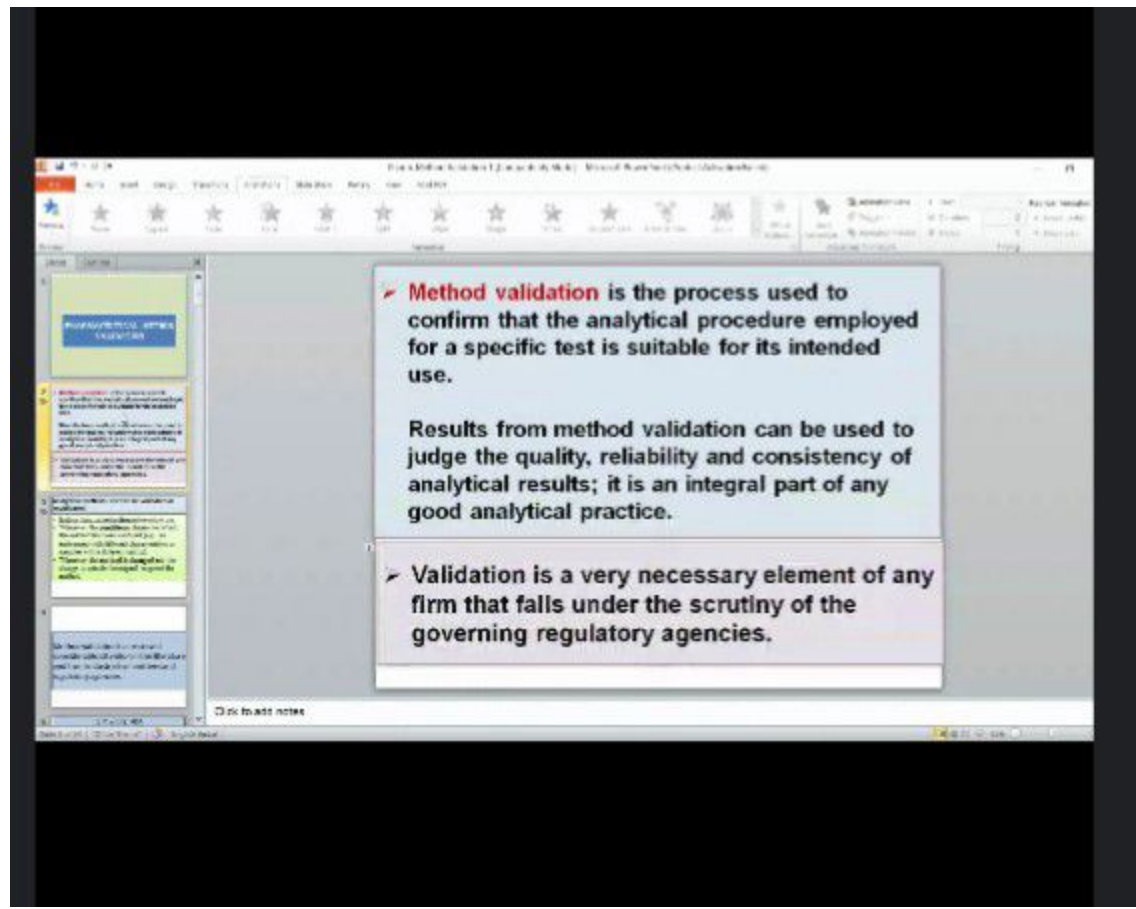
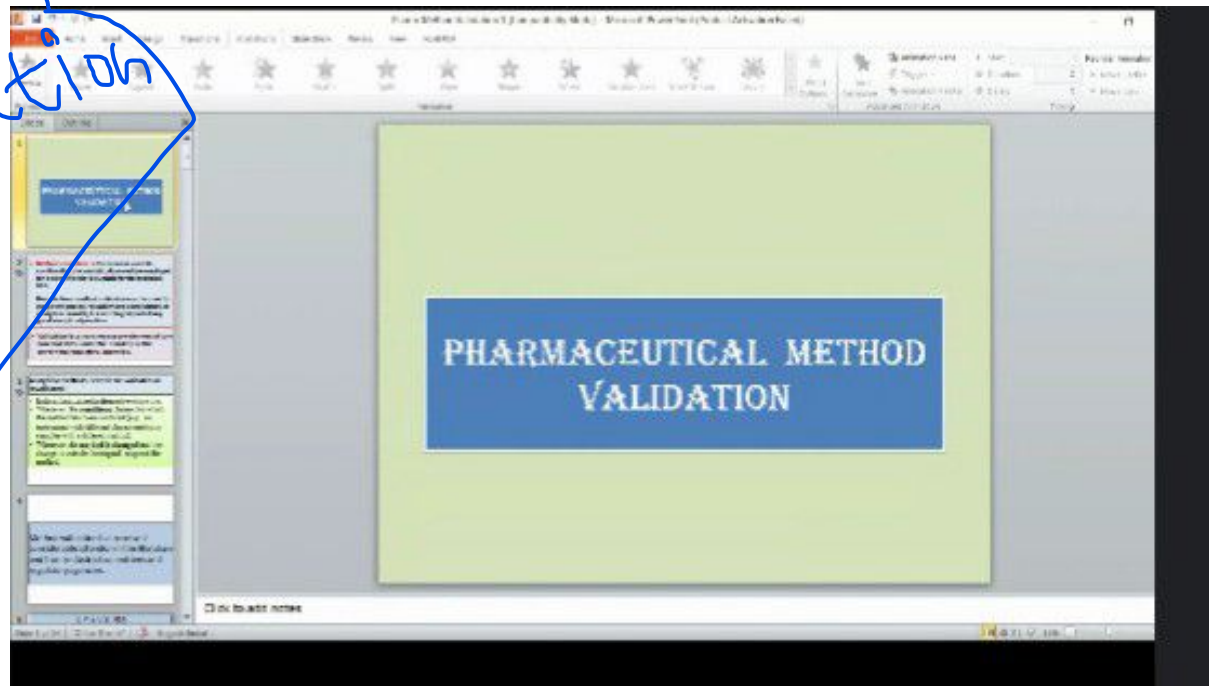


Pharmaceutical  
Validation  
Pg  
52

Selectivity



**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.



Alka Bali

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

Pharm. Method Validation 1 [Compatibility Mode] - Microsoft PowerPoint (Product Activation Failed)

View Font PDF

Animation

Animation Pane

Start

Duration

Delay

## 1. The U.S. FDA

- The **Food and Drug Administration (FDA or USFDA)** is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments.
- Responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, etc.



