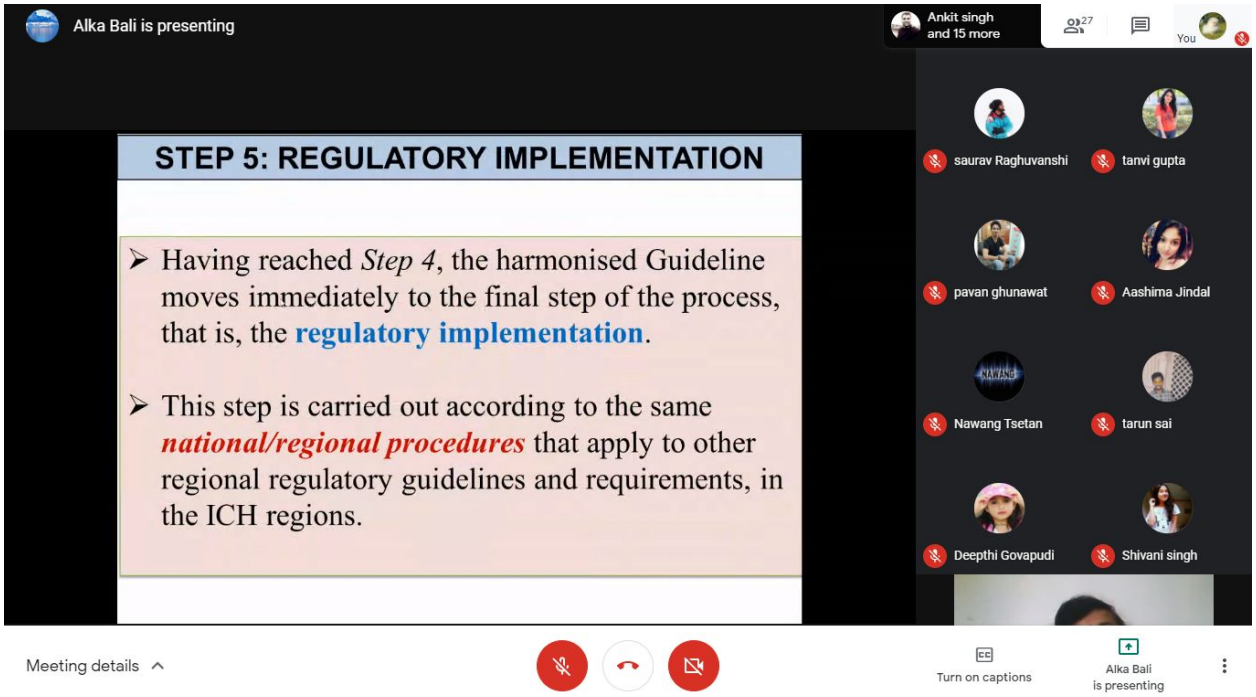

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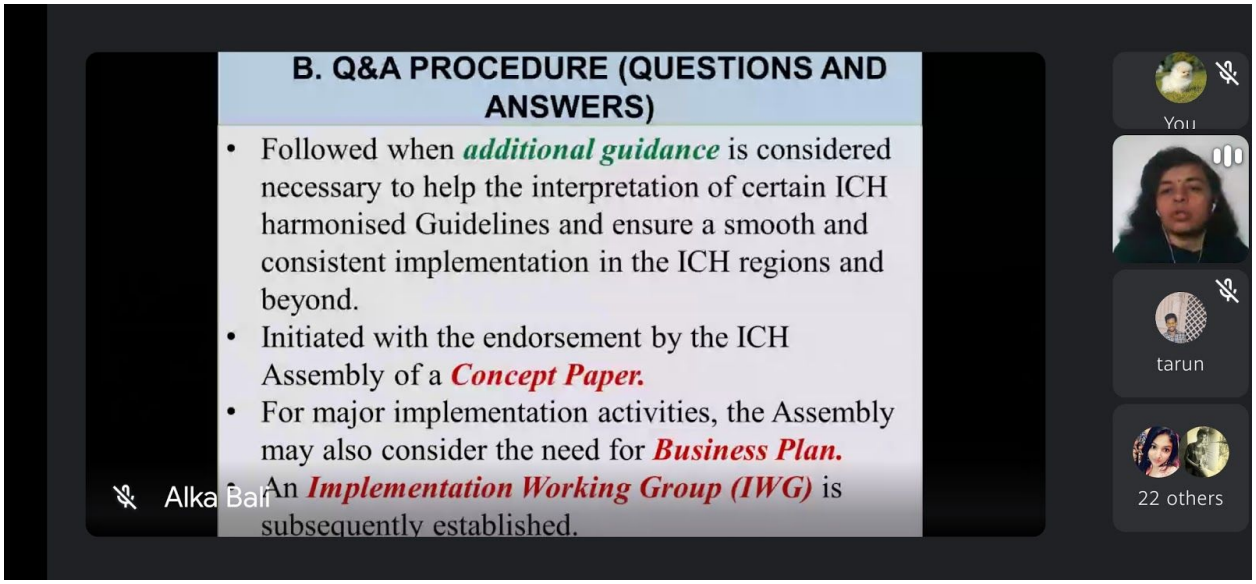

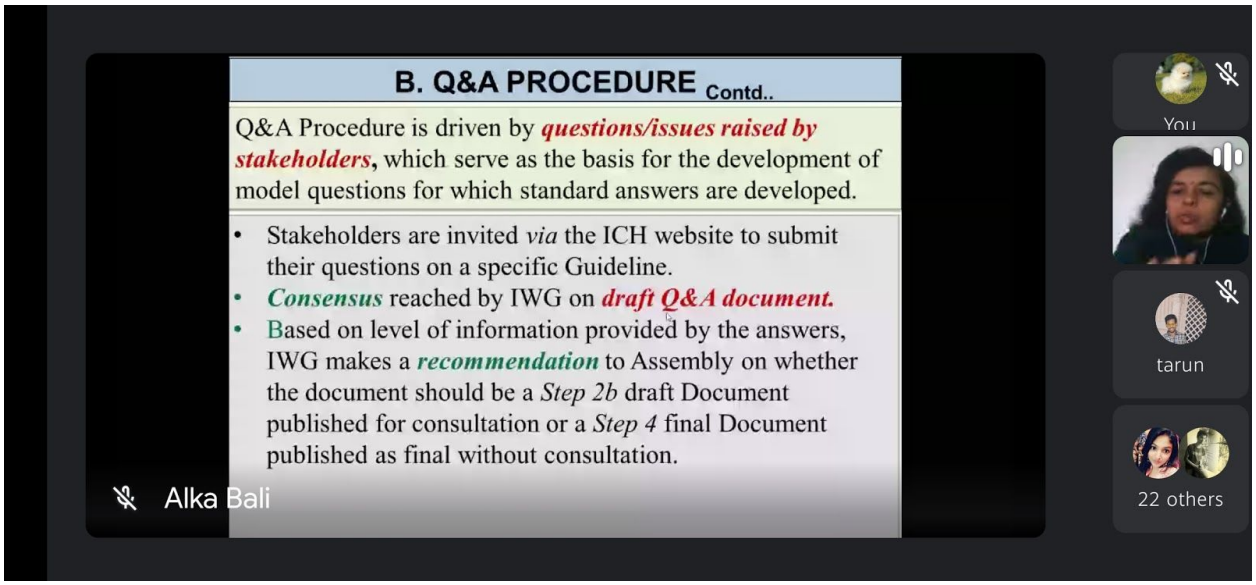

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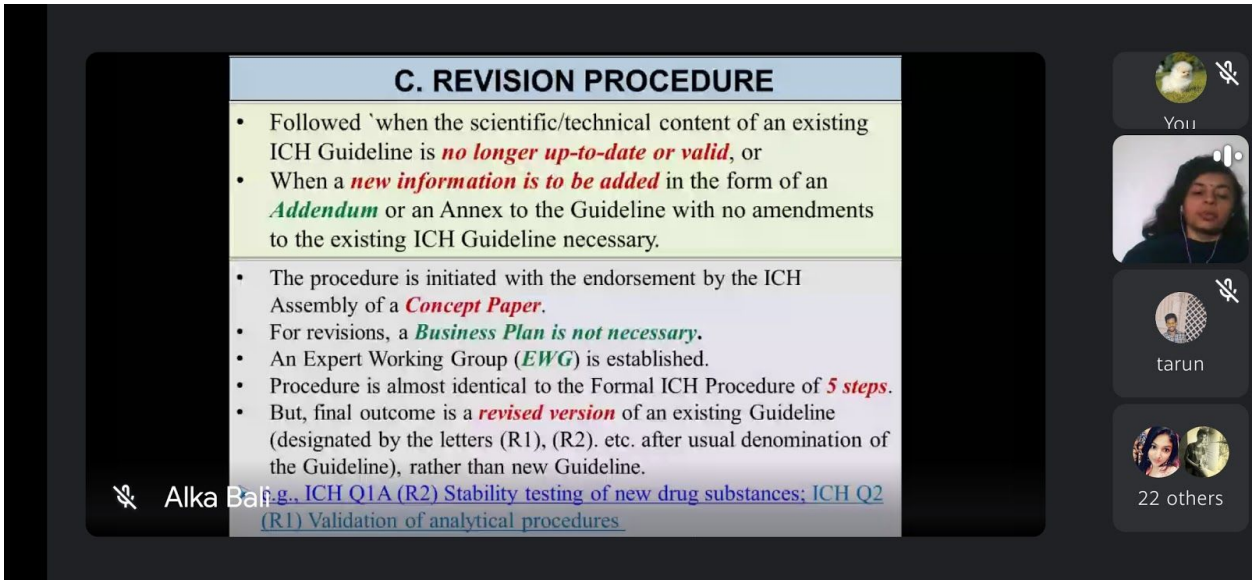

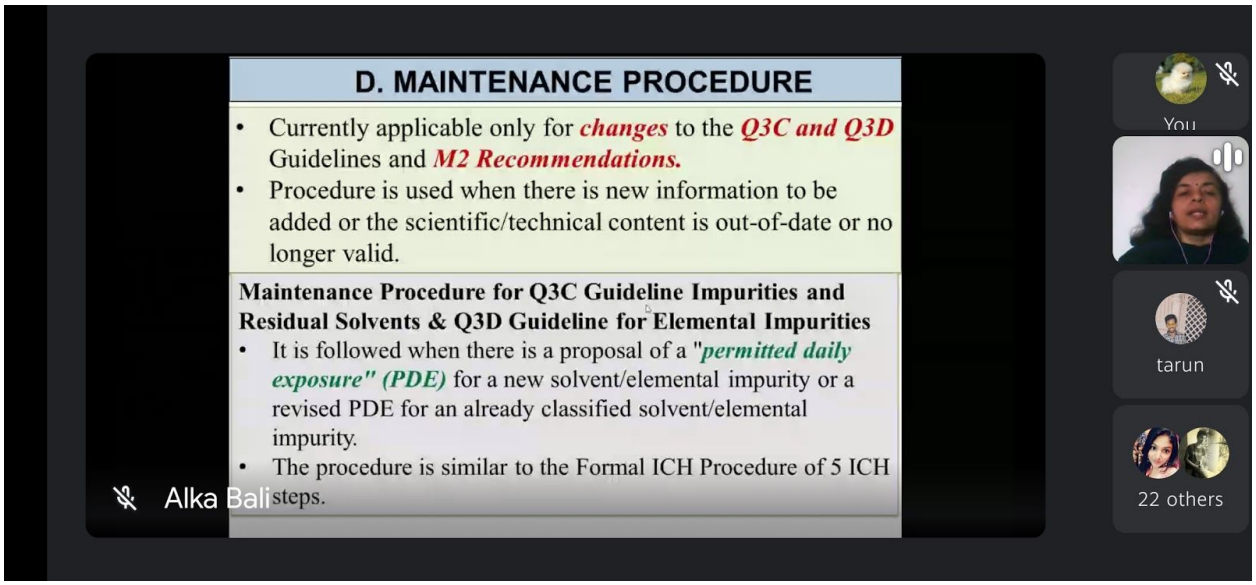

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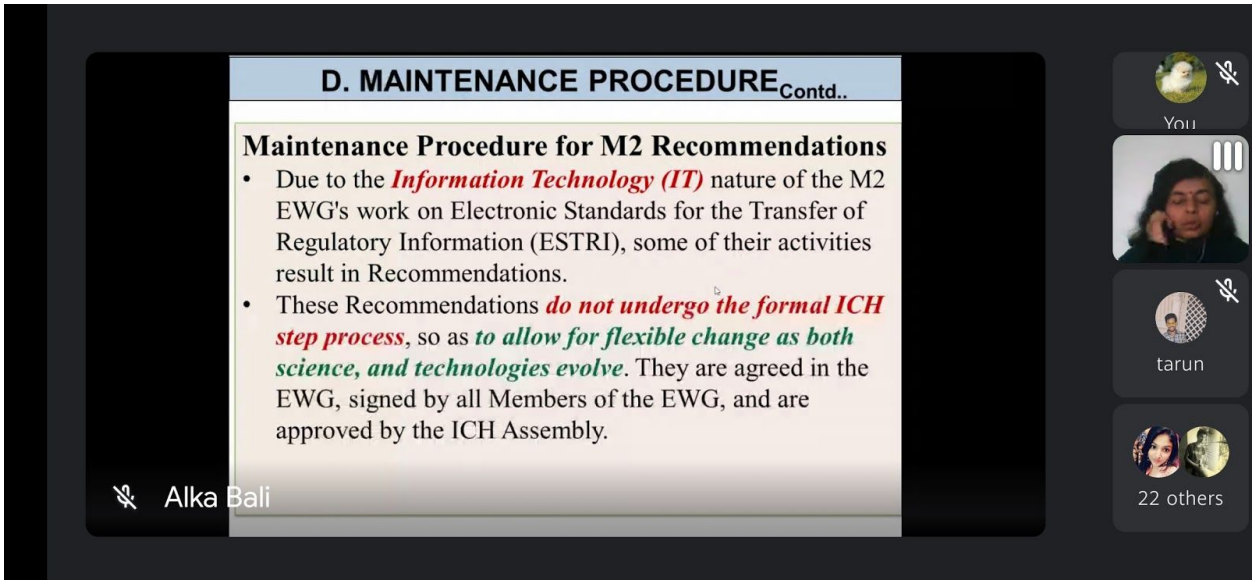

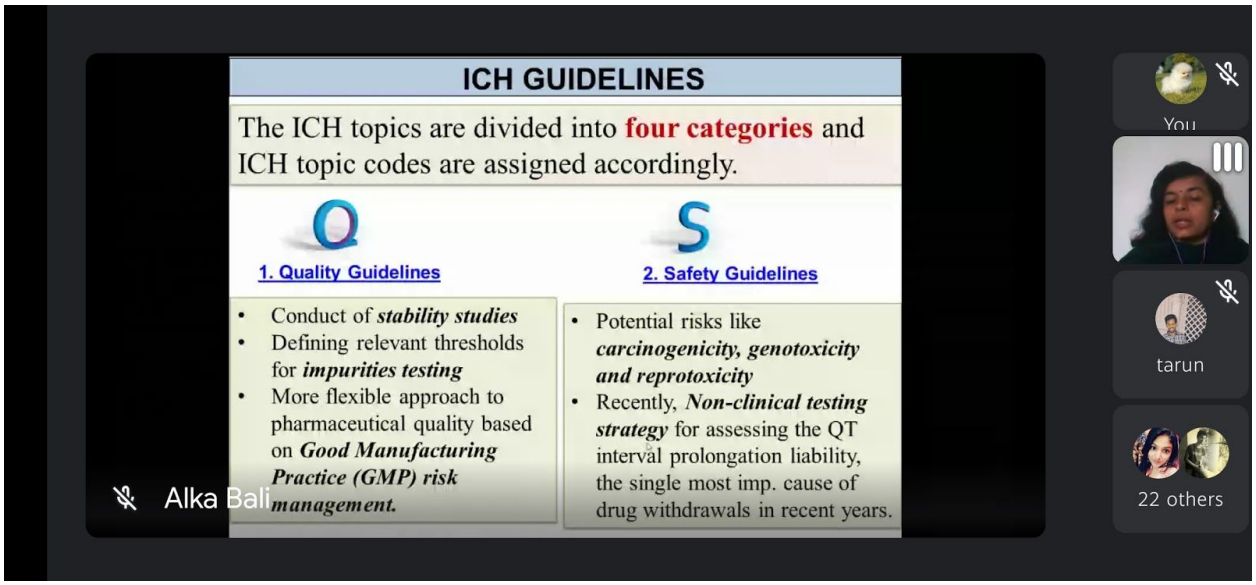

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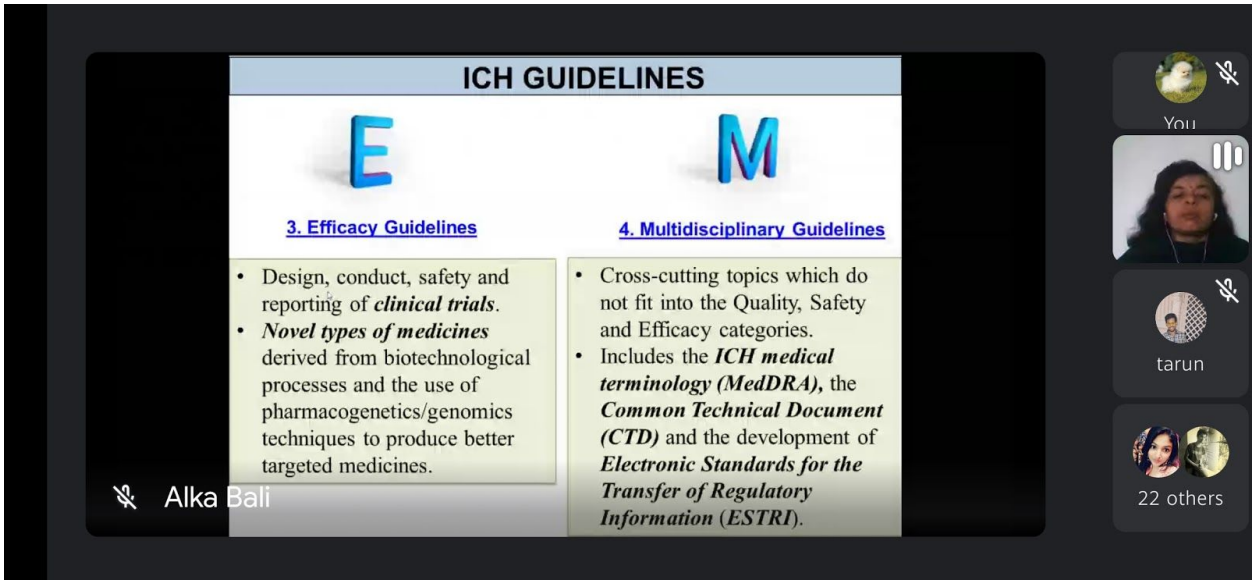