Alka Bali

## 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

- 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.

## Guidance document for industry

### **‘Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry’**

July 2015. U.S. Department of Health and Human Services, Food and Drug Administration

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)



Alka Bali

### 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.



### 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.

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 ^



Alka Bali is presenting

Prajakta Pawar and 15 more

27 You

### 5. AOAC INTERNATIONAL

- Globally recognized, independent, third party, not-for-profit association and voluntary consensus standards developing organization.
- Founded in 1884.
- When analytical needs arise within a community or industry, AOAC INTERNATIONAL serves as a forum for finding appropriate solutions for analytical problems through the development of microbiological and chemical standards.
- *Primary activity* of AOAC is the development of globally accepted standards to promote trade and to facilitate public health and safety.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Shailendra Sisodiya, Harsh Jugani, Nawang Tsetan, DeepaK Askar

Alka Bali is presenting

Deepthi Govap... and 15 more

27 You

### 5. AOAC INTERNATIONAL

AOAC develops analytical methods for a broad spectrum of safety interests including:

- foods and beverages
- dietary supplements
- infant formula
- feeds
- fertilizers
- soil and water
- veterinary drugs
- pharmaceuticals
- and more!

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Shailendra Sisodiya, Harsh Jugani, Nawang Tsetan, DeepaK Askar

Alka Bali is presenting

mahesh marella and 14 more

09:26

You

### 5. AOAC INTERNATIONAL

*AOAC's standards development process* relies on:

- *stakeholder panels* to develop consensus-based method performance requirements
- *volunteer expert review panels* to evaluate potential methods – all based on the community's specific method needs.

➤ AOAC's independent third party status, vast experience, and volunteer leadership all contribute to the credibility, defensibility, and acceptability of standards and methods developed. The AOAC, the EPA and other scientific organizations provide methods that are validated through multi-laboratory studies.

AOAC has developed a *Peer-Verified Methods validation* program detailing which parameters should be validated.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Shailendra Sisodiya, Harsh Jugani, DeepaK Askar, Shivani singh

Alka Bali is presenting

mahesh marella and 14 more

09:26

You

### 5. USP

The **USP** has published specific guidelines for method validation for compound evaluation. USP defines eight steps for validation:

- Accuracy
- Precision
- Specificity
- Limit of detection
- Limit of quantitation
- Linearity and range
- Ruggedness
- Robustness

Are you talking? Your mic is off. Click the mic to turn it on.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, DeepaK Askar, Harsh Jugani, Nawang Tsetan, Shivani singh

Alka Bali is presenting

tarvi gupta and 15 more

27 You

### 6. REPRESENTATIVES OF THE PHARMACEUTICAL AND CHEMICAL INDUSTRY

Have *published papers* on the validation of anal. methods.

- Hokanson applied life cycle approach, developed for computerized systems, to the validation/revalidation of methods.
- Green gave a practical guide for analytical method validation, with a description of a set of minimum requirements for a method.
- Renger and his colleagues described the validation of a specific analytical procedure for the analysis of theophylline in a tablet using high-performance thin layer chromatography (HPTLC). The validation procedure in this particular article is based on requirements for EU multistate registration.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, DeepaK Askar, Harsh Jugani, Nawang Tsetan, Shivani singh

Alka Bali is presenting

Prajakta Pawar and 15 more

27 You

### 5. REPRESENTATIVES OF THE PHARMACEUTICAL AND CHEMICAL INDUSTRY ...

- Winslow and Meyer recommend the definition and application of a master plan for validating analytical methods.
- J. Breaux and colleagues have published a study on analytical methods development and validation.
- O. Krause published a guide for analytical method transfer, comparability, maintenance and acceptance criteria for the testing of biopharmaceuticals.

Meeting details ^

Turn on captions


Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, DeepaK Askar, Harsh Jugani, Nawang Tsetan, Shivani singh

Alka Bali is presenting

Simran Gill and 15 more

27 You



Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, DeepaK Askar, Harsh Jugani, Nawang Tsetan, Shivani singh

Alka Bali is presenting

Maapdeep Singh and 15 more

27 You

**THE INTERNATIONAL COUNCIL FOR HARMONISATION ICH: MISSION**

**Harmonisation for Better Health**

- Is unique in bringing together the **regulatory authorities** and **pharmaceutical industry** to discuss scientific and technical aspects of drug registration.
- Since its inception in **1990**, ICH has gradually evolved, to respond to the increasingly global face of drug development.
- ICH's mission is **to achieve greater harmonisation** worldwide to ensure that safe, effective & high quality medicines are developed and registered in most resource-efficient manner.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, DeepaK Askar, Harsh Jugani, Nawang Tsetan, Shivani singh

Alka Bali is presenting

mahesh marella and 15 more

09:27

You

- ICH was established as an international non-profit Association under Swiss law on **October 23, 2015**, ICH's mission has been embodied in its **Articles of Association** as:
- Make **recommendations** towards achieving greater harmonisation in the interpretation and application of **technical guidelines and requirements for pharmaceutical product registration** and the maintenance of such registrations.
- To maintain a **forum for a constructive dialogue** on scientific issues between regulatory authorities and the pharmaceutical industry on the harmonisation of the technical requirements for pharmaceutical products;

Meeting details ^

Turn on captions

Alka Bali is presenting

Alka Bali is presenting

PRITIMAN POTH... and 15 more

09:27

You

**ICH: MISSION CONTD..**

- **Encourage the implementation and integration of common standards** by **dissemination** of, **communication** of information about, and **provision of training** on, harmonised guidelines and their use.
- Develop policy for the **ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA)** whilst ensuring the scientific and technical **maintenance, development and dissemination of MedDRA as a standardised dictionary** which facilitates the sharing of regulatory information internationally for medicinal products used by humans.

Meeting details ^

Turn on captions

Alka Bali is presenting

Alka Bali is presenting

Supriya Pandit and 15 more

27 You

### ICH: HISTORY

- The International Council for Harmonisation (ICH), formerly, the *International Conference on Harmonisation (ICH)* held inaugural assembly meetings on **23<sup>rd</sup> Oct. 2015** establishing ICH as an international association, a legal entity under Swiss law.
- Built upon a **25-year** track record of successful delivery of harmonised guidelines for global pharmaceutical development as well as their regulation, and a longer standing recognition of the need to harmonise.

saurav Raghuvanshi Mahima Thusu

pavan ghunawat Aashima Jindal

Deepthi Govapudi Harsh Jugani

Nawang Tsetan Shivani singh

Meeting details Meeting controls Turn on captions Alka Bali is presenting

Alka Bali is presenting

Nilam Soni and 15 more

27 You

### ICH: HISTORY CONTD.. WHY HARMONISE??

**The realization:** ‘An independent evaluation of medicinal products is needed before they are allowed into market.’ This realization was reached at different times in different regions.