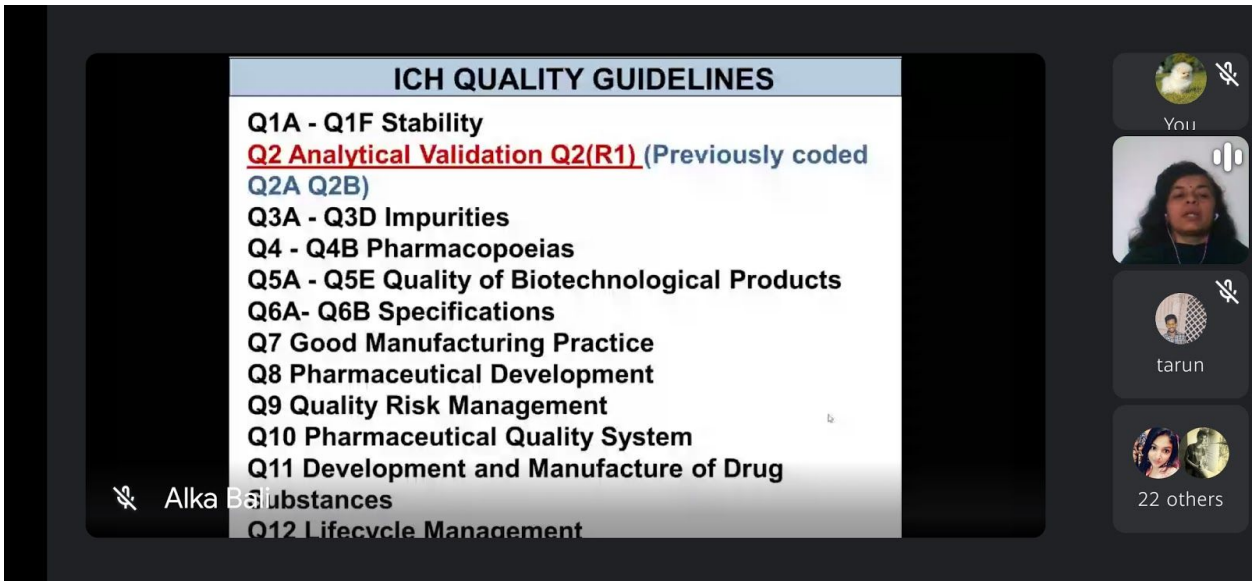

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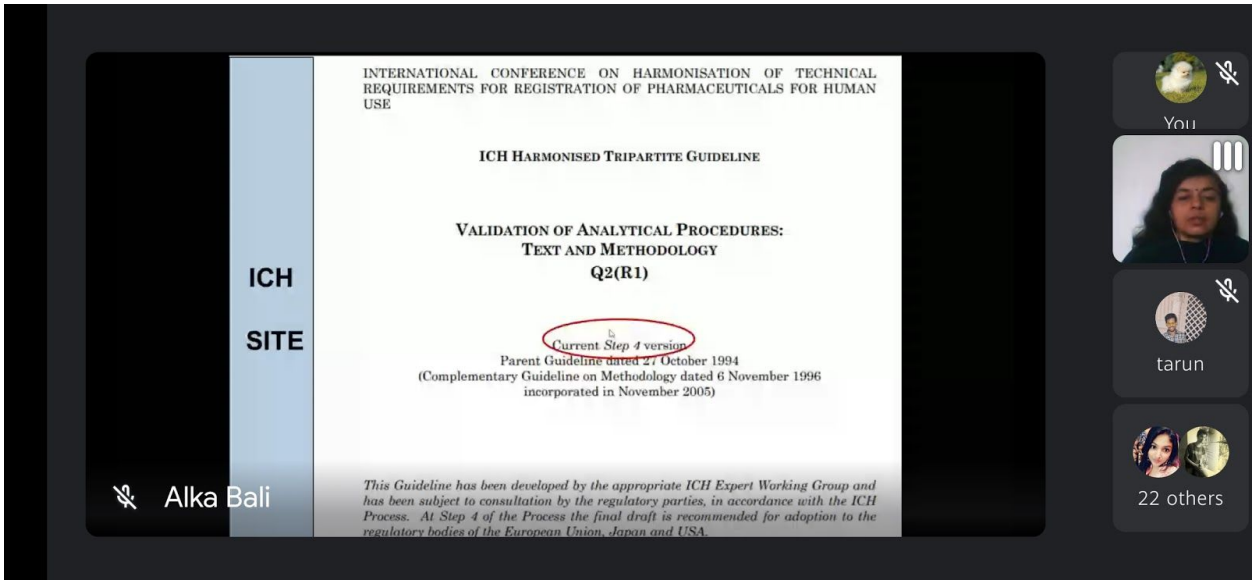

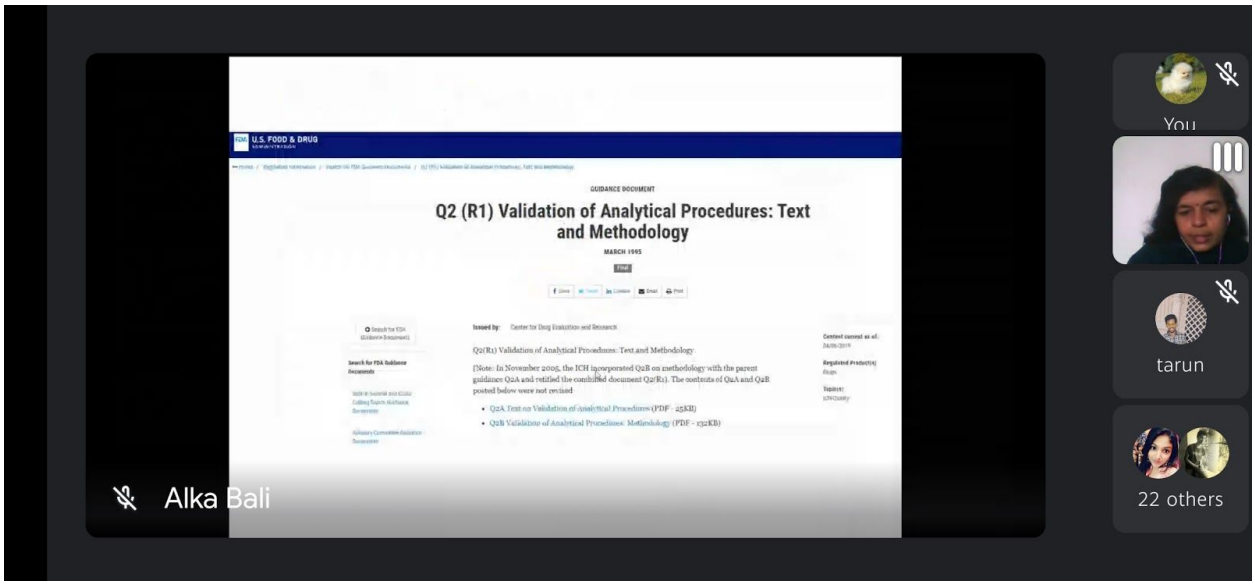

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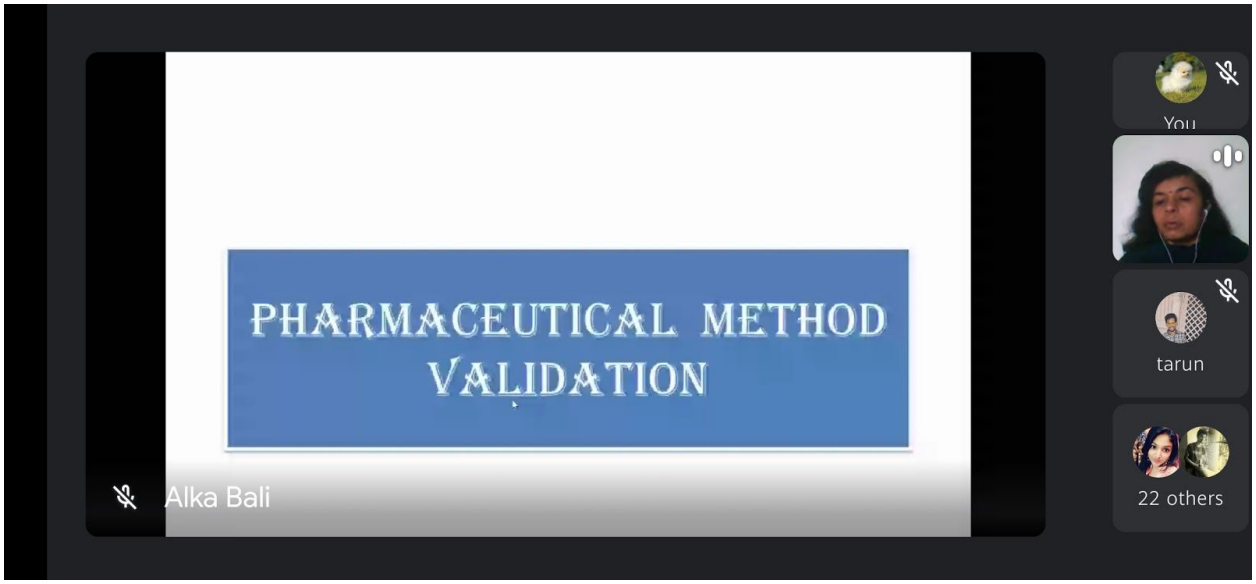

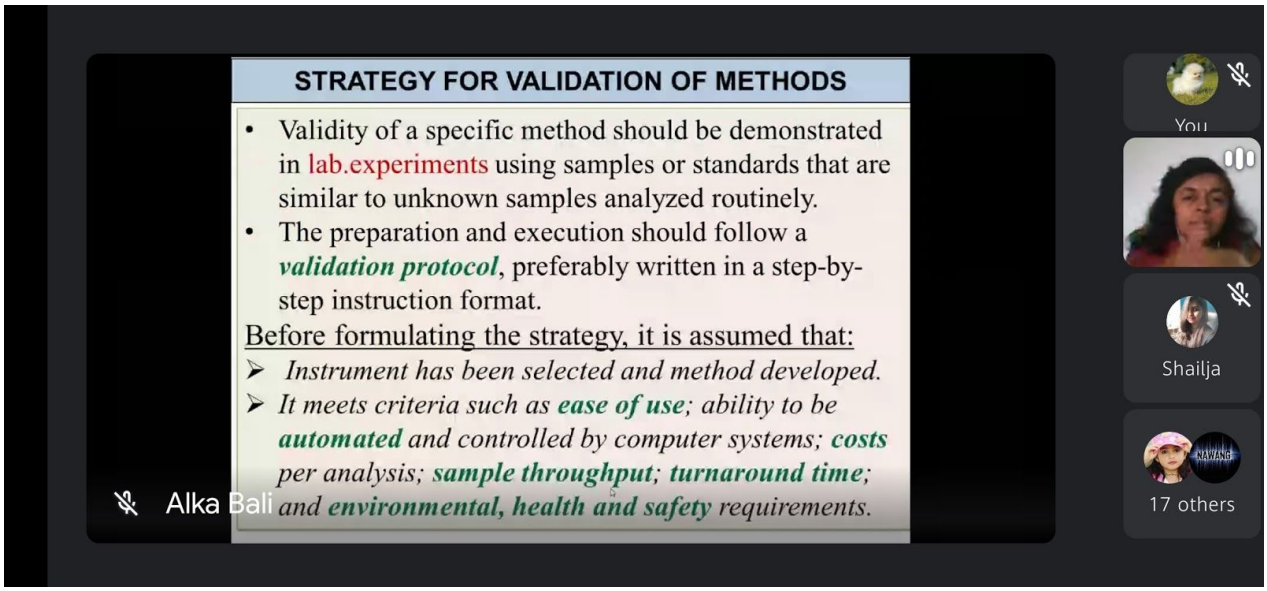

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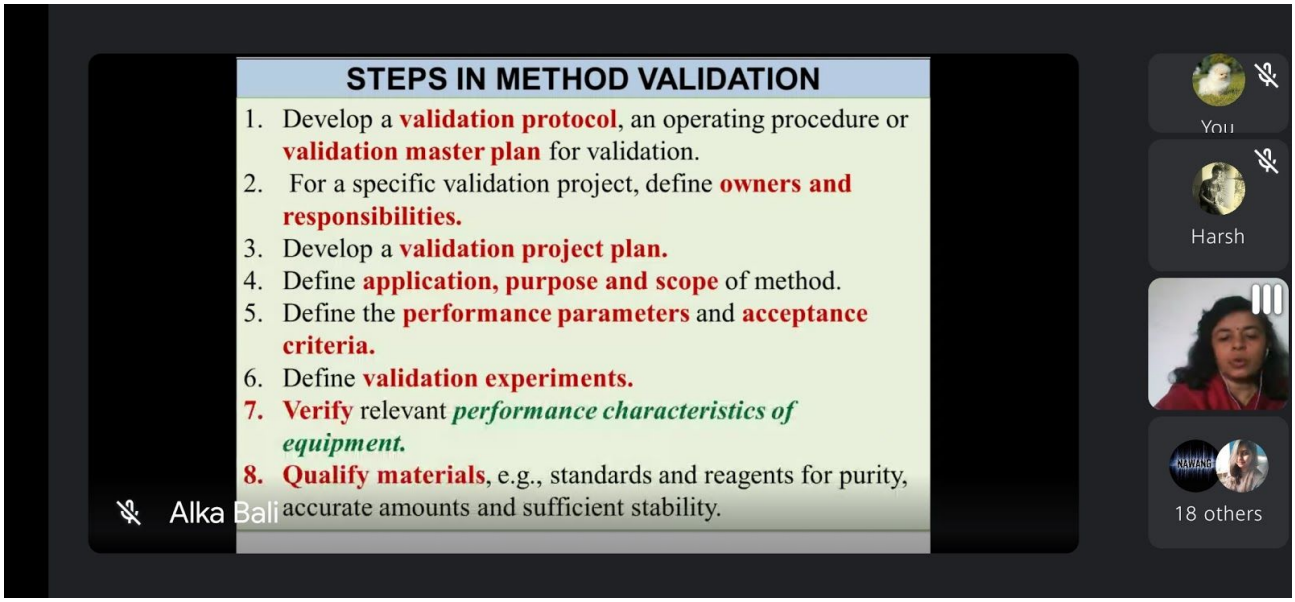

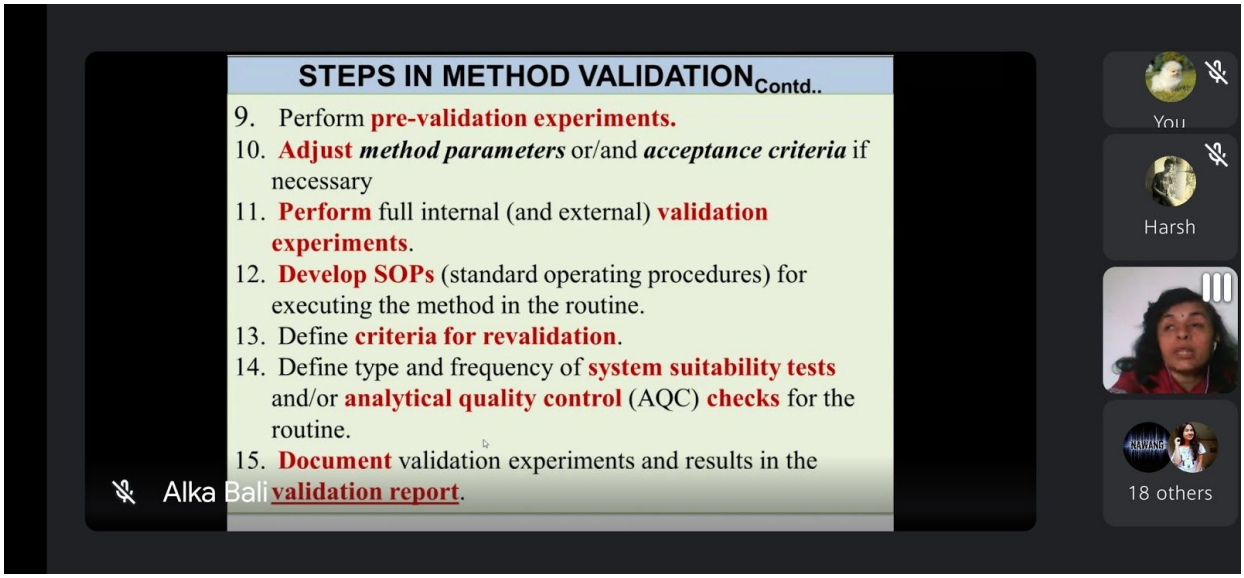

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Successful acceptance of the validation parameters and performance criteria, by all parties involved, requires the ***cooperative efforts*** of several departments, including:

Analytical development, QC, regulatory affairs and the individuals requiring the analytical data.

- ***The operating procedure or the Validation Master Plan (VMP) should clearly define the roles and responsibilities of each department involved in the validation of analytical methods.***

Bali

SCOPE OF METHOD & ITS VALIDATION CRITERIA

- ***Should be defined early in the process to answer the following questions..***

- What **analytes** should be detected?
- What are the expected **concentration levels**?
- What are the **sample matrices**?
- Are there **interfering substances** expected, and, if so, should they be detected and quantified?
- Are there any specific legislative or **regulatory requirements**?
- Should information be **qualitative or quantitative**?
- What are the required **detection** and **quantitation limits?**

Alka Bali

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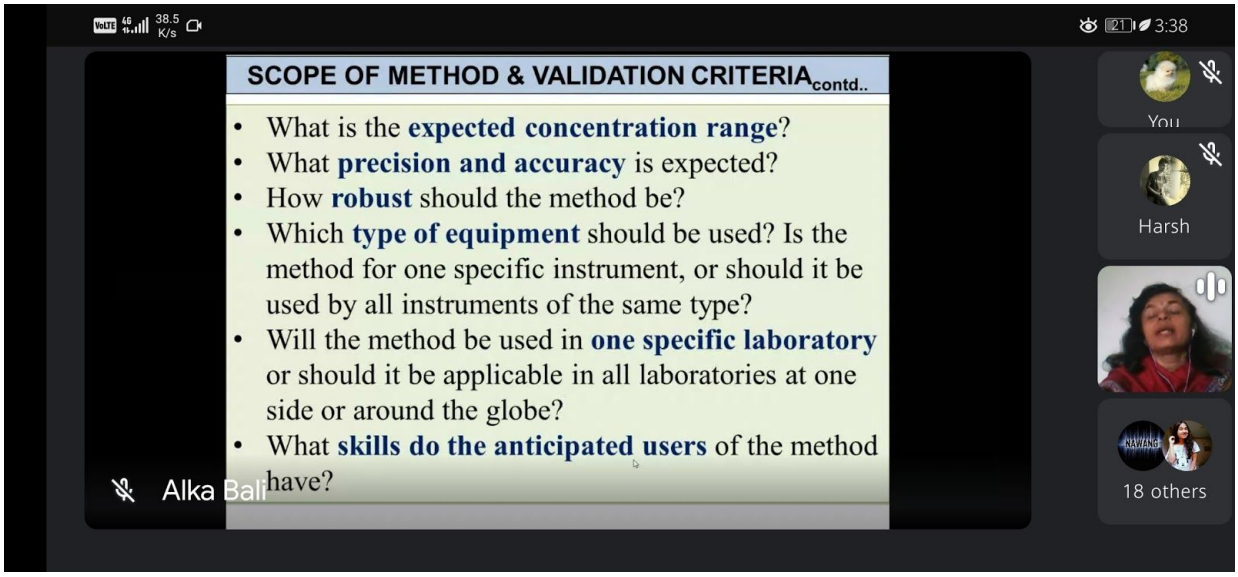

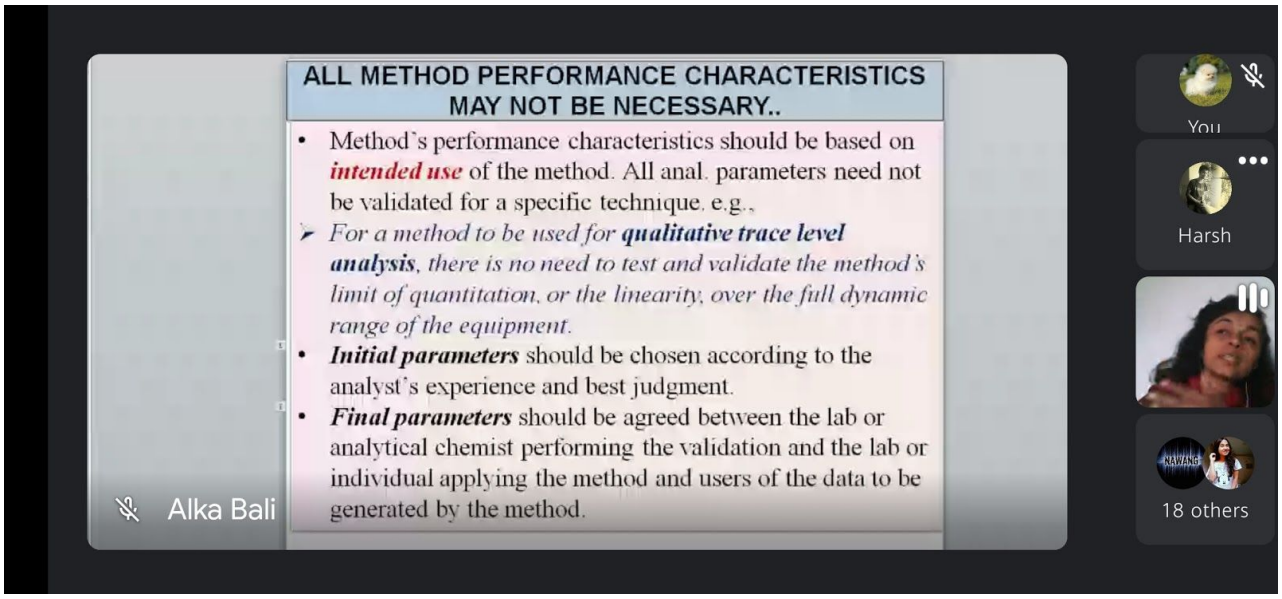

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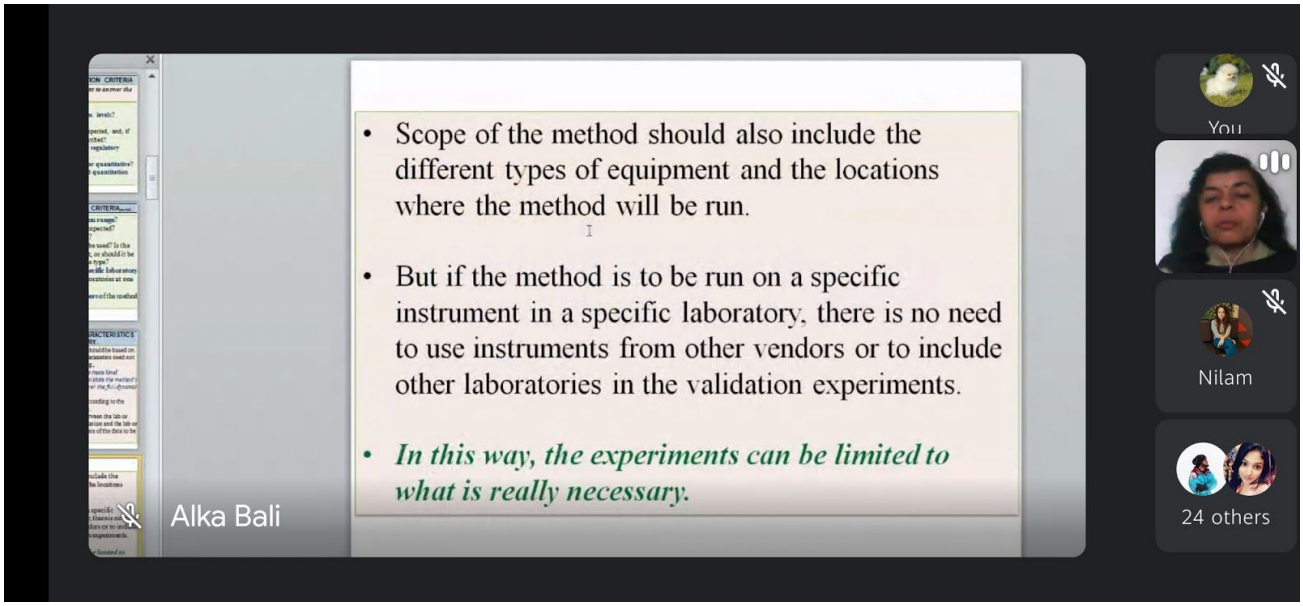

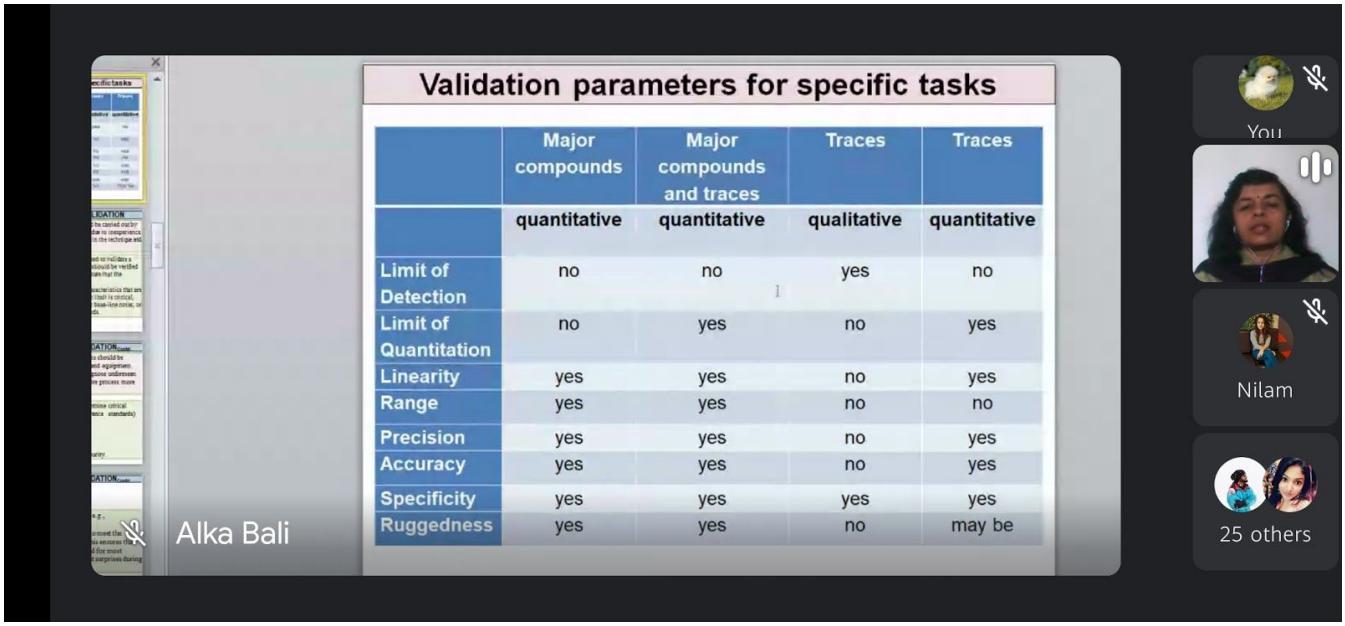

	Major compounds	Major compounds and traces	Traces	Traces
	quantitative	quantitative	qualitative	quantitative
Limit of Detection	no	no	yes	no
Limit of Quantitation	no	yes	no	yes
Linearity	yes	yes	no	yes
Range	yes	yes	no	no
Precision	yes	yes	no	yes
Accuracy	yes	yes	no	yes
Specificity	yes	yes	yes	yes
Ruggedness	yes	yes	no	may be

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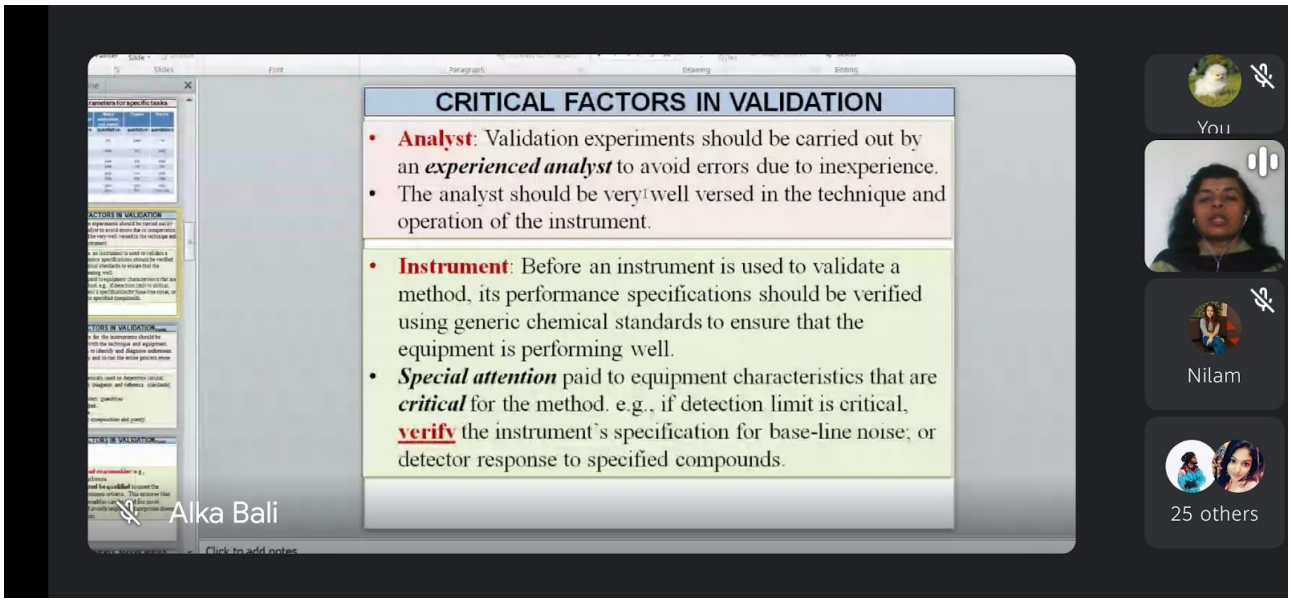

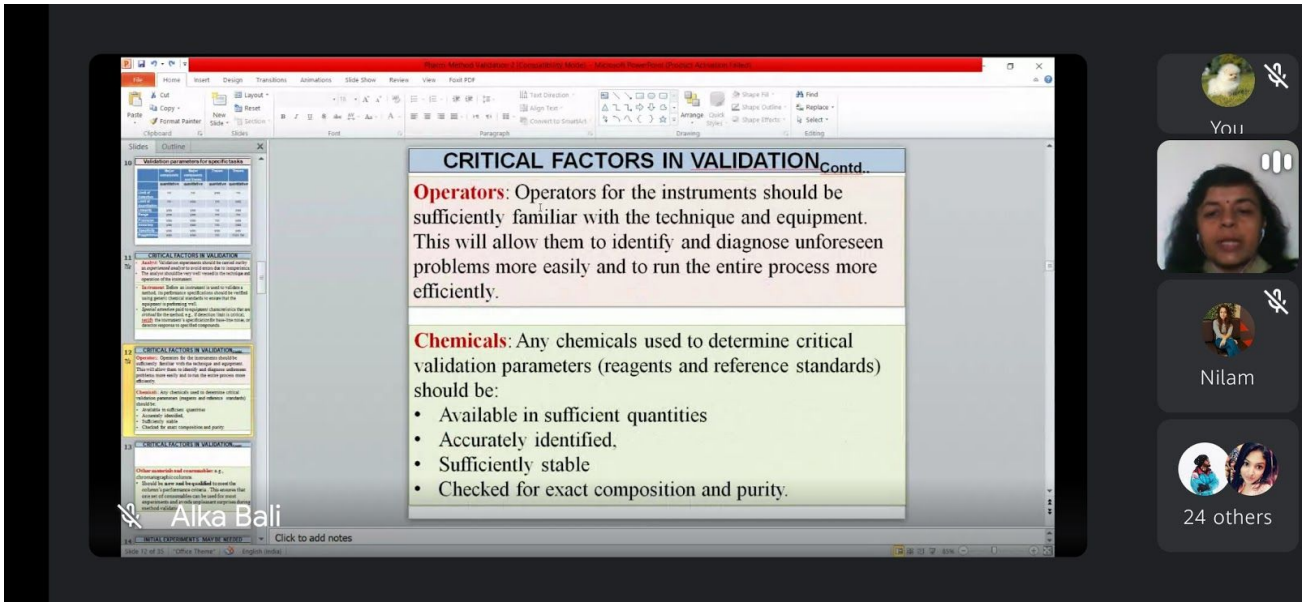

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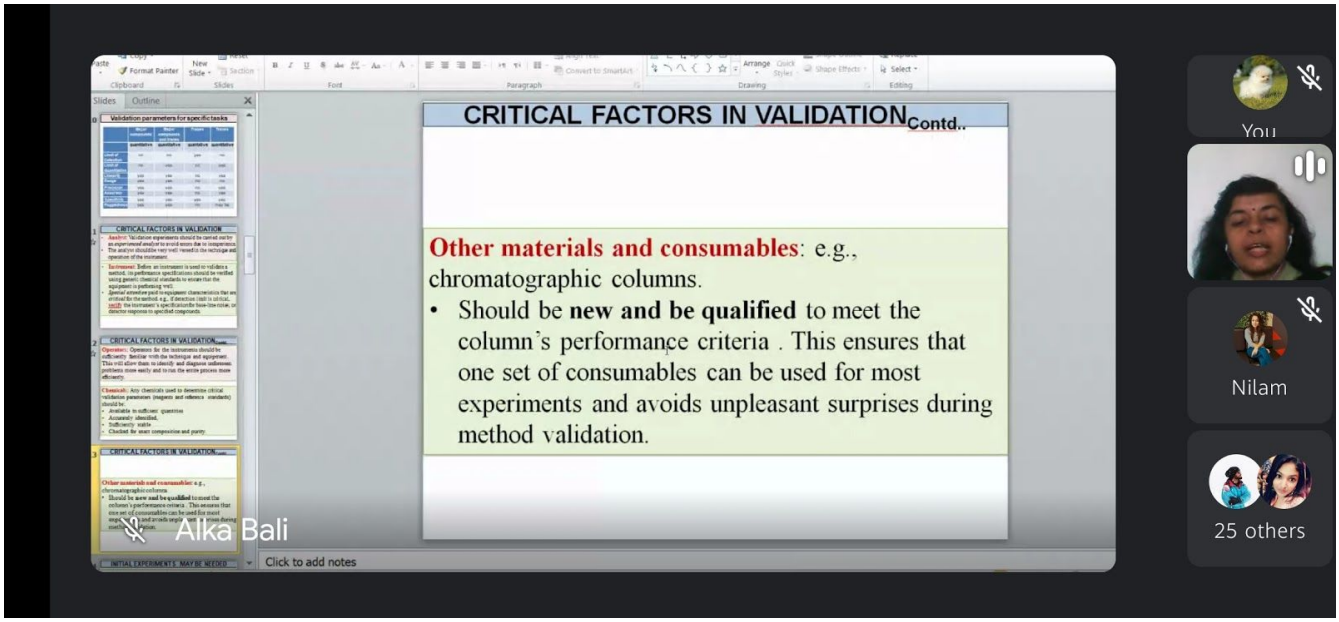

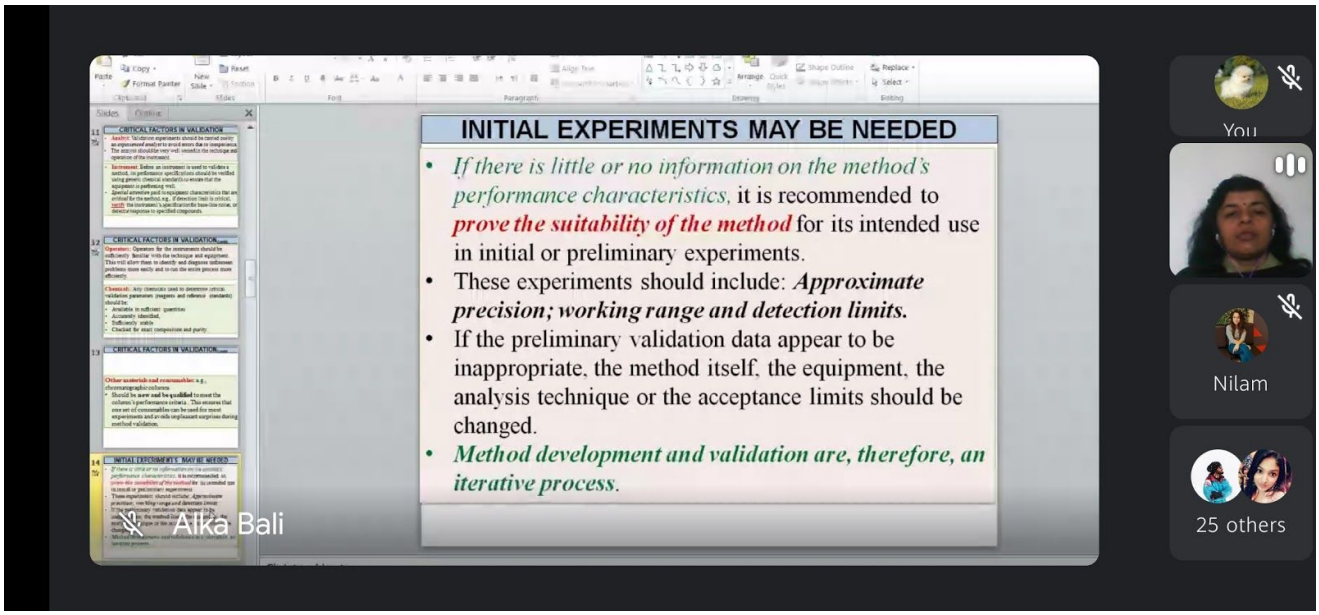

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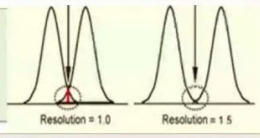
PRELIMINARY EXPERIMENTS: AN EXAMPLE

- For example, in **liquid chromatography**, selectivity is achieved through the selection of mobile phase composition. For quantitative measurements, the resolution factor R_s between two peaks should be **2.5 or higher.**

$R_s = 2\,(t_{R\,B} - t_{R\,A}) / (W_A + W_B)$

t_{RA} and t_{RB} are the retention times of the two peaks (peak A elutes first), and W_A and W_B are baseline widths of the peaks.