➤ *In many cases the realisation was driven by tragedies (e.g., thalidomide tragedy in Europe in the 1960s.*

saurav Raghuvanshi Mahima Thusu

pavan ghunawat Aashima Jindal

Deepthi Govapudi Harsh Jugani

Nawang Tsetan Shivani singh

Meeting details Meeting controls Turn on captions Alka Bali is presenting



Alka Bali is presenting

tarun.sai... and 15 more

27 You

**ICH: HISTORY<sub>CONTD..</sub> WHY HARMONISE??**

- Stringent regulatory requirements:** For most countries, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products.
- Global market:** The industry, at the time, was becoming more international and seeking *new global markets*. The *divergence in technical requirements* from country to country made international marketing of new products difficult.

saurav Raghuvanshi Mahima Thusu

pavan ghunawat Aashima Jindal

Nawang Tsetan Harsh Jugani

Deepthi Govapudi Shivani singh

Meeting details Meeting controls Turn on captions Alka Bali is presenting

Alka Bali is presenting

Niharika Goswa... and 14 more

26 You

**ICH: HISTORY<sub>CONTD..</sub> WHY HARMONISE??**

- General healthcare costs:** Urgent need to rationalise and harmonise regulation was impelled by concerns over *rising costs of health care*.
  - Escalation of the cost of R&D* was ultimately borne by the consumer.
- Time:** Need to meet the public expectation that there should be a minimum of *delay in making safe and efficacious new treatments available* to patients in need.

INITIATION OF ICH

DeepaK Askar Harsh Jugani

Deepthi Govapudi Shivani singh

Meeting details Meeting controls Turn on captions Alka Bali is presenting

Alka Bali is presenting

Nagraj Duvvu and 15 more

27 You

### INITIATION OF ICH

Pioneered by the **European Commission, Europe**, in the 1980s, as Europe moved towards development of a single market for pharmaceuticals. The **success** achieved in Europe demonstrated that harmonisation was feasible.

Same time: Discussions between Europe, Japan and the US on possibilities for harmonisation.

The WHO Conference of Drug Regulatory Authorities (ICDRA), Paris, 1989: Plans begin to materialise.

Authorities approached **International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)** to discuss a joint regulatory-industry initiative on international harmonisation, and **ICH was conceived**.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Nawang Tsetan, Harsh Jugani, Nawang Tsetan joined

Alka Bali is presenting

tarun sai and 15 more

27 You

### INCEPTION OF ICH 1990

- The birth of ICH: At meeting in **April 1990**, hosted by European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels.
- Representatives of the regulatory agencies and industry associations of **Europe, Japan and the US** met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH.
- At the first ICH Steering Committee meeting, the Terms of Reference were agreed and it was decided that the Topics selected for harmonisation would be divided into **Quality, Safety, and Efficacy** to reflect the three criteria which are the basis for approving and authorising new medicinal products.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Nawang Tsetan, Harsh Jugani, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

PRITIMAN POT... and 15 more

27 You

### EVOLUTION OF ICH

- ICH's first decade saw significant progress in the development of ICH Guidelines on *Quality, Safety and Efficacy* topics.
- A number of important multidisciplinary topics, included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).
- Currently, the need to expand communication and dissemination of information on ICH Guidelines beyond the founding ICH regions (*non-ICH regions*) has become a key focus.

Meeting details Meeting controls Turn on captions Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Nawang Tsetan, Harsh Jugani, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

tanvi gupta and 15 more

27 You

### ICH: CONSTITUTION

```

graph TD
    ICH[ICH] --- MEMBERS[MEMBERS]
    ICH --- OBSERVERS[OBSERVERS]
  
```

Meeting details Meeting controls Turn on captions Alka Bali is presenting

Participants: saurav Raghuvanshi, Mahima Thusu, pavan ghunawat, Aashima Jindal, Nawang Tsetan, Harsh Jugani, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

Ankit singh and 15 more

09:27

You

WCG FDANEWS Simplifying Global Compliance

ICH to Bring India On Board

March 17, 2020

India will soon become a full member of the International Council for Harmonisation (ICH), according to the country's Drug Controller General.

India's Central Drugs Standard Control Organization (CDSCO) joined the council as an observer in February 2016, so it currently has no voting rights although it can attend ICH meetings and nominate experts to working groups.

The organization currently has 16 members and 32 observers. ICH's founding members include the European Commission, the FDA and Japan's Pharmaceuticals and Medical Devices Agency.

Upcoming Events

- 13 Develop World-Class SOPs that Minimize Human Error
- 14 Spreadsheet Validation: Best Practices to Maintain Compliance
- 19 Pharmaceutical Quality Risk Management: Navigating the Intersection Between Regulatory Requirements & Risk

Meeting details

Turn on captions

Alka Bali is presenting

Alka Bali is presenting

Niharika Goswa... and 15 more

09:27

You

PHARMABIZ.com India's most comprehensive pharma portal

India soon to become ICH member

Lucent Yadav, Mumbai

Tuesday, March 3, 2020, 08:00 Hrs. [5/7]

India will soon become the member of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which aims at promoting public health by achieving greater harmonisation through the development of technical guidelines and requirements for pharmaceutical product registration.

The announcement to this effect was made by Drugs Controller General of India (DCGI) Dr VG Somani at Indian Pharmaceutical Alliance's 8th India Pharmaceutical Forum held in Mumbai on February 27-28, 2020.

India is moving towards becoming member of ICH and Pharmaceutical Inspection Co-operation Scheme (PICIS). Currently, it is among 22 observers in ICH and will soon become member of it. Harmonisation is being worked across the agencies to avoid duplication in product registration.

The objective of the ICH is to promote public health through international harmonization of technical requirements that contributes to the timely introduction of new medicines and continued availability of the approved medicines to patients, to the prevention of unnecessary duplication of clinical trials in humans, to the development, registration and manufacturing of safe, effective, and high quality medicines in an efficient and cost-effective manner, and to the minimization of the use of animal testing without compromising safety and effectiveness.

To become a member of ICH, the country needs to follow certain guidelines on good manufacturing practice (GMP), good laboratory practice (GLP), good clinical practice (GCP) etc. as well as good regulatory practice, said Somani.