- If this value is not achieved, mobile phase composition *needs further optimization.*
- Influence of operating parameters on method performance should be assessed at this stage if not done during development and optimization of method.

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SEQUENCE OF VALIDATION

There are no official guidelines on the correct sequence of validation experiments and the optimal sequence may depend on the method itself.

e.g., In **LC method**, the following sequence can be useful:

1. **Selectivity** of standards (optimizing separation and detection of standard mixtures if selectivity is insuff.)
2. Linearity, limit of quantitation, limit of detection, range
3. **Repeatability** (short-term precision) of retention times and peak areas
4. **Intermediate precision**
5. **Selectivity** with real samples
6. Trueness/**accuracy** at different concentrations
7. **Ruggedness** (inter-laboratory studies)

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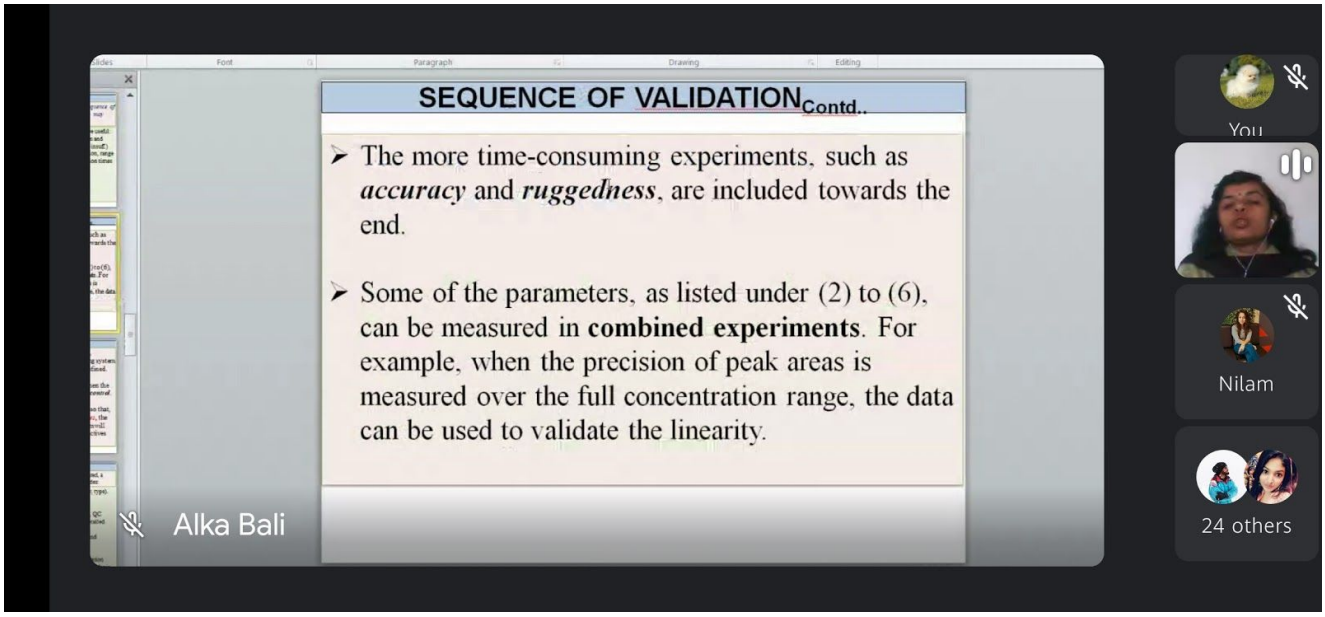

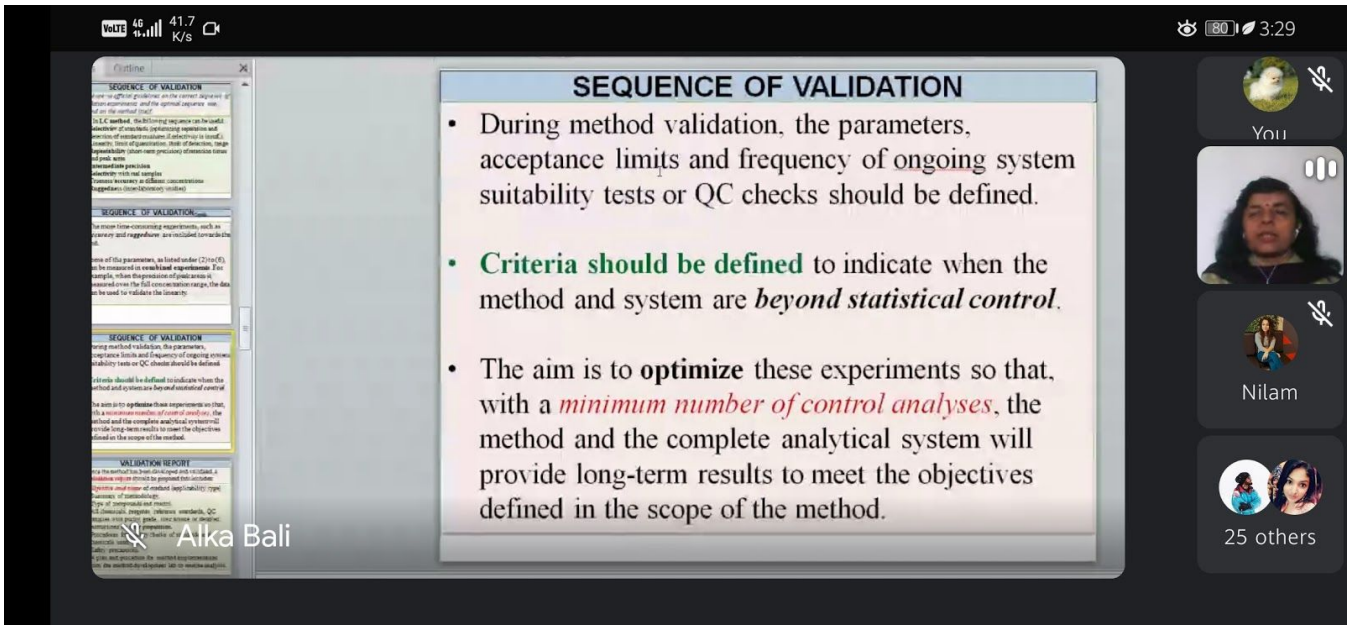

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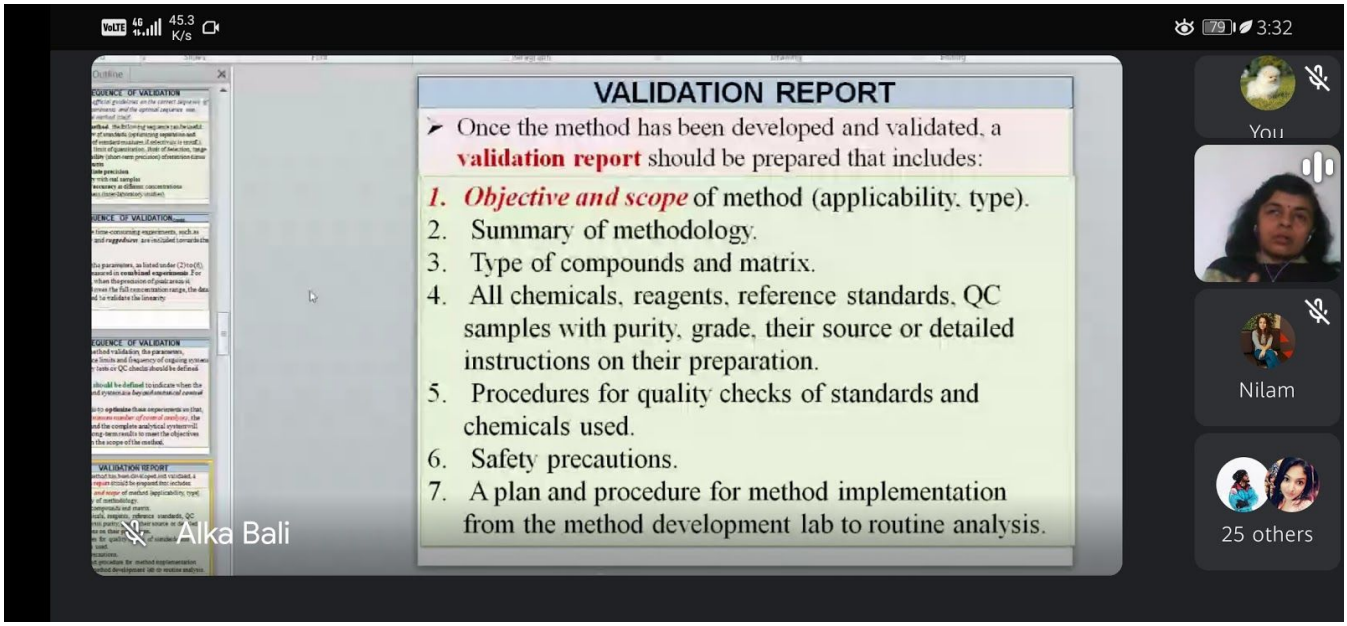

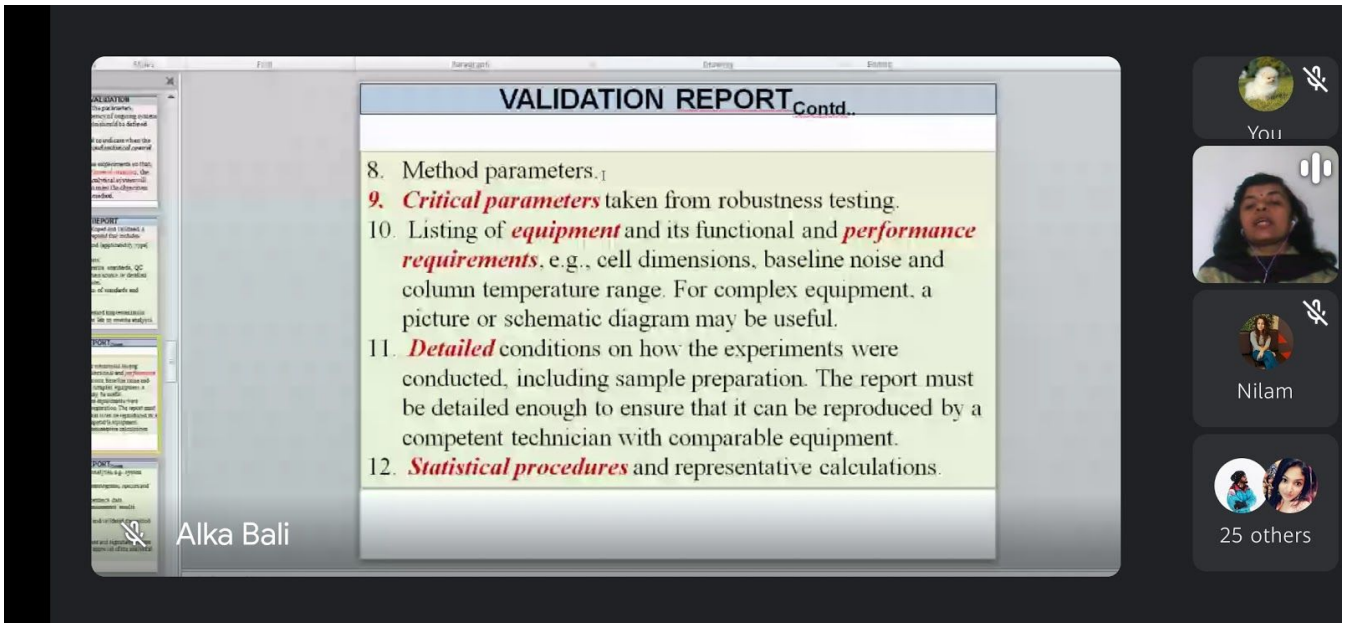

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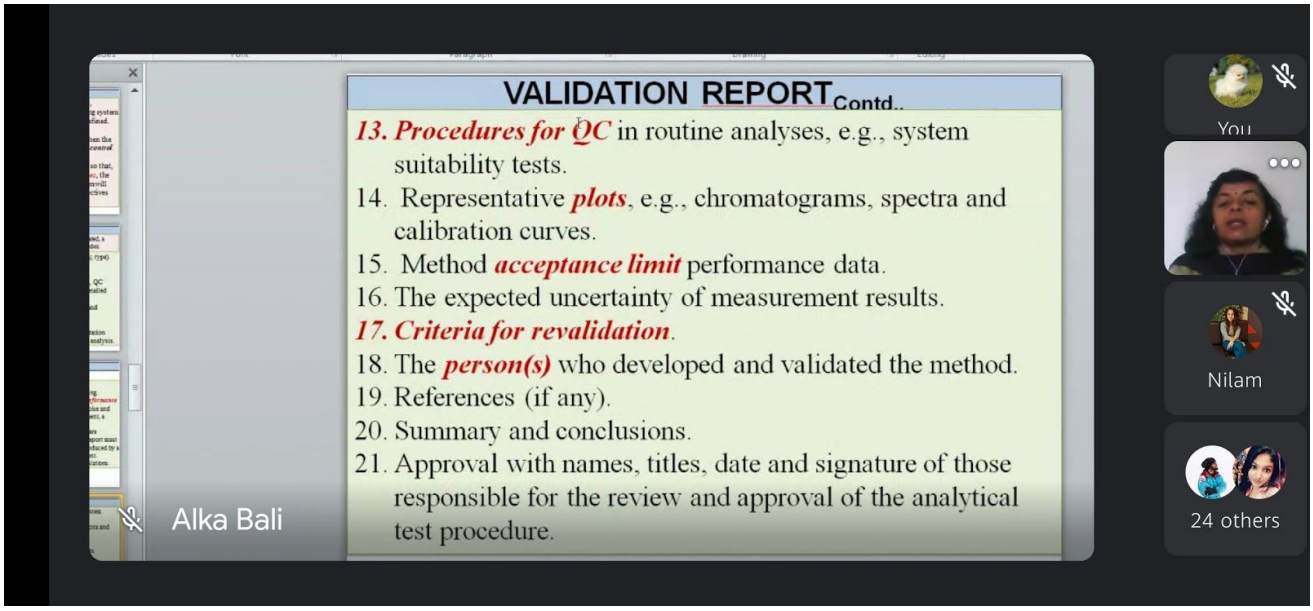

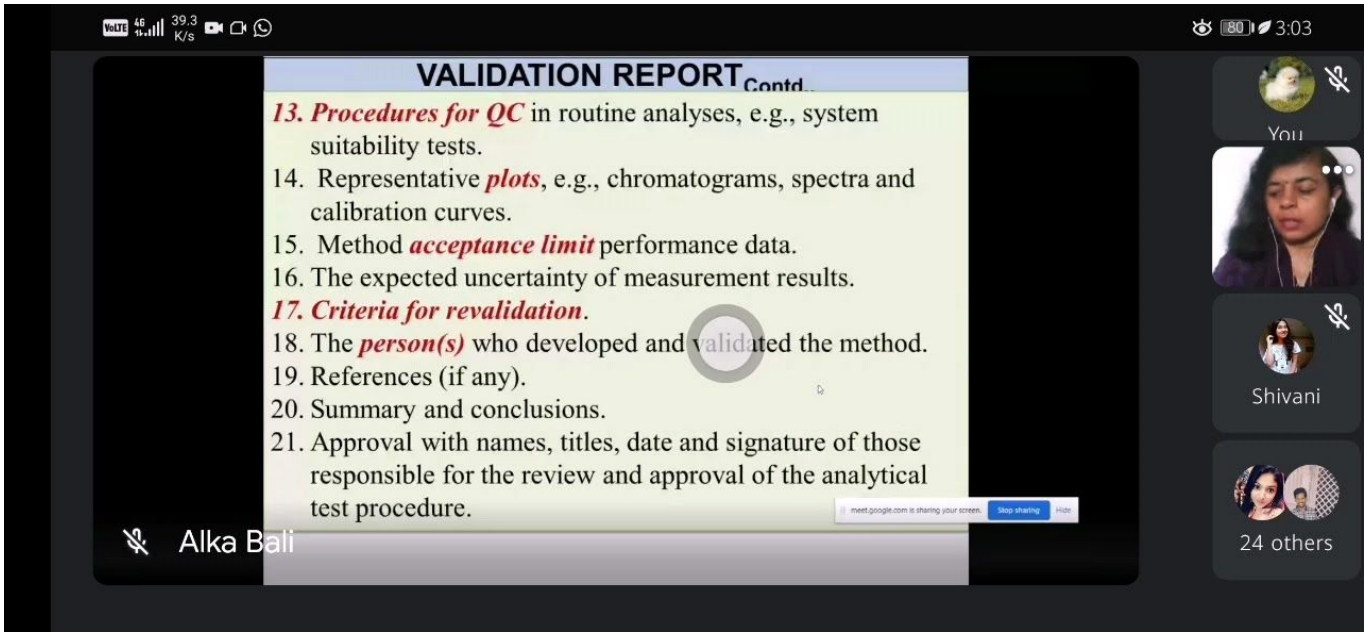

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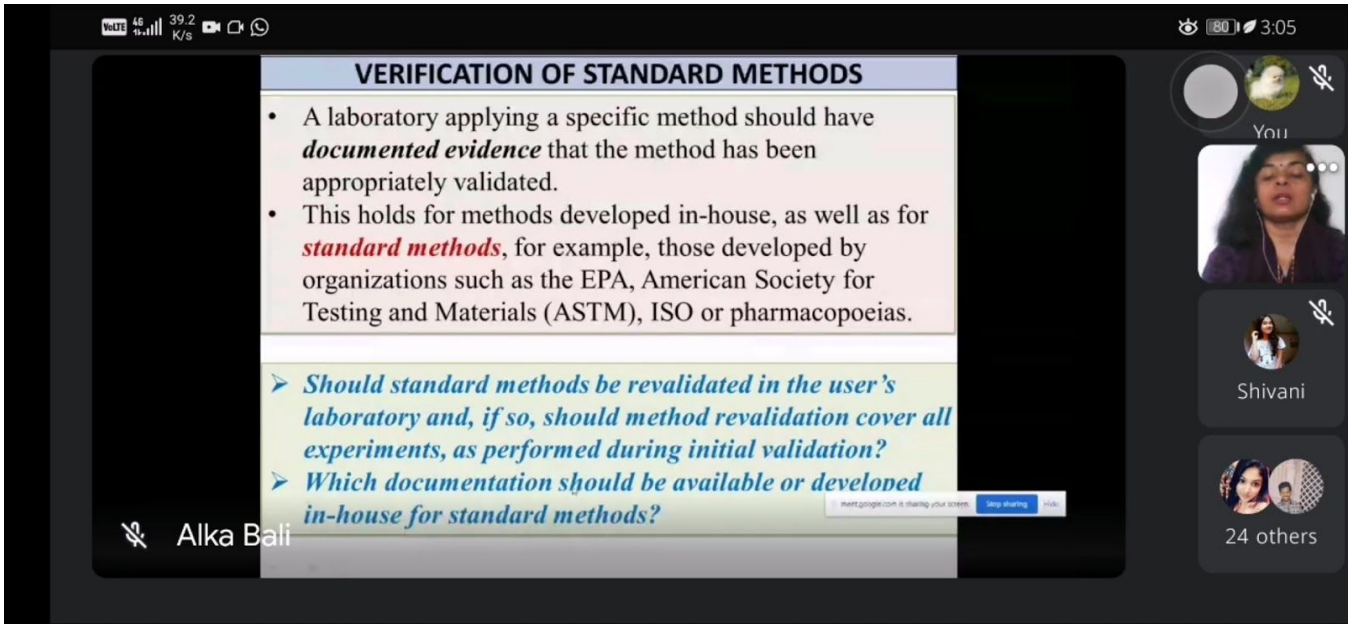

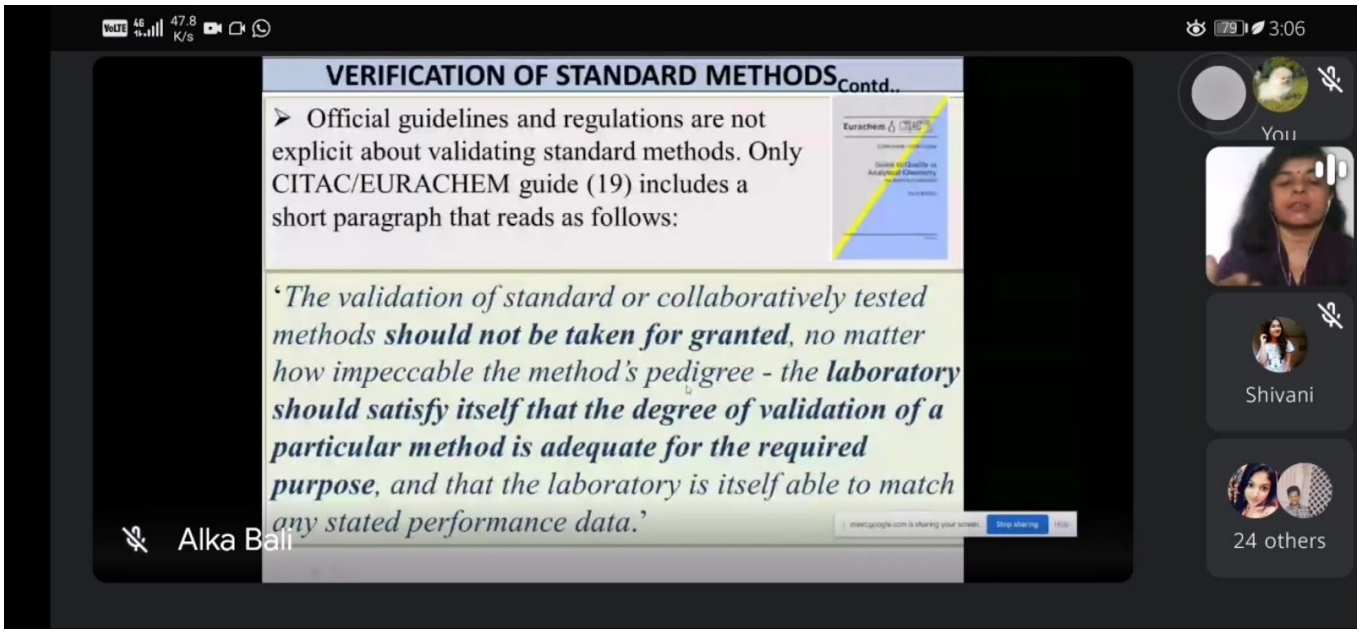

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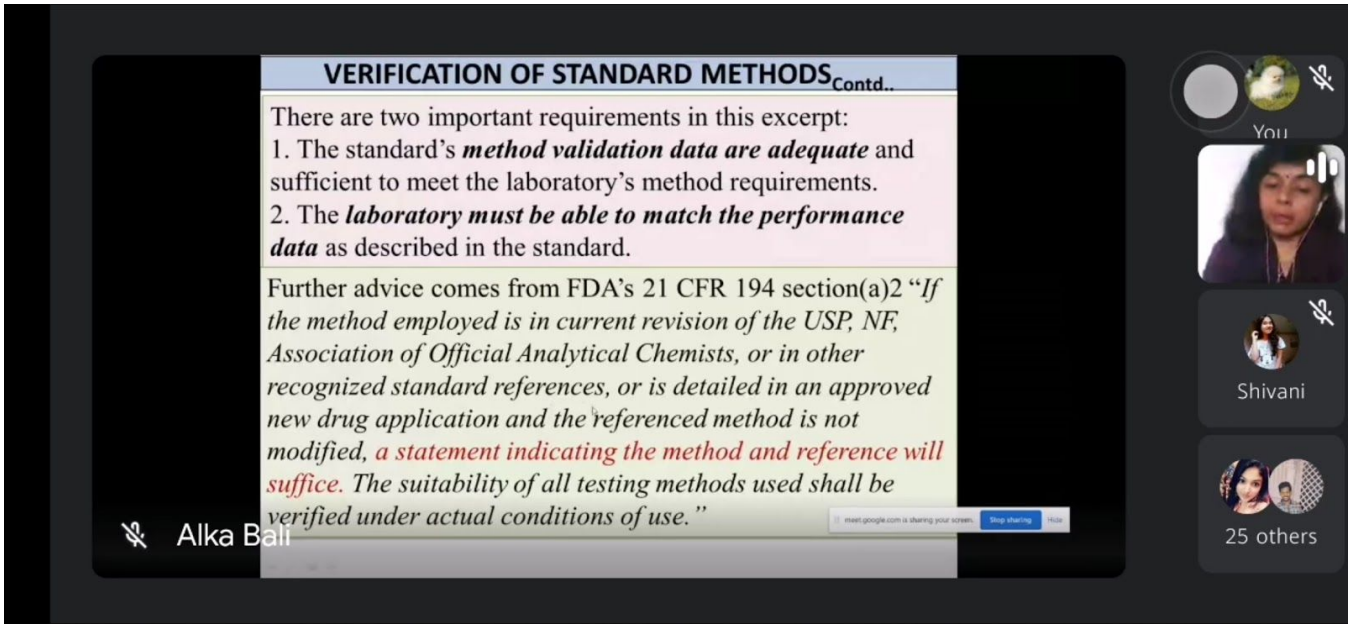

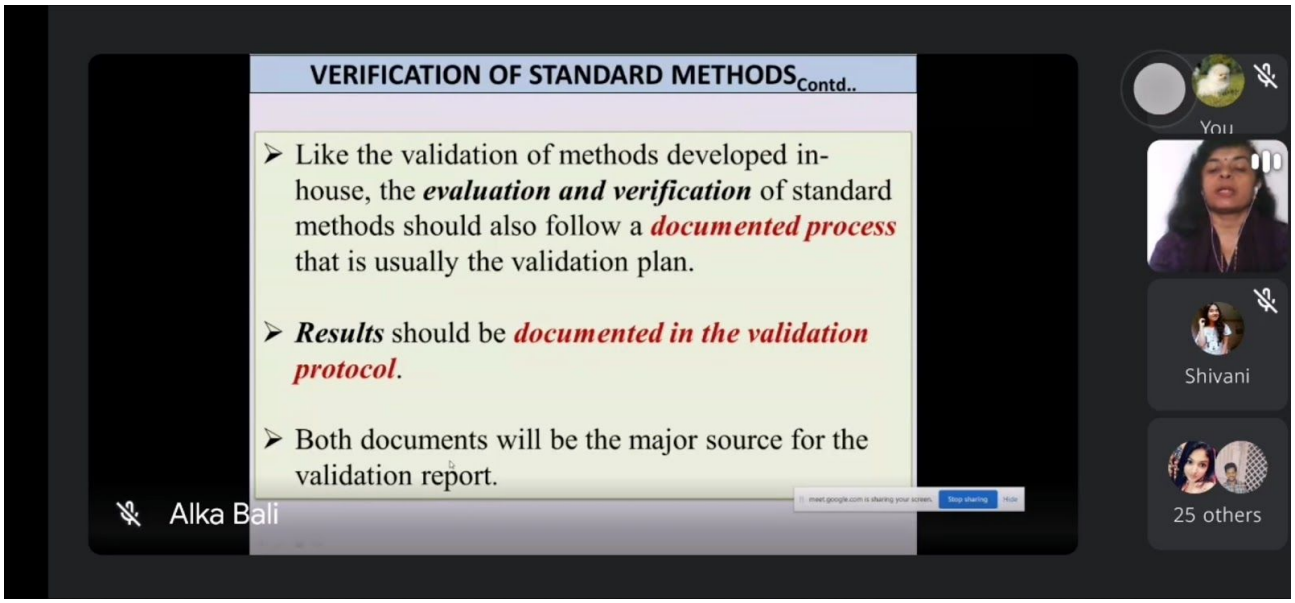

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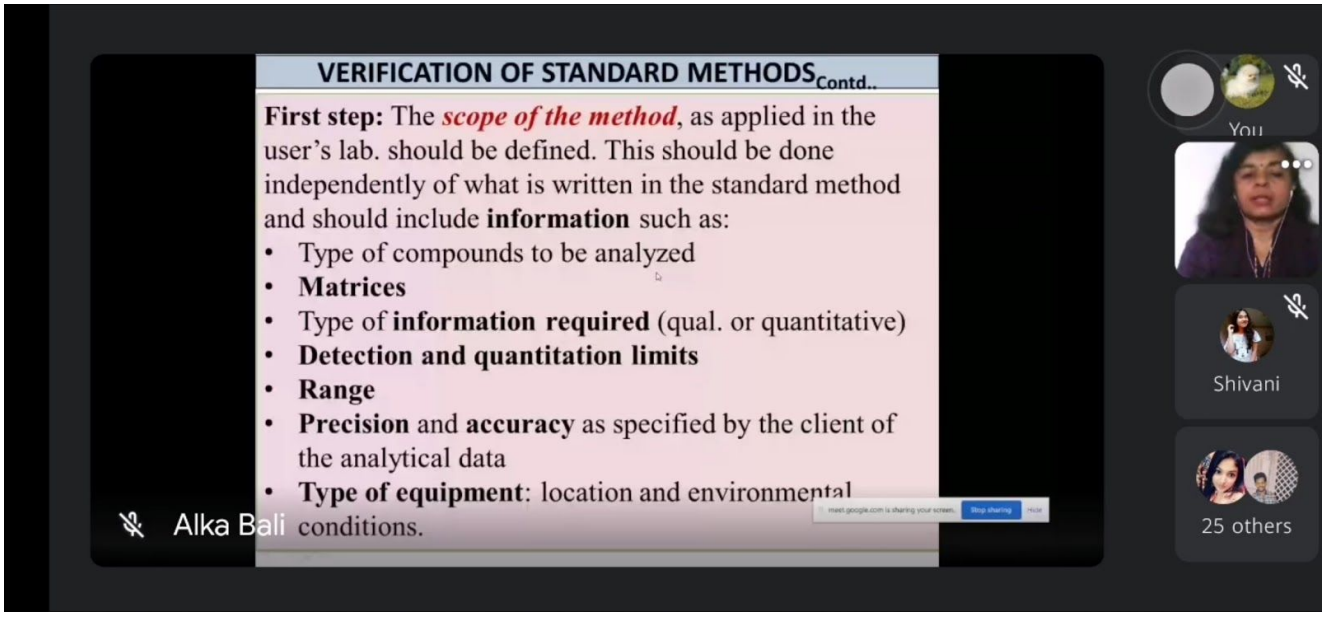

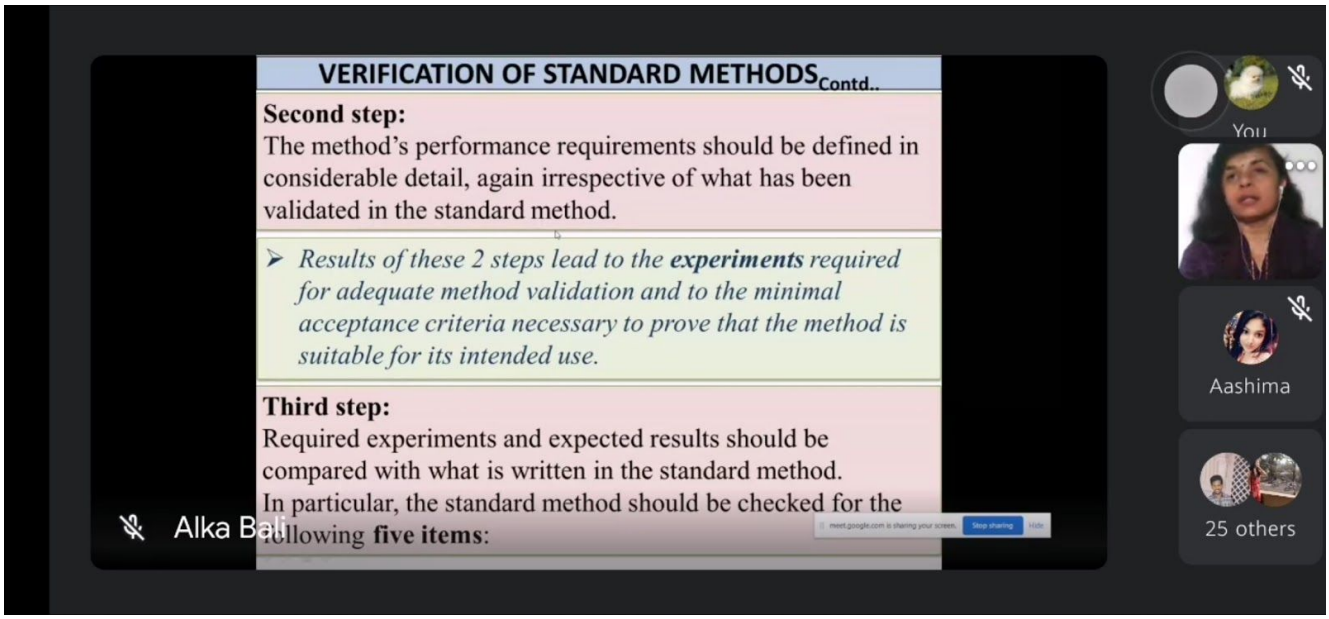

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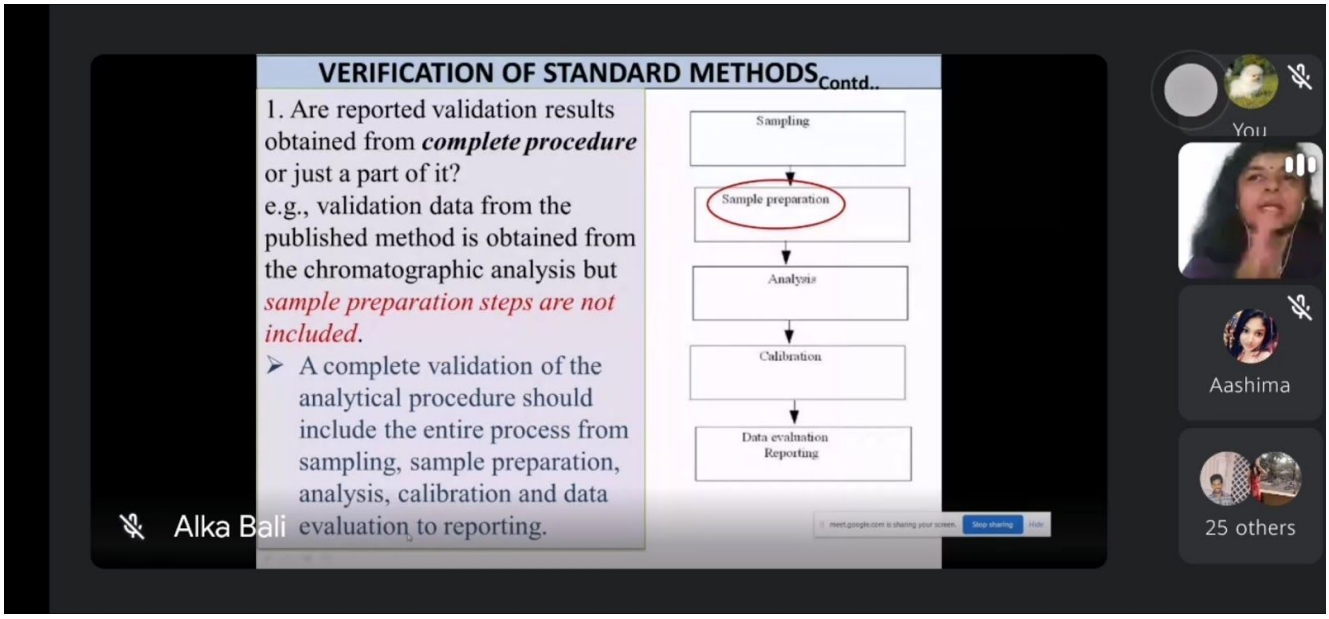