Meeting details

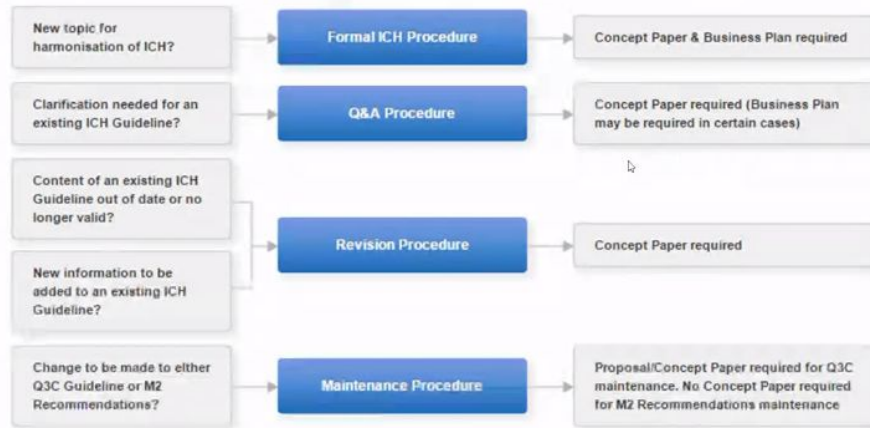
Turn on captions

Alka Bali is presenting

## 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).



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 ^



Alka Bali is presenting

JAYSHRI SWARN... and 15 more

09:27

You

### A. Formal ICH Procedure

#### STEP 1: Consensus building

- EWG prepares a **consensus draft** of the Technical Document, based on the **objectives** set out in the **Concept Paper**. Work is conducted **via** e-mail, teleconferences and web conferences.
- If **endorsed** by **ICH Management Committee**, the EWG also meets face-to-face at the biannual Assembly meetings. Interim reports on progress of the draft are made to the Assembly on a regular basis.
- When **consensus** on the draft is reached within the EWG, the technical experts of the EWG will **sign the Step 1 Experts sign-off sheet**.
- The **Step 1 Experts Technical Document** with EWG signatures is then submitted to the Assembly to request adoption under **Step 2** of the ICH process

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, tanvi gupta, pavan ghunawat, Aashima Jindal, Nawang Tsetan, tarun sai, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

Shailendra Siso... and 15 more

09:27

You

### A. Formal ICH Procedure

#### STEP 2: Consensus building

**Step 2a: Confirmation of consensus on the Technical Document.**  
 Step 2a reached when **Assembly agrees, based on the report of the EWG**, that there is **sufficient scientific consensus on technical issues** for the Technical Document to proceed to the next stage of regulatory consultation.

**Step 2b: Adoption of draft Guideline by Regulatory Members.**  
 On the basis of the Technical Document, the ICH Regulatory Members will take the actions they deem necessary to develop the draft Guideline.  
 Step 2b is reached when the **Regulatory Members endorse the draft Guideline**.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, tanvi gupta, pavan ghunawat, Aashima Jindal, Nawang Tsetan, tarun sai, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

Nagraj Duvvu and 15 more

27 You

### STEP 3: Regulatory consultation & Discussion

**Stage I - Regional regulatory consultation:** The Guideline embodying the scientific consensus *leaves ICH process* and becomes subject of *wide-ranging regulatory consultation in the ICH regions*.

- Regulatory authorities and industry associations in *other regions may also provide their comments* on draft consultation documents to the ICH Secretariat.

**Stage II - Discussion of regional consultation comments:** After obtaining all comments from the consultation process, the EWG works to *address the comments* received.

- Reach consensus: called the *Step 3 Experts Draft Guideline*.

Meeting details ^

Turn on captions

Alka Bali is presenting

Alka Bali is presenting

Manpreet Singh and 15 more

27 You

### STEP 3: Regulatory consultation & Discussion<sub>CONTD</sub>

**Stage III - Finalisation of Step 3 Experts Draft Guideline:** If, after due consideration of the consultation results by the EWG, *consensus* is reached amongst the experts on a *revised version of the Step 2b draft Guideline*.

- The *Step 3 Expert Draft Guideline* is *signed* by the experts of the ICH Regulatory Members.
- The *Step 3 Expert Draft Guideline* with regulatory EWG signatures is submitted to the *Regulatory Members of the Assembly* to request adoption as *Step 4* of the ICH process.

Meeting details ^

Turn on captions

Alka Bali is presenting

Alka Bali is presenting

Shailendra Siso... and 15 more

03:27

You

### STEP 4: Adoption of an ICH Harmonised Guideline

- *Step 4* is reached when the **Assembly agrees** that there is sufficient consensus on the draft Guideline.
- The **Step 4 Final Document** is **adopted** by the ICH Regulatory Members of the ICH Assembly as an **ICH Harmonised Guideline** at *Step 4* of the ICH process.

Meeting details ^

Turn on captions

Alka Bali is presenting

Participants: saurav Raghuvanshi, tanvi gupta, pavan ghunawat, Aashima Jindal, Nawang Tsetan, tarun sai, Deepthi Govapudi, Shivani singh

Alka Bali is presenting

Ankit singh and 15 more

03:27

You

### STEP 5: REGULATORY IMPLEMENTATION

- Having reached *Step 4*, the harmonised Guideline moves immediately to the final step of the process, that is, the **regulatory implementation**.
- This step is carried out according to the same **national/regional procedures** that apply to other regional regulatory guidelines and requirements, in the ICH regions.

Meeting details ^

Turn on captions

Alka Bali is presenting

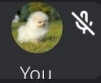
Participants: saurav Raghuvanshi, tanvi gupta, pavan ghunawat, Aashima Jindal, Nawang Tsetan, tarun sai, Deepthi Govapudi, Shivani singh



## B. Q&A PROCEDURE (QUESTIONS AND ANSWERS)

- Followed when *additional guidance* is considered necessary to help the interpretation of certain ICH harmonised Guidelines and ensure a smooth and consistent implementation in the ICH regions and beyond.
- Initiated with the endorsement by the ICH Assembly of a *Concept Paper*.
- For major implementation activities, the Assembly may also consider the need for *Business Plan*. An *Implementation Working Group (IWG)* is subsequently established.

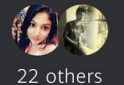
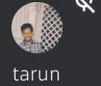
Alka Bali



You



tarun



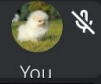
22 others

## B. Q&A PROCEDURE Contd..

Q&A Procedure is driven by *questions/issues raised by stakeholders*, which serve as the basis for the development of model questions for which standard answers are developed.