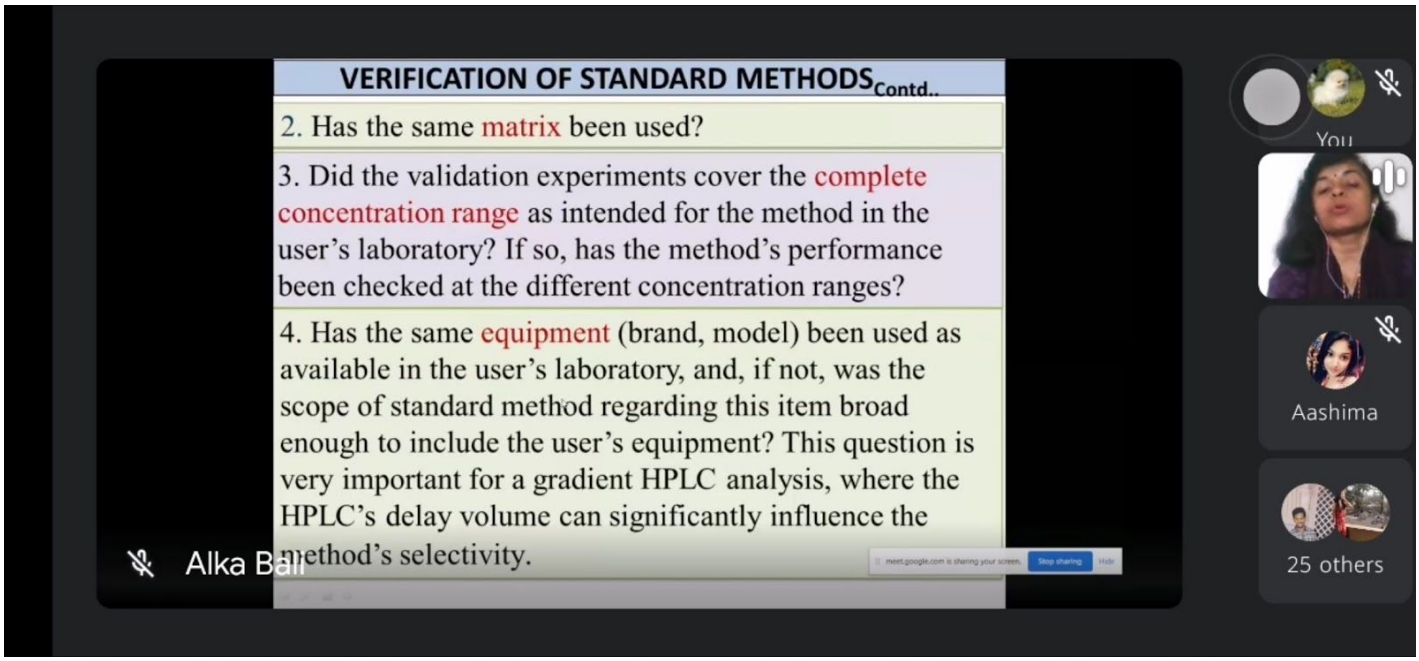

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VERIFICATION OF STANDARD METHODS Contd..

5. Have performance characteristics, e.g., the limit of quantitation, been checked in compliance with the most recent guidelines, as required for the user's laboratory (e.g., the ICH guideline, for pharmaceutical laboratories)? If not, does the test procedure have equivalency to the guideline?

From points 1-5:

- ***Check the overlap*** of the user requirements with the scope and results, as described in the standard method.
- If there is no overlap, a complete validation should be carried out.
- In the case of a complete overlap, validation experiments may not be necessary.

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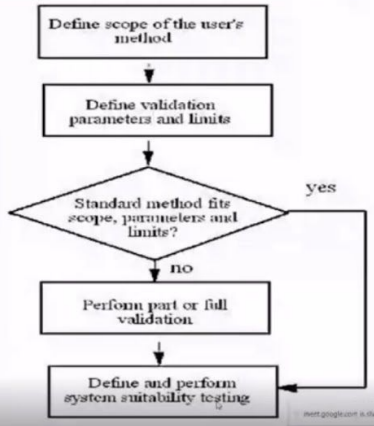
VERIFICATION OF STANDARD METHODS Contd..

SUMMARY:
Workflow for evaluation and validation of standard methods



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⟨1226⟩ VERIFICATION OF COMPENDIAL PROCEDURES

The intent of this general information chapter is to provide general information on the verification of compendial procedures that are being performed for the first time to yield acceptable results utilizing the personnel, equipment, and reagents available. This chapter is not intended for retroactive application to already successfully established laboratory procedures. The chapter *Validation of Compendial Procedures* ⟨1225⟩ provides general information on characteristics that should be considered for various test categories and on the documentation that should accompany analytical procedures submitted for inclusion in *USP–NF*. Verification consists of assessing selected analytical performance characteristics, such as those that are described in chapter ⟨1225⟩, to generate appropriate, relevant data rather than repeating the validation process.

Users of compendial analytical procedures are not required to validate these procedures when first used in their laboratories, but documented evidence of suitability should be established under actual conditions of use. In the United States, this requirement is established in 21 CFR 211.194(a)(2) of the current Good Manufacturing Practice regulations, which states that the "suitability of all testing methods used shall be verified under actual conditions of use."

Verification of microbiological procedures is not covered in this chapter because it is covered in USP general test chapters *Antimicrobial Effectiveness Testing* ⟨51⟩, *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, *Sterility Tests* ⟨71⟩, and in general information chapter *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩.

VERIFICATION PROCESS

The verification process for compendial test procedures is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use for a specified drug substance and/or drug product matrix.

Users should have the appropriate experience, knowledge, and training to understand and be able to perform the compendial procedures as written. Verification should be conducted by the user such that the results will provide confidence that the compendial procedure will perform suitably as intended.

If the verification of the compendial procedure is not successful, and assistance from USP staff has not resolved the problem, it may be concluded that the procedure may not be suitable for use with the article being tested in that laboratory. It may then be necessary to develop and validate an alternate procedure as allowed in the *General Notices*. The alternate procedure may be submitted to USP, along with the appropriate data, to support a proposal for inclusion or replacement of the current compendial procedure.

VERIFICATION REQUIREMENTS

Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied. Although complete revalidation of a compendial method is not required to verify the suitability of a procedure under actual conditions of use, some of the analytical performance characteristics listed in chapter ⟨1225⟩, *Table 2*, may be used for the verification process. Only those characteristics that are considered to be appropriate for the verification of the particular procedure need to be evaluated. The process of assessing the suitability of a compendial analytical test procedure under the conditions of actual use may or may not require actual laboratory performance of each analytical performance characteristic. The degree and extent of the verification process may depend on the level of training and

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of the user, on the type of procedure and its associated equipment or instrumentation, on the specific procedural

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tion which is being tested.

Verification should assess whether the compendial procedure is suitable for the drug substance and/or the drug product matrix, taking into account the drug substance's synthetic route, the method of manufacture for the drug product, or both, if

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applicable. Verification should include an assessment of elements such as the effect of the matrix on the recovery of impurities and drug substances from the drug product matrix, as well as the suitability of chromatographic conditions and column, the appropriateness of detector signal response, etc.

As an example, an assessment of specificity is a key parameter in verifying that a compendial procedure is suitable for use in assaying drug substances and drug products. For instance, acceptable specificity for a chromatographic method may be verified by conformance with system suitability resolution requirements (if specified in the procedure). However, drug substances from different suppliers may have different impurity profiles that are not addressed by the compendial test procedure. Similarly, the excipients in a drug product can vary widely among manufacturers and may have the potential to directly interfere with the procedure or cause the formation of impurities that are not addressed by the compendial procedure. In addition, drug products containing different excipients, antioxidants, buffers, or container extractives may affect the recovery of the drug substance from the matrix. In these cases, a more thorough assessment of the matrix effects may be required to demonstrate suitability of the procedure for the particular drug substance or product. Other analytical performance characteristics such as an assessment of the limit of detection or quantitation and precision for impurities procedures may be useful to demonstrate the suitability of the compendial procedure under actual conditions of use.

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Verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. Examples of basic compendial procedures include, but are not limited to, loss on drying, residue on ignition, various wet chemical procedures such as acid value, and simple instrumental determinations such as pH measurements. However, for the application of already established routine procedures to compendial articles tested for the first time, it is recommended that consideration be given to any new or different sample handling or solution preparation requirements.

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Quality Control Plan and Implementation for Routine

For any method for routine analysis, a **QC plan** should be developed. This plan should ensure that the method, together with the equipment, delivers consistently accurate results. The plan may include recommendations for:

1. **Selection, handling and testing** of QC standards.

2. **Type and frequency of equipment checks and calibrations** (for example, should the wavelength accuracy and the baseline noise of an HPLC UV detector be checked after each sample analysis, or on a daily or weekly basis?)

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QC Plan and Implementation for Routine Contd..

3. **Type and frequency of system suitability testing** (for example, at which point during the sequence system should suitability standards be analyzed?)

4. **Type and frequency of QC samples** (for example, should a QC sample be analyzed after 1, 5, 20 or 50 unknown samples, and should there be single or duplicate QC sample analysis, or should this be run at one or several concentrations?)

5. **Acceptance criteria** for equipment checks, system suitability tests and QC sample analysis

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6. **Action plan** in case criteria 2, 3 and/or 4 are ***not met***.

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QC Plan and Implementation for Routine Contd..

- Many times, methods are developed and validated in ***service laboratories*** specialized in this task.
- When the method is ***transferred to the routine analytical laboratory***, care should be taken that method and its critical parameters are well understood by the workers in the departments who apply the method.
- A detailed ***validation protocol, a documented procedure*** for method implementation and ***good communication*** between the development and operation departments are equally important.

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QC Plan and Implementation for Routine Contd..

- If the method is to be used by ***a number of departments***, it is recommended to **verify** method validation parameters and test applicability & usability of method ***in a couple of these departments*** before it is distributed to other departments.

- If the method is intended to be used by ***just one or two departments***, an analyst from the development department should assist the users of the method during initial operation. Users of the method should be encouraged to give constant feedback on the applicability and usability of the method to the development department. The latter should correct problems if any arise.

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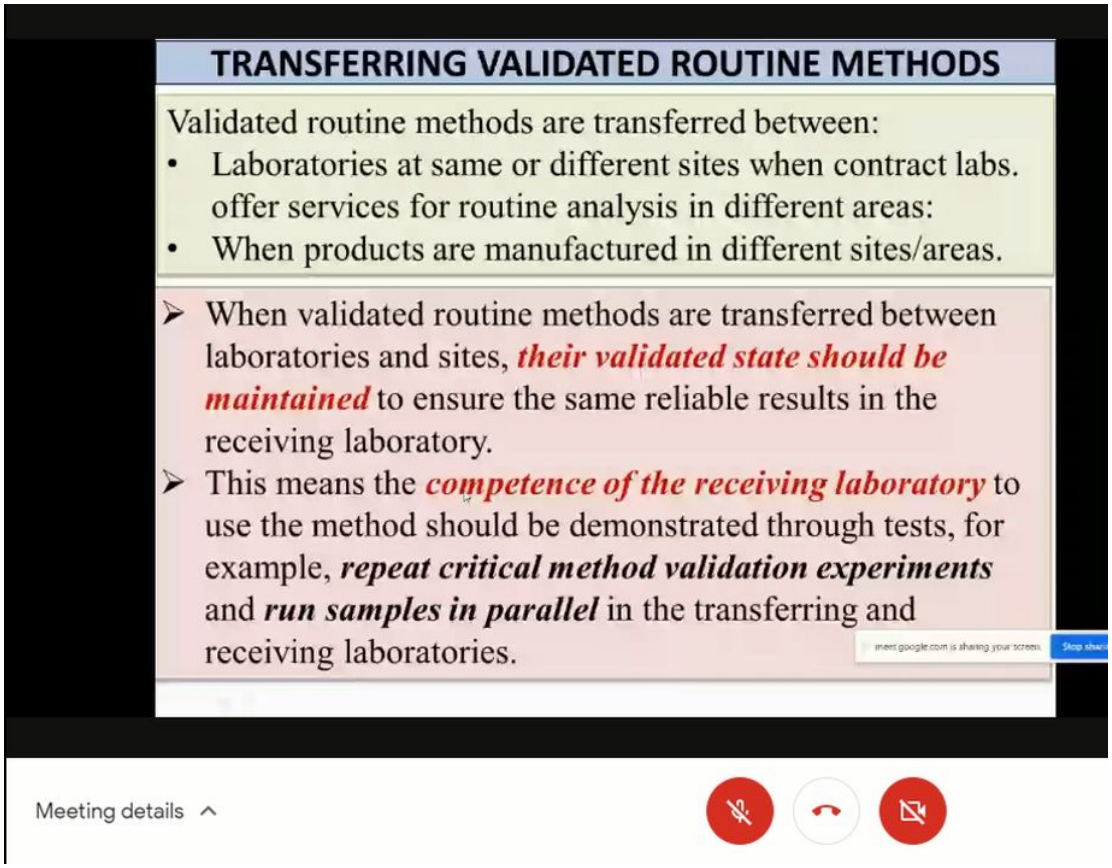

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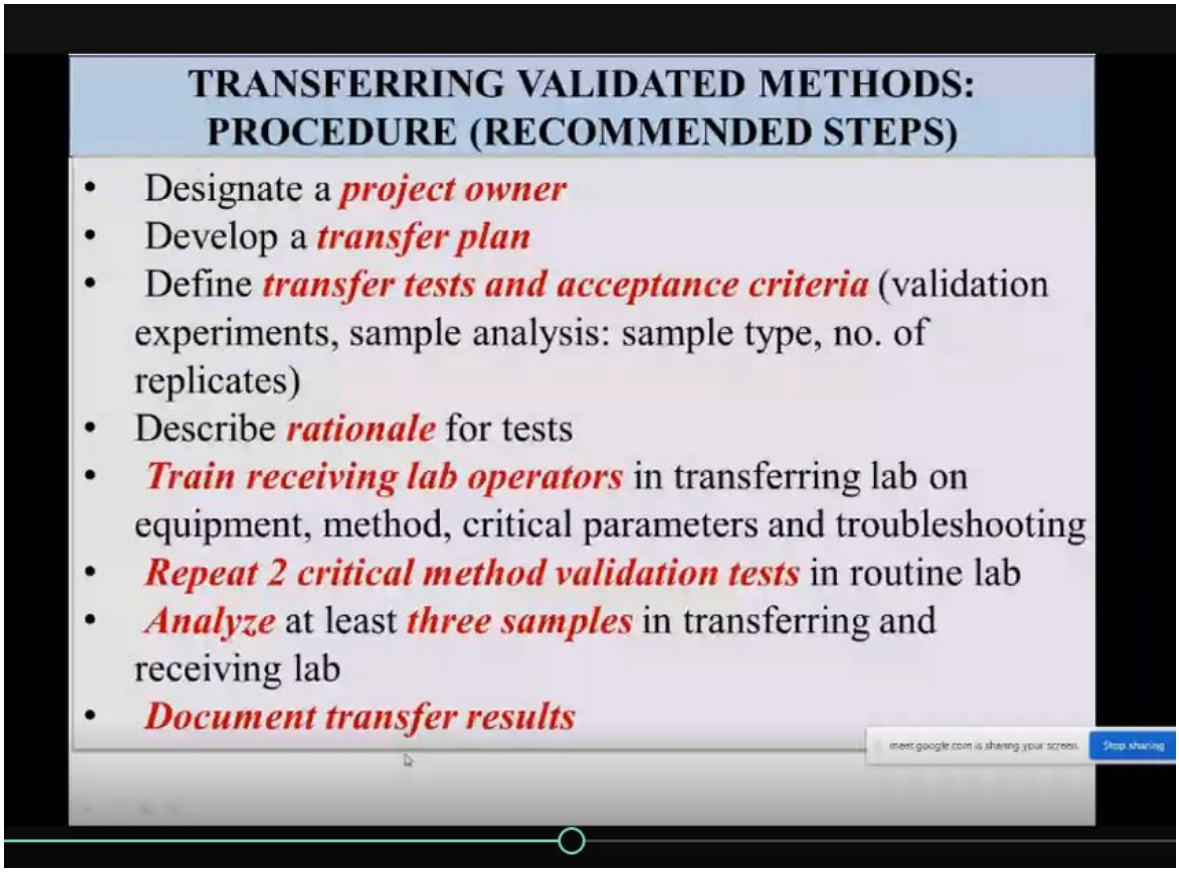

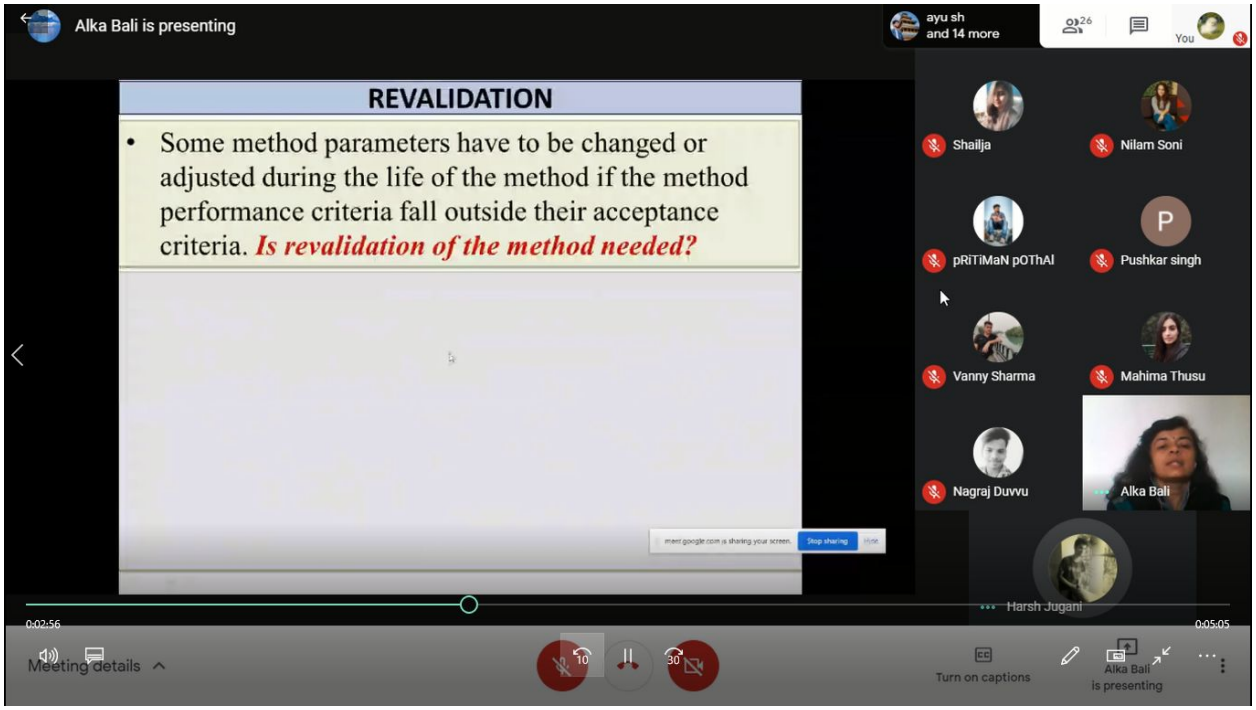

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REVALIDATION

- Some method parameters have to be changed or adjusted during the life of the method if the method performance criteria fall outside their acceptance criteria. ***Is revalidation of the method needed?***

- **Define Operating Ranges** to maintain clarity regarding revalidation.
  - ➢ Based on experience with similar methods or
  - ➢ Investigated during method development.
- **Verify Operating Ranges** during method validation in robustness studies; include as a part of the ***method characteristics***.
  - ➢ Availability of such operating ranges makes it easier to decide when a method should be revalidated.