- Stakeholders are invited *via* the ICH website to submit their questions on a specific Guideline.
- *Consensus* reached by IWG on *draft Q&A document*.
- Based on level of information provided by the answers, IWG makes a *recommendation* to Assembly on whether the document should be a *Step 2b* draft Document published for consultation or a *Step 4* final Document published as final without consultation.

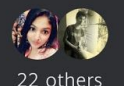
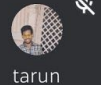
Alka Bali



You



tarun



22 others

### C. REVISION PROCEDURE

- Followed when the scientific/technical content of an existing ICH Guideline is **no longer up-to-date or valid**, or
  - When a **new information is to be added** in the form of an **Addendum** or an Annex to the Guideline with no amendments to the existing ICH Guideline necessary.
  - The procedure is initiated with the endorsement by the ICH Assembly of a **Concept Paper**.
  - For revisions, a **Business Plan is not necessary**.
  - An Expert Working Group (**EWG**) is established.
  - Procedure is almost identical to the Formal ICH Procedure of **5 steps**.
  - But, final outcome is a **revised version** of an existing Guideline (designated by the letters (R1), (R2). etc. after usual denomination of the Guideline), rather than new Guideline.
- e.g., ICH Q1A (R2) Stability testing of new drug substances; ICH Q2 (R1) Validation of analytical procedures*

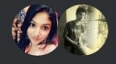
Alka Bali



You



tarun



22 others

### D. MAINTENANCE PROCEDURE

- Currently applicable only for **changes** to the **Q3C and Q3D** Guidelines and **M2 Recommendations**.
- Procedure is used when there is new information to be added or the scientific/technical content is out-of-date or no longer valid.

#### Maintenance Procedure for Q3C Guideline Impurities and Residual Solvents & Q3D Guideline for Elemental Impurities

- It is followed when there is a proposal of a "**permitted daily exposure**" (**PDE**) for a new solvent/elemental impurity or a revised PDE for an already classified solvent/elemental impurity.
- The procedure is similar to the Formal ICH Procedure of 5 ICH steps.

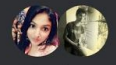
Alka Bali



You



tarun



22 others

## D. MAINTENANCE PROCEDURE<sub>Contd..</sub>

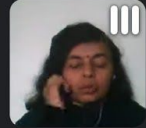
### Maintenance Procedure for M2 Recommendations

- Due to the **Information Technology (IT)** nature of the M2 EWG's work on Electronic Standards for the Transfer of Regulatory Information (ESTRI), some of their activities result in Recommendations.
- These Recommendations **do not undergo the formal ICH step process**, so as **to allow for flexible change as both science, and technologies evolve**. They are agreed in the EWG, signed by all Members of the EWG, and are approved by the ICH Assembly.

Alka Bali



You



tarun



22 others

## ICH GUIDELINES

The ICH topics are divided into **four categories** and ICH topic codes are assigned accordingly.



### 1. Quality Guidelines

- Conduct of *stability studies*
- Defining relevant thresholds for *impurities testing*
- More flexible approach to pharmaceutical quality based on *Good Manufacturing Practice (GMP) risk management*.



### 2. Safety Guidelines

- Potential risks like *carcinogenicity, genotoxicity and reprotoxicity*
- Recently, *Non-clinical testing strategy* for assessing the QT interval prolongation liability, the single most imp. cause of drug withdrawals in recent years.

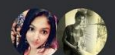
Alka Bali



You



tarun



22 others

## ICH GUIDELINES

# E

[3. Efficacy Guidelines](#)

- Design, conduct, safety and reporting of *clinical trials*.
- *Novel types of medicines* derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

# M

[4. Multidisciplinary Guidelines](#)

- Cross-cutting topics which do not fit into the Quality, Safety and Efficacy categories.
- Includes the *ICH medical terminology (MedDRA)*, the *Common Technical Document (CTD)* and the development of *Electronic Standards for the Transfer of Regulatory Information (ESTRI)*.

Alka Bali

You

tarun

22 others

## ICH QUALITY GUIDELINES

- Q1A - Q1F Stability
- Q2 Analytical Validation Q2(R1)** (Previously coded Q2A Q2B)
- Q3A - Q3D Impurities
- Q4 - Q4B Pharmacopoeias
- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- Q11 Development and Manufacture of Drug Substances
- Q12 Lifecycle Management

Alka Bali

You

tarun

22 others

ICH  
SITE


INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE


ICH HARMONISED TRIPARTITE GUIDELINE

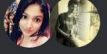
VALIDATION OF ANALYTICAL PROCEDURES:  
TEXT AND METHODOLOGY  
Q2(R1)


Current Step 4 version  
Parent Guideline dated 27 October 1994  
(Complementary Guideline on Methodology dated 6 November 1996  
incorporated in November 2005)

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*

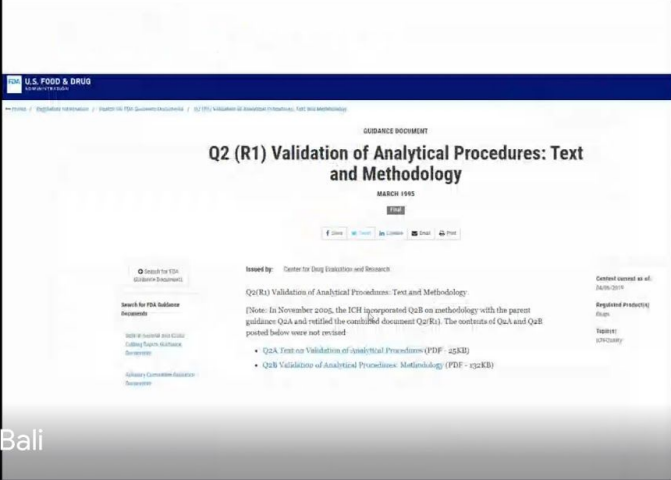
  
You

  
tarun

  
22 others

 Alka Bali

ICH  
SITE



U.S. FOOD & DRUG ADMINISTRATION

GUIDANCE DOCUMENT

**Q2 (R1) Validation of Analytical Procedures: Text and Methodology**


MARCH 1995


Issued by: Center for Drug Evaluation and Research

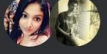
Q2(R1) Validation of Analytical Procedures: Text and Methodology


[Note: In November 2005, the ICH incorporated Q2E on methodology with the parent guidance Q2A and revised the combined document Q2(R1). The contents of Q2A and Q2E posted below were not revised.]

- Q2A: Test on Validation of Analytical Procedures (PDF - 25KB)
- Q2B: Validation of Analytical Procedures: Methodology (PDF - 132KB)

  
You

  
tarun

  
22 others

 Alka Bali



# PHARMACEUTICAL METHOD VALIDATION

Alka Bali

Zoom meeting participant list:

- You
- [Muted]
- tarun
- 22 others

## STRATEGY FOR VALIDATION OF METHODS

- Validity of a specific method should be demonstrated in **lab.experiments** using samples or standards that are similar to unknown samples analyzed routinely.
- The preparation and execution should follow a **validation protocol**, preferably written in a step-by-step instruction format.

Before formulating the strategy, it is assumed that:

- *Instrument has been selected and method developed.*
- *It meets criteria such as **ease of use**; ability to be **automated** and controlled by computer systems; **costs per analysis**; **sample throughput**; **turnaround time**; and **environmental, health and safety** requirements.*

Alka Bali

Zoom meeting participant list:

- You
- [Muted]
- Shailja
- 17 others

## STEPS IN METHOD VALIDATION

1. Develop a **validation protocol**, an operating procedure or **validation master plan** for validation.
2. For a specific validation project, define **owners and responsibilities**.
3. Develop a **validation project plan**.
4. Define **application, purpose and scope** of method.
5. Define the **performance parameters** and **acceptance criteria**.
6. Define **validation experiments**.
7. **Verify** relevant *performance characteristics of equipment*.
8. **Qualify materials**, e.g., standards and reagents for purity, accurate amounts and sufficient stability.

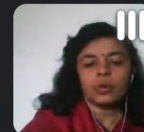
Alka Bali



You



Harsh

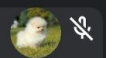


18 others

## STEPS IN METHOD VALIDATION<sub>Contd..</sub>

9. Perform **pre-validation experiments**.
10. **Adjust method parameters** or/and **acceptance criteria** if necessary
11. **Perform** full internal (and external) **validation experiments**.
12. **Develop SOPs** (standard operating procedures) for executing the method in the routine.
13. Define **criteria for revalidation**.
14. Define type and frequency of **system suitability tests** and/or **analytical quality control (AQC) checks** for the routine.
15. **Document** validation experiments and results in the **validation report**.

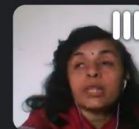
Alka Bali



You



Harsh



18 others

***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**?

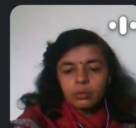
Alka Bali



You



Harsh



18 others



4G 38.5 K/s

3:38

### SCOPE OF METHOD & VALIDATION CRITERIA<sub>contd..</sub>

- What is the **expected concentration range**?
- What **precision and accuracy** is expected?
- How **robust** should the method be?
- Which **type of equipment** should be used? Is the method for one specific instrument, or should it be used by all instruments of the same type?
- Will the method be used in **one specific laboratory** or should it be applicable in all laboratories at one side or around the globe?
- What **skills do the anticipated users** of the method have?

Alka Bali

You

Harsh

18 others

### ALL METHOD PERFORMANCE CHARACTERISTICS MAY NOT BE NECESSARY..

- Method's performance characteristics should be based on **intended use** of the method. All anal. parameters need not be validated for a specific technique. e.g.,
  - *For a method to be used for **qualitative trace level analysis**, there is no need to test and validate the method's limit of quantitation, or the linearity, over the full dynamic range of the equipment.*
- **Initial parameters** should be chosen according to the analyst's experience and best judgment.
- **Final parameters** should be agreed between the lab or analytical chemist performing the validation and the lab or individual applying the method and users of the data to be generated by the method.

Alka Bali

You

Harsh

18 others

Alka Bali

- Scope of the method should also include the different types of equipment and the locations where the method will be run.
- But if the method is to be run on a specific instrument in a specific laboratory, there is no need to use instruments from other vendors or to include other laboratories in the validation experiments.
- *In this way, the experiments can be limited to what is really necessary.*

Video call participants: You, Nilam, 24 others

Alka Bali

### Validation parameters for specific tasks

	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

Video call participants: You, Nilam, 25 others

**CRITICAL FACTORS IN VALIDATION**

- **Analyst:** Validation experiments should be carried out by an *experienced analyst* to avoid errors due to inexperience.
- The analyst should be very well versed in the technique and operation of the instrument.
- **Instrument:** Before an instrument is used to validate a method, its performance specifications should be verified using generic chemical standards to ensure that the equipment is performing well.
- **Special attention** paid to equipment characteristics that are *critical* for the method. e.g., if detection limit is critical, **verify** the instrument's specification for base-line noise; or detector response to specified compounds.

Alka Bali

Click to add notes

Participants: You, Nilam, 25 others

**CRITICAL FACTORS IN VALIDATION Contd.**

**Operators:** Operators for the instruments should be sufficiently familiar with the technique and equipment. This will allow them to identify and diagnose unforeseen problems more easily and to run the entire process more efficiently.

**Chemicals:** Any chemicals used to determine critical validation parameters (reagents and reference standards) should be:

- Available in sufficient quantities
- Accurately identified,
- Sufficiently stable
- Checked for exact composition and purity.

Alka Bali

Click to add notes

Participants: You, Nilam, 24 others

Validation parameters for specific tasks

Parameter	Method	Equipment	Reagents	Consumables
Accuracy	100%	100%	100%	100%
Precision	100%	100%	100%	100%
Linearity	100%	100%	100%	100%
Specificity	100%	100%	100%	100%
Robustness	100%	100%	100%	100%
Stability	100%	100%	100%	100%
Resolution	100%	100%	100%	100%
Detection Limit	100%	100%	100%	100%
Quantification Limit	100%	100%	100%	100%

### CRITICAL FACTORS IN VALIDATION

**Other materials and consumables: e.g., chromatographic columns.**

- Should be **new and be qualified** to meet the column's performance criteria. This ensures that one set of consumables can be used for most experiments and avoids unpleasant surprises during method validation.

Aika Bali

Click to add notes

25 others

### INITIAL EXPERIMENTS MAY BE NEEDED

- If there is little or no information on the method's performance characteristics, it is recommended to **prove the suitability of the method** for its intended use in initial or preliminary experiments.
- These experiments should include: **Approximate precision; working range and detection limits.**
- If the preliminary validation data appear to be inappropriate, the method itself, the equipment, the analysis technique or the acceptance limits should be changed.
- Method development and validation are, therefore, an iterative process.**

Aika Bali

25 others

**VALIDATION**

primary should be  
type and application  
of diagnostic substances  
to other processes must

to determine critical  
of influence, experimental  
method priority

**VALIDATION**

Other e.g.,  
method content the  
is. This means that  
used for must  
method development testing

**MAY BE NEEDED**

on the method?  
recommended to  
for its intended use  
only

the. Approaches  
demonstrate  
to appear in the  
the experiment, the  
also. This should be  
before any, change, or

**IS AN EXAMPLE**

Complete selectivity is  
achieved. The resolution  
factor is 1.5 or higher.