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WHEN IS REVALIDATION NEEDED?

1. Whenever a method is changed, and the new parameter ***lies outside the operating range***. e.g., if the operating range of the column temperature has been specified to be between 30 and 40°C, the method should be revalidated if, for whatever reason, the new operating parameter is 41°C.

2. When the ***scope of the method*** has been ***changed or extended***, for example, if the sample matrix changes or if operating conditions change.

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WHEN IS REVALIDATION NEEDED? CONTD..

3. If ***instruments*** used are ***with different characteristics*** which weren't covered by initial validation. e.g., an HPLC method was developed, validated on a pump with delay volume of 5 mL, but new pump has delay volume 0.5 mL.

4. Part or full revalidation may also be considered if system suitability tests, or the results of QC sample analysis, lie outside preset acceptance criteria and where source of error cannot be traced back to the instruments or any other cause.

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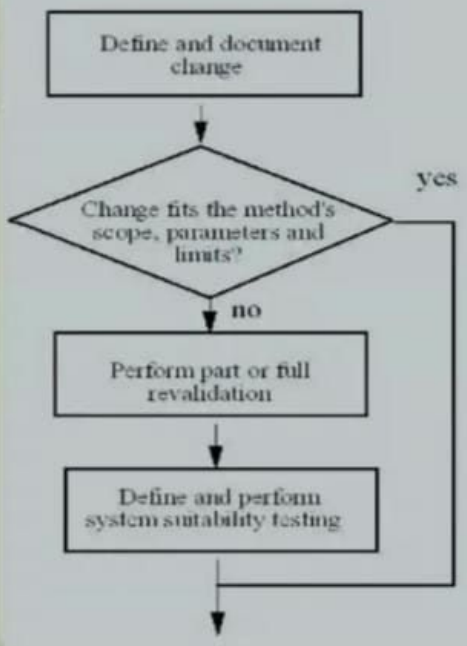
REVALIDATION

- An evaluation should determine whether the change is within the scope of the method.
- If so, no revalidation is required.
- If the change lies outside the scope, the parameters for revalidation should be defined.
- After the validation experiments, the system suitability test parameters should be investigated and redefined, if necessary.



Flow diagram for rev

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REVALIDATION

- Whenever there is a change that may require part or full revalidation, the change should follow a ***documented change control system.***
- The change should be ***defined, authorized for implementation and documented***.

Possible changes may include:

- New samples with new compounds or new matrices
- New analysts with different skills
- New instruments with different characteristics
- New location with different environmental conditions
- New chemicals and/or reference standards and
- Modification of analytical parameters.

PARAMETERS FOR METHOD VALIDATION

- Defined in different working groups of national and international committees.
- Unfortunately, some of the definitions vary between the different organizations.
- An attempt at harmonization was made for pharmaceutical applications through the ICH, where representatives from the industry and regulatory agencies from the United States, Europe and Japan defined parameters, requirements and, to some extent, methodology for analytical methods validation

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PARAMETERS FOR METHOD VALIDATION

Parameter	Included in ICH	Included in USP	Terminology included in ICH publication but not part of required parameters
Specificity	YES	YES	--
Selectivity	--	--	--
Precision	YES	YES	--
Repeatability	YES	--	--
Intermediate precision	YES	--	--
Reproducibility	--	--	YES
Accuracy	YES	YES	--
Trueness	--	--	--
Bias	--	--	--
Linearity	YES	YES	--
Range	YES	YES	--
Limit of detection	YES	YES	--
Limit of quantitation	YES	YES	--
Robustness	--	YES	YES
Ruggedness	--	YES	--

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SELECTIVITY/SPECIFICITY

- Terms selectivity and specificity are often used interchangeably.
- Although not consistent with the ICH, the term ***specific*** generally refers to a method that produces a response ***for a single analyte only,*** while the term ***selective*** refers to a method that provides responses for a number of chemical entities that may or may not be distinguished from each other. If the response is distinguished from all other responses, the method is said to be selective.
- Since there are very few methods that respond to only one analyte, the ***term selectivity is usually more appropriate.***

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SELECTIVITY/SPECIFICITY

- **USP** monograph defines selectivity of an analytical method as its ability to ***measure accurately an analyte in the presence of interference***, such as synthetic precursors, excipients, enantiomers & known (or likely) degradation products that are expected to be present in sample matrix.
- ***Selectivity in liq. chromatography*** is obtained by choosing optimal columns and chromatographic conditions like mobile phase composition, column temp. & detector wavelength.
- Selectivity studies should also assess ***interferences that may be caused by the matrix***, e.g., urine, blood, soil, water or food. Optimized sample preparation can eliminate most of the matrix components.
- The absence of matrix interferences for a quantitative method should be demonstrated by the ***analysis of at least five independent sources of control matrix.***

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SELECTIVITY/SPECIFICITY

- ***UV/visible photodiode-array detectors (PDA)*** and ***mass spectrometers*** acquire spectra on-line throughout the entire chromatogram. The spectra acquired during the elution of a peak are normalized and overlaid for graphical presentation. If the normalized spectra are different, the peak consists of at least two compounds.

- PDA detectors give indication of **peak purity,** i.e., whether a chromatographic peak pertains to a single compound or more than one compounds.
- A chromatographic signal may indicate no impurities in the peak, but spectral evaluation identifies the peak as impure.

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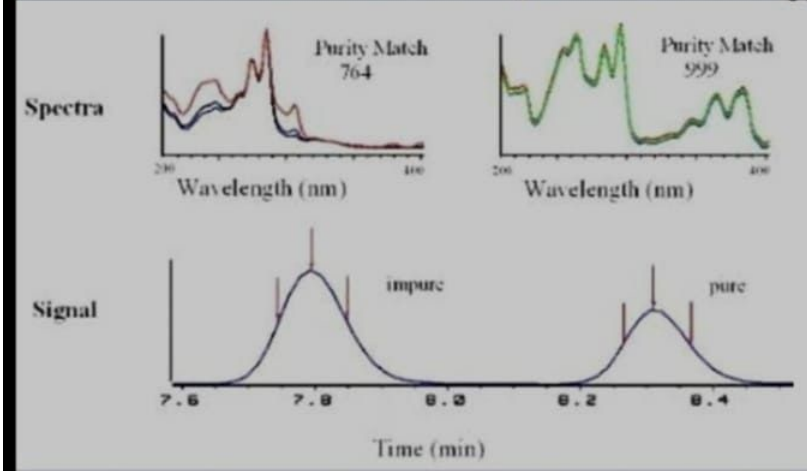
SELECTIVITY/SPECIFICITY CONTD..



Pure and impure HPLC peaks. Chromatographic signal does not indicate any impurity in either peak. Spectral evaluation, however, identifies the peak on the left as impure.

- The level of impurities detected with this method depends on the **spectral difference**, on the **detector's performance** and on the **software algorithm**.
- Under ideal conditions, peak impurities of **0.05 to 0.1 percen**t can be detected.

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SELECTIVITY/SPECIFICITY CONTD..

Analyte peak for six impurities and Drug							
	I	II	III	IV	V	VI	Drug
Purity angle	0.109	13.985	0.102	0.382	0.136	0.477	0.040
Purity Threshold	0.268	2.066	0.285	0.521	0.305	0.718	0.219

- The ***purity angle*** for the peak should be less than the ***purity threshold***, indicating the absence of any co-eluting peak.
- In above data, except for II, all other peaks are pure

SELECTIVITY/SPECIFICITY CONTD..

How to calculate peak purity?

- ***1. First calculate the spectral contrast angle.***
- **Spectral Contrast** measures the ***shape difference between two spectra***.
- Spectra are **baseline corrected** by subtracting interpolated baseline spectra between peak baseline liftoff and baseline touchdown.
- Spectra are **converted into a vector** in n dimensional space.
- Vector lengths (concentration) are minimized using least-squares solution.
- The vectors are moved into a two dimensional plane and the **angle** between them is measured.
- ***An angle of 0 degrees means the spectral shape is identical and an angle of 90 degrees indicates no spectral overlap.***

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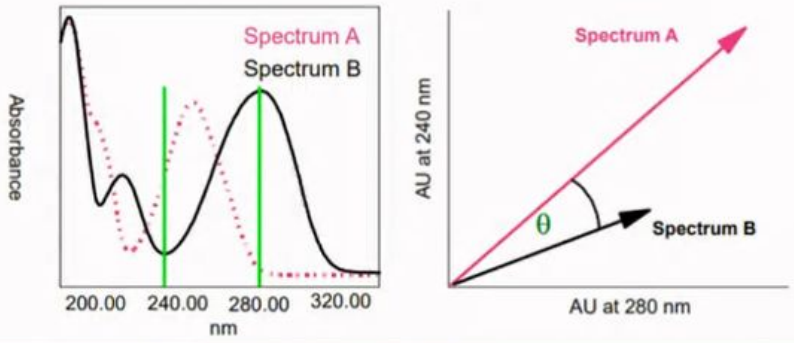
SELECTIVITY/SPECIFICITY CONTD..



- The shapes of Spectrum A and Spectrum B (Ethylparaben and EthylPABA) are represented by vectors.
- θ is the **Spectral Contrast Angle** which is the difference between spectral shapes

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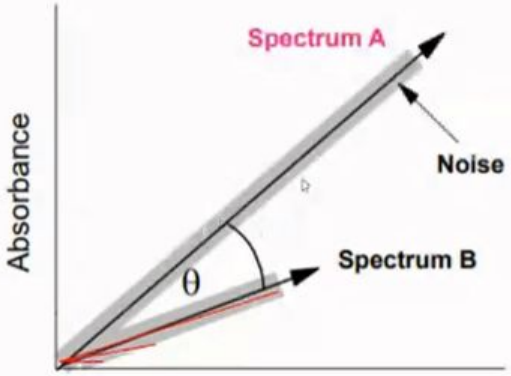
SELECTIVITY/SPECIFICITY$_{CONTD}$

Calculating peak purity$_{Contd..}$

2. Calculate the Threshold Angle

- It is the Detector Noise Angle calculated from the chromatographic baseline and is inversely proportional to the peak height.



- The Noise Region in gray forms a constant cylinder of uncertainty around the vector.
- A vector drawn from the origin to the edge of the cylinder creates the noise angle.
- The shorter the vector (lower concentration) the larger the noise angle.

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The Peak Purity Algorithm uses Spectral Contrast to **compare all spectra within a peak** to the **Apex spectrum**.

- The resulting **Purity Angle** is a **weighted average of all of the calculated angles**.
- If the **Purity Angle is less than** the calculated **Threshold Angle**, within the noise of the system the peak is spectrally homogeneous.
- If the **Purity Angle is greater than** the calculated **Threshold Angle**, there is something within the peak that can not be explained by noise. The peak is impure.

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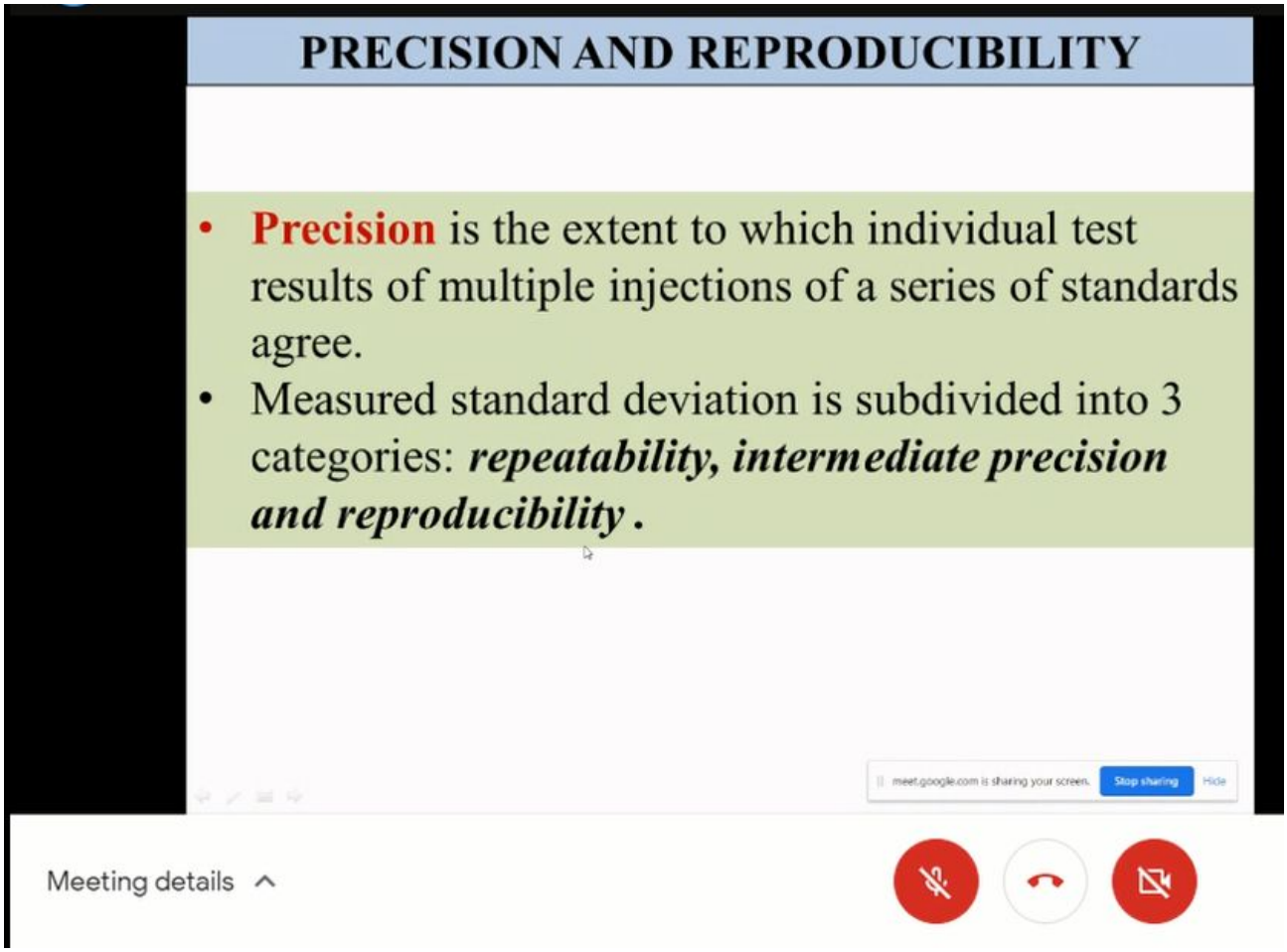