### 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**.

$$R_s = 2(t_{RB} - t_{RA}) / (W_A + W_B)$$

$t_{RA}$  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.

You

You

Nilam

25 others

Alka Bali

**VALIDATION**

primary should be  
type and application  
of diagnostic substances  
to other processes must

to determine critical  
of influence, experimental  
method priority

**VALIDATION**

Other e.g.,  
method content the  
is. This means that  
used for must  
method development testing

**MAY BE NEEDED**

on the method?  
recommended to  
for its intended use  
only

the. Approaches  
demonstrate  
to appear in the  
the experiment, the  
also. This should be  
before any, change, or

**IS AN EXAMPLE**

Complete selectivity is  
achieved. The resolution  
factor is 1.5 or higher.

### 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)

You

You

Nilam

25 others

Alka Bali

SEQUENCE OF VALIDATION<sub>Contd..</sub>

- The more time-consuming experiments, such as *accuracy* and *ruggedness*, are included towards the end.
- Some of the parameters, as listed under (2) to (6), can be measured in **combined experiments**. For example, when the precision of peak areas is measured over the full concentration range, the data can be used to validate the linearity.

Alka Bali

You  
Nilam  
24 others

SEQUENCE OF VALIDATION

- During method validation, the parameters, acceptance limits and frequency of ongoing system suitability tests or QC checks should be defined.
- **Criteria should be defined** to indicate when the method and system are *beyond statistical control*.
- The aim is to **optimize** these experiments so that, with a *minimum number of control analyses*, the method and the complete analytical system will provide long-term results to meet the objectives defined in the scope of the method.

Alka Bali

You  
Nilam  
25 others

4G 45.3 K/s 3:32

Alka Bali

### VALIDATION REPORT

➤ Once the method has been developed and validated, a **validation report** should be prepared that includes:

1. **Objective and scope** of method (applicability, type).
2. Summary of methodology.
3. Type of compounds and matrix.
4. All chemicals, reagents, reference standards, QC samples with purity, grade, their source or detailed instructions on their preparation.
5. Procedures for quality checks of standards and chemicals used.
6. Safety precautions.
7. A plan and procedure for method implementation from the method development lab to routine analysis.

You

Nilam

25 others

Alka Bali

### VALIDATION REPORT Contd.

8. Method parameters.
9. **Critical parameters** taken from robustness testing.
10. Listing of **equipment** and its functional and **performance requirements**, e.g., cell dimensions, baseline noise and column temperature range. For complex equipment, a picture or schematic diagram may be useful.
11. **Detailed** conditions on how the experiments were conducted, including sample preparation. The report must be detailed enough to ensure that it can be reproduced by a competent technician with comparable equipment.
12. **Statistical procedures** and representative calculations.

You

Nilam

25 others

**VALIDATION REPORT** Contd..

**13. Procedures for QC** in routine analyses, e.g., system suitability tests.

14. Representative **plots**, e.g., chromatograms, spectra and calibration curves.

15. Method **acceptance limit** performance data.

16. The expected uncertainty of measurement results.

**17. Criteria for revalidation.**

18. The **person(s)** who developed and validated the method.

19. References (if any).

20. Summary and conclusions.

21. Approval with names, titles, date and signature of those responsible for the review and approval of the analytical test procedure.

Alka Bali

You

Nilam

24 others

4G 39.3 K/s

**VALIDATION REPORT** Contd..

**13. Procedures for QC** in routine analyses, e.g., system suitability tests.

14. Representative **plots**, e.g., chromatograms, spectra and calibration curves.

15. Method **acceptance limit** performance data.

16. The expected uncertainty of measurement results.

**17. Criteria for revalidation.**

18. The **person(s)** who developed and validated the method.

19. References (if any).

20. Summary and conclusions.

21. Approval with names, titles, date and signature of those responsible for the review and approval of the analytical test procedure.

Alka Bali

You

Shivani

24 others

meet.google.com is sharing your screen. Stop sharing Hide



4G 39.2 K/s 3:05

### VERIFICATION OF STANDARD METHODS

- A laboratory applying a specific method should have **documented evidence** that the method has been appropriately validated.
- This holds for methods developed in-house, as well as for **standard methods**, for example, those developed by organizations such as the EPA, American Society for Testing and Materials (ASTM), ISO or pharmacopoeias.

➤ *Should standard methods be revalidated in the user's laboratory and, if so, should method revalidation cover all experiments, as performed during initial validation?*

➤ *Which documentation should be available or developed in-house for standard methods?*

Alka Bai


meet.google.com is sharing your screen. Stop sharing Hide

You  
Shivani  
24 others

4G 47.8 K/s 3:06

### VERIFICATION OF STANDARD METHODS Contd..

➤ Official guidelines and regulations are not explicit about validating standard methods. Only CITAC/EURACHEM guide (19) includes a short paragraph that reads as follows:



*'The validation of standard or collaboratively tested methods **should not be taken for granted**, no matter how impeccable the method's pedigree - the **laboratory should satisfy itself that the degree of validation of a particular method is adequate for the required purpose**, and that the laboratory is itself able to match any stated performance data.'*

Alka Bai

meet.google.com is sharing your screen. Stop sharing Hide

You  
Shivani  
24 others

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

There are two important requirements in this excerpt:

1. The standard's **method validation data are adequate** and sufficient to meet the laboratory's method requirements.
2. The **laboratory must be able to match the performance data** as described in the standard.

Further advice comes from FDA's 21 CFR 194 section(a)2 "*If the method employed is in current revision of the USP, NF, Association of Official Analytical Chemists, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice. The suitability of all testing methods used shall be verified under actual conditions of use.*"

Alka Bali

meet.google.com is sharing your screen. Stop sharing Hide

Zoom meeting interface showing participant avatars and names: You, Shivani, and 25 others.

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

- Like the validation of methods developed in-house, the **evaluation and verification** of standard methods should also follow a **documented process** that is usually the validation plan.
- **Results** should be **documented in the validation protocol**.
- Both documents will be the major source for the validation report.