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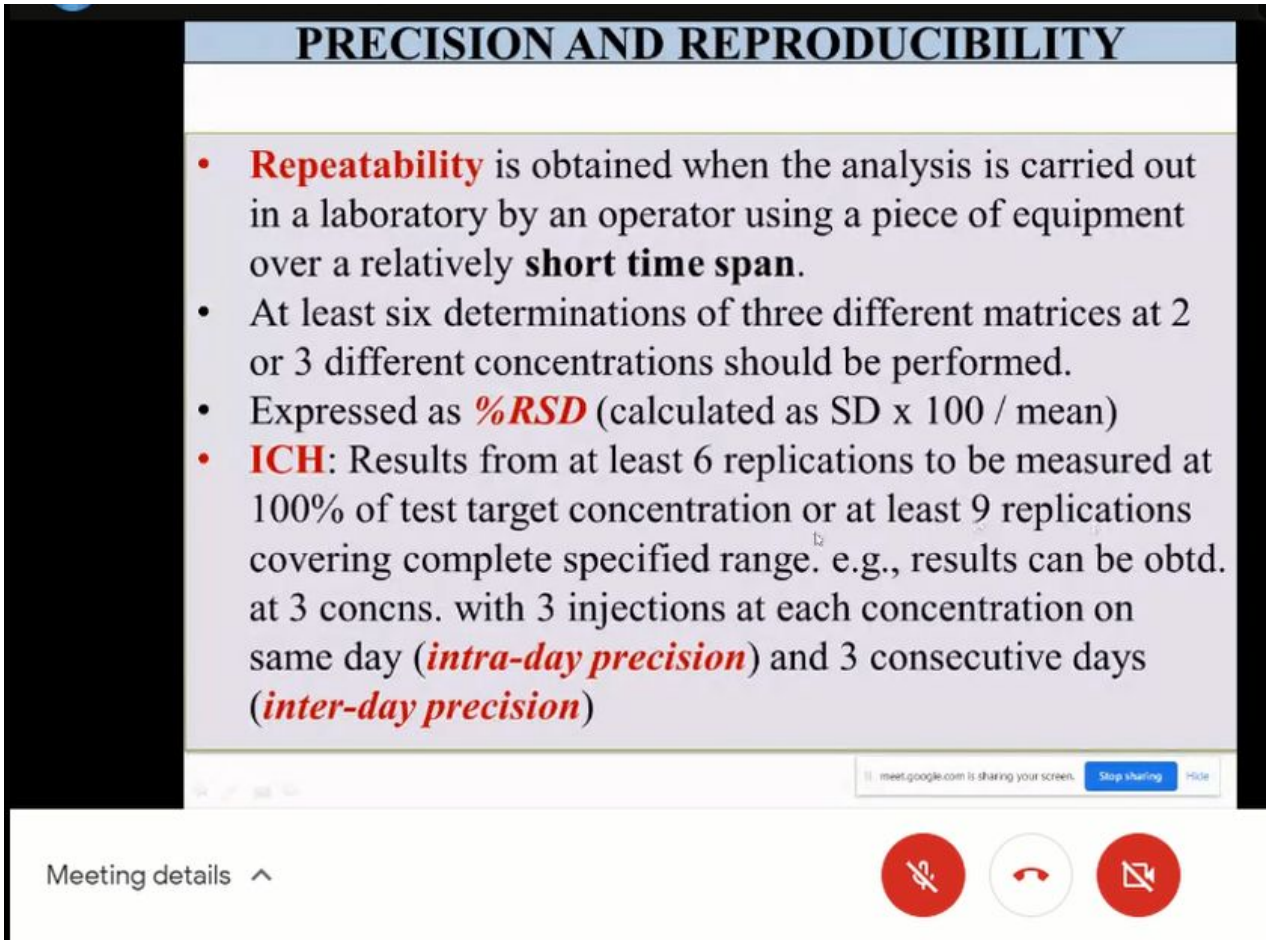

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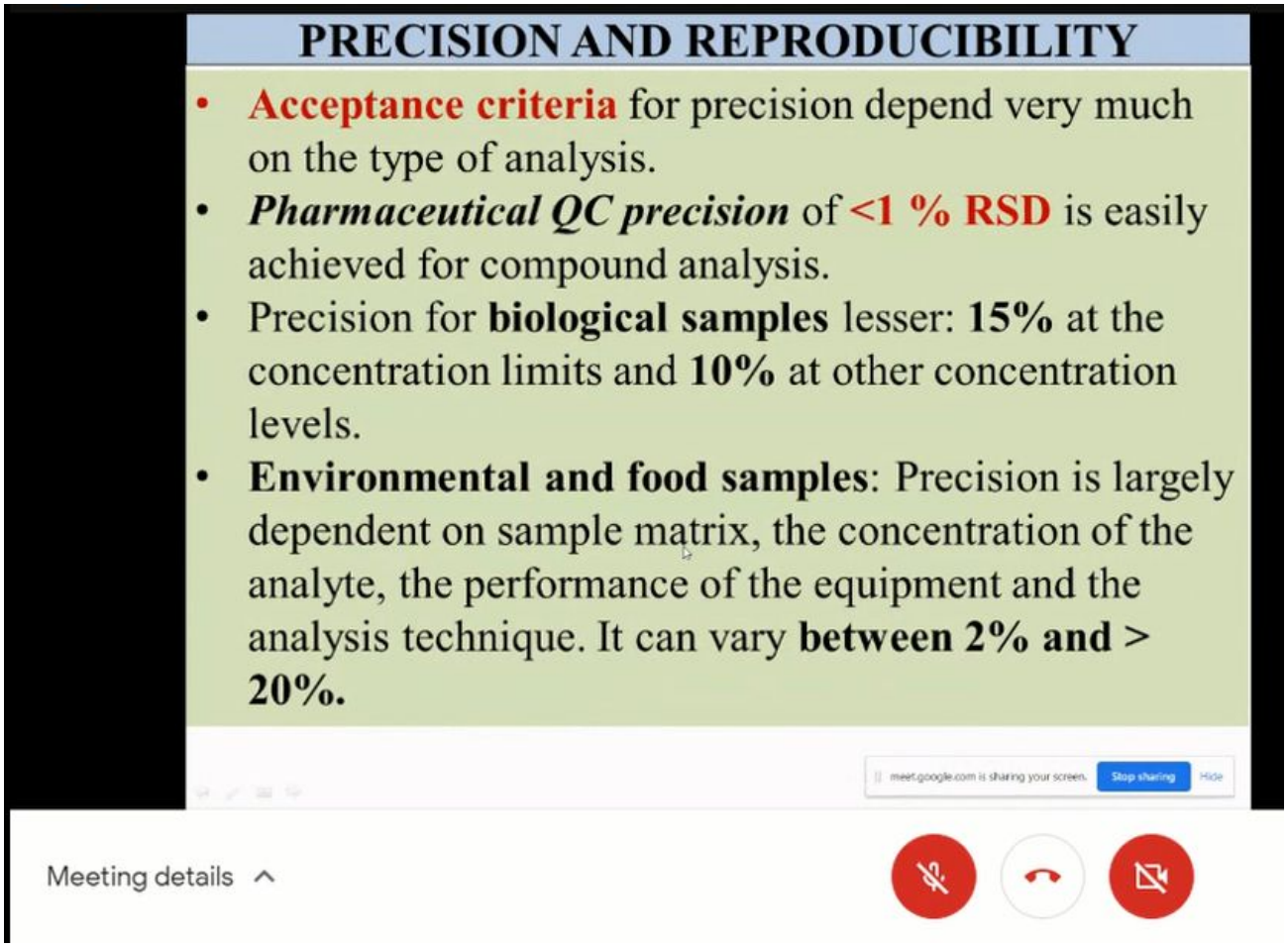

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Estimated Precision & Analyte Concentration

Analyte%	Analyte Ratio	Unit	RSD%
100	1	100%	1.3
10	10^{-1}	10%	2.8
1	10^{-2}	1 %	2.7
0.1	10^{-3}	0.1%	3.7
0.01	10^{-4}	100 ppm	5.3
0.001	10^{-5}	10 ppm	7.3
0.0001	10^{-6}	1 ppm	11
0.00001	10^{-7}	100 ppb	15
0.000001	10^{-8}	10 ppb	21
0.0000001	10^{-9}	1 ppb	30

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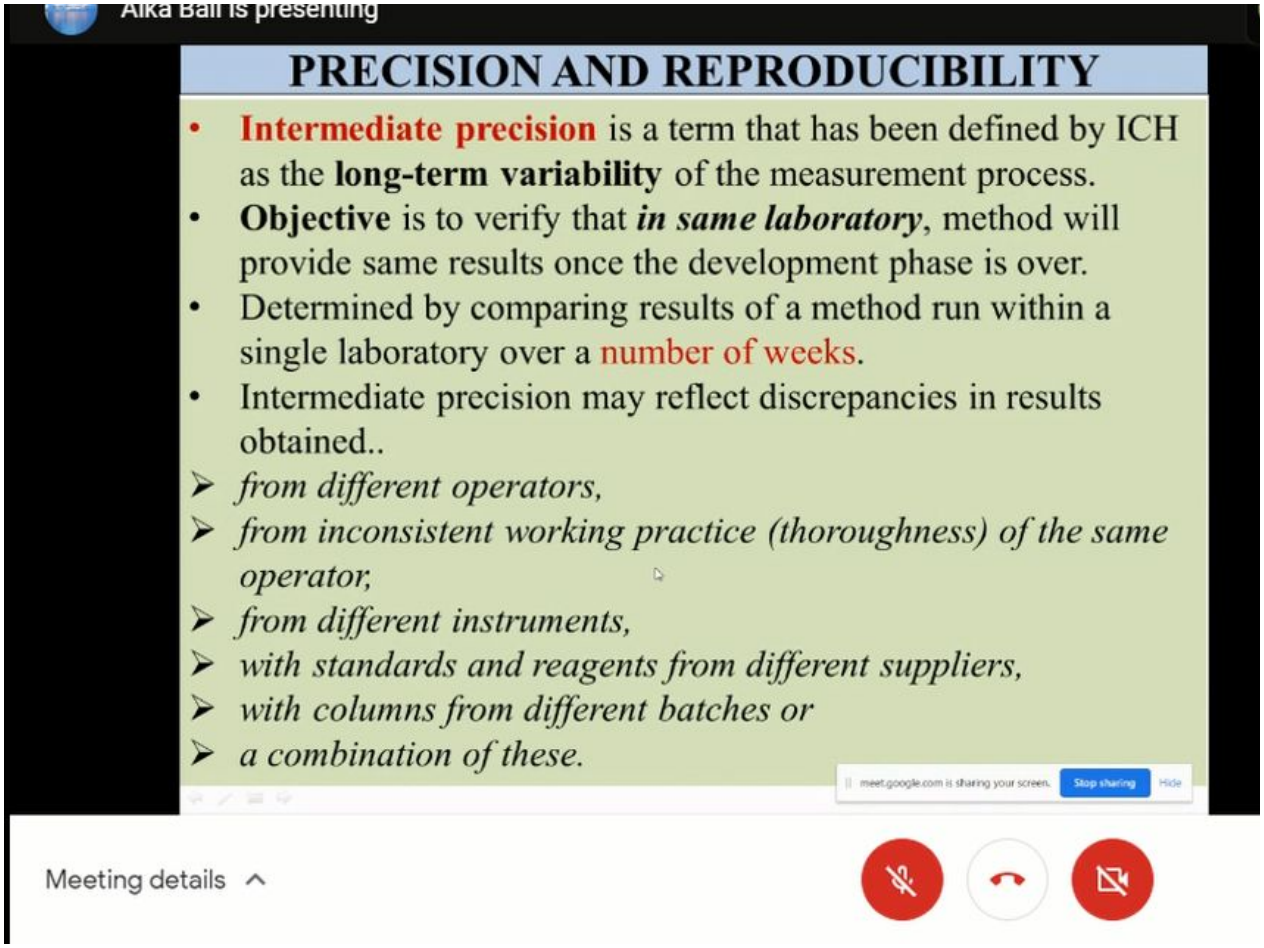

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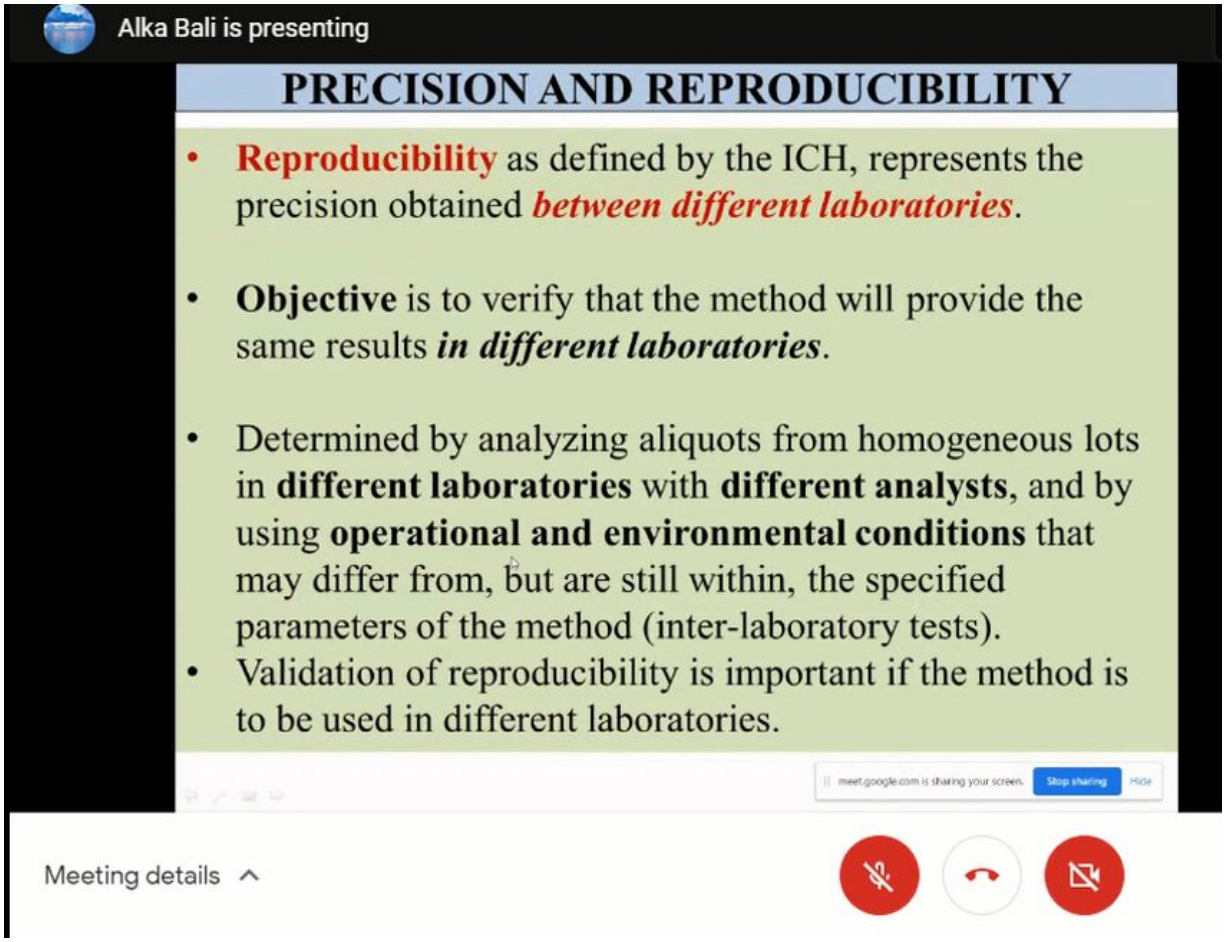

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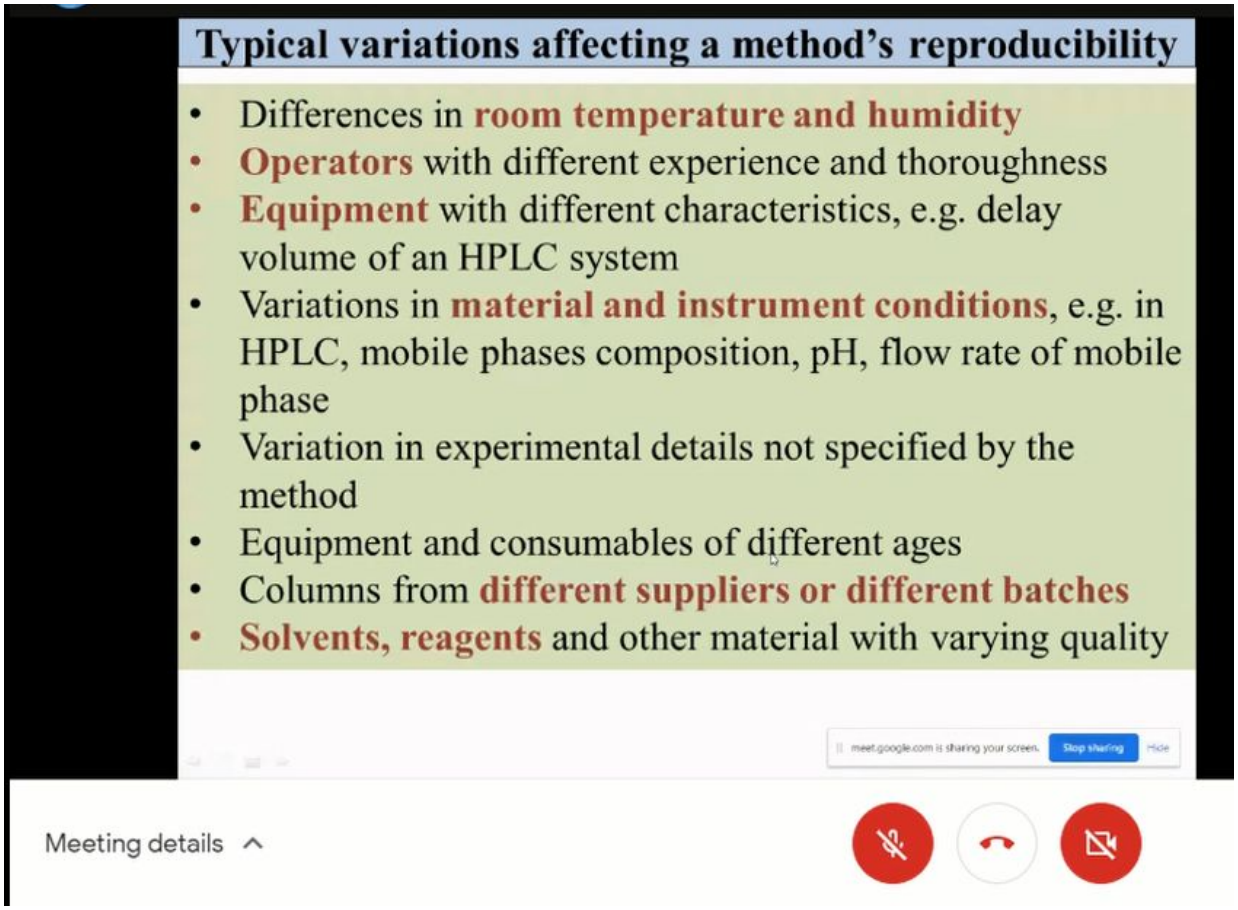

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Variables for measurements of precision, intermediate precision and reproducibility

	Precision	Intermediate Precision	Reproducibility
Instrument	same	different	different
Batches of accessories e.g., chrom. columns	same	different	different
Operators	same	different	different
Sample matrices	different	different	different
Concentration	different	different	different
Batches of material, e.g., reagents	same	different	different
Environmental conditions, e.g., temperature	same	different	different
Laboratory	same	same	different

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