Alka Bali

meet.google.com is sharing your screen. Stop sharing Hide

Zoom meeting interface showing participant avatars and names: You, Shivani, and 25 others.

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

**First step:** The *scope of the method*, as applied in the user's lab, should be defined. This should be done independently of what is written in the standard method and should include **information** such as:

- Type of compounds to be analyzed
- **Matrices**
- Type of **information required** (qual. or quantitative)
- **Detection and quantitation limits**
- **Range**
- **Precision and accuracy** as specified by the client of the analytical data
- **Type of equipment:** location and environmental conditions.

Alka Bali

Zoom meeting interface showing participants: You, Shivani, and 25 others.

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

### Second step:

The method's performance requirements should be defined in considerable detail, again irrespective of what has been validated in the standard method.

➤ *Results of these 2 steps lead to the **experiments** required for adequate method validation and to the minimal acceptance criteria necessary to prove that the method is suitable for its intended use.*

### Third step:

Required experiments and expected results should be compared with what is written in the standard method.

In particular, the standard method should be checked for the following **five items**:

Alka Bali

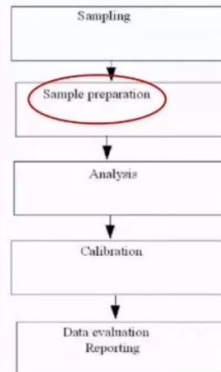
Zoom meeting interface showing participants: You, Aashima, and 25 others.

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

1. Are reported validation results obtained from **complete procedure** or just a part of it?

e.g., validation data from the published method is obtained from the chromatographic analysis but **sample preparation steps are not included.**

➤ A complete validation of the analytical procedure should include the entire process from sampling, sample preparation, analysis, calibration and data evaluation to reporting.



Alka Bali

meet.google.com is sharing your screen. Stop sharing

You

Aashima

25 others

## VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

2. Has the same **matrix** been used?

3. Did the validation experiments cover the **complete concentration range** as intended for the method in the user's laboratory? If so, has the method's performance been checked at the different concentration ranges?

4. Has the same **equipment** (brand, model) been used as available in the user's laboratory, and, if not, was the scope of standard method regarding this item broad enough to include the user's equipment? This question is very important for a gradient HPLC analysis, where the HPLC's delay volume can significantly influence the method's selectivity.

Alka Bali

meet.google.com is sharing your screen. Stop sharing

You

Aashima

25 others

VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

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.

Alka Bali

meet.google.com is sharing your screen. Stop sharing

Participants: You, Aashima, 25 others

VERIFICATION OF STANDARD METHODS<sub>Contd..</sub>

**SUMMARY:**  
Workflow for evaluation and validation of standard methods

```

graph TD
    A[Define scope of the user's method] --> B[Define validation parameters and limits]
    B --> C{Standard method fits scope, parameters and limits?}
    C -- yes --> D[Define and perform system suitability testing]
    C -- no --> E[Perform part or full validation]
    E --> D
  
```

Alka Bali

meet.google.com is sharing your screen. Stop sharing

Participants: You, tarun, 24 others

## (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 Pharmaceutical 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

*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 Pharmaceutical 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 of the user, on the type of procedure and its associated equipment or instrumentation, on the specific procedural conditions, and on the article 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

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.

 Alka Bali

---

## 2 (1226) Verification of Compendial Procedures / *General Information*

USP 40

➔ 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.

 Alka Bali

## 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?)

## QC Plan and Implementation for Routine<sub>Contd..</sub>

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



## QC Plan and Implementation for Routine<sub>Contd..</sub>

- 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.

meet.google.com is sharing your screen. Stop sharing

ball is presenting

## QC Plan and Implementation for Routine<sub>Contd..</sub>

- 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.

meet.google.com is sharing your screen. Stop sharing

## TRANSFERRING VALIDATED ROUTINE METHODS

Validated routine methods are transferred between:

- Laboratories at same or different sites when contract labs. offer services for routine analysis in different areas:
- When products are manufactured in different sites/areas.

- When validated routine methods are transferred between laboratories and sites, ***their validated state should be maintained*** to ensure the same reliable results in the receiving laboratory.
- This means the ***competence of the receiving laboratory*** to use the method should be demonstrated through tests, for example, ***repeat critical method validation experiments*** and ***run samples in parallel*** in the transferring and receiving laboratories.

meet.google.com is sharing your screen. Stop share

Meeting details ^



## TRANSFERRING VALIDATED METHODS: PROCEDURE (RECOMMENDED STEPS)

- Designate a **project owner**
- Develop a **transfer plan**
- Define **transfer tests and acceptance criteria** (validation experiments, sample analysis: sample type, no. of replicates)
- Describe **rationale** for tests
- **Train receiving lab operators** in transferring lab on equipment, method, critical parameters and troubleshooting
- **Repeat 2 critical method validation tests** in routine lab
- **Analyze** at least **three samples** in transferring and receiving lab
- **Document transfer results**

meet.google.com is sharing your screen.

Stop sharing

Alka Bali is presenting

ayy sh and 14 more

03:26

Messages

You

## 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?**

meet.google.com is sharing your screen.

Stop sharing

0:02:56

Meeting details



Turn on captions

Alka Bali is presenting

0:05:05

## 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.

## 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.

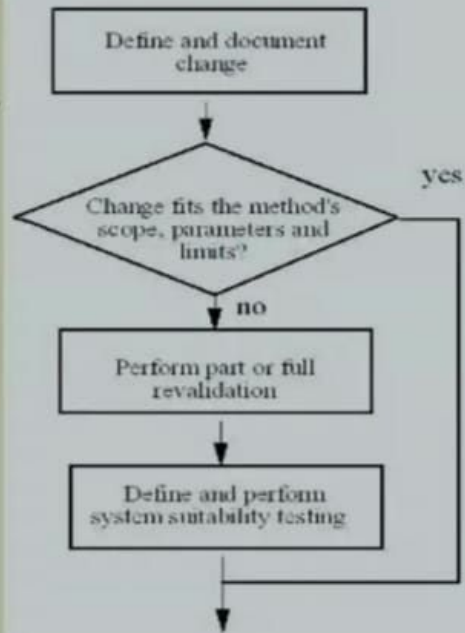
meet.google.com is sharing your screen

## 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.

## 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 revalidation

meet.google.com/6-sharing-your-screen

## 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.

meet.google.com is sharing your

## 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

meet.google.com is sharing your

## 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	--



## 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.*

meet.google.com a sharing your screen

## SELECTIVITY/SPECIFICITY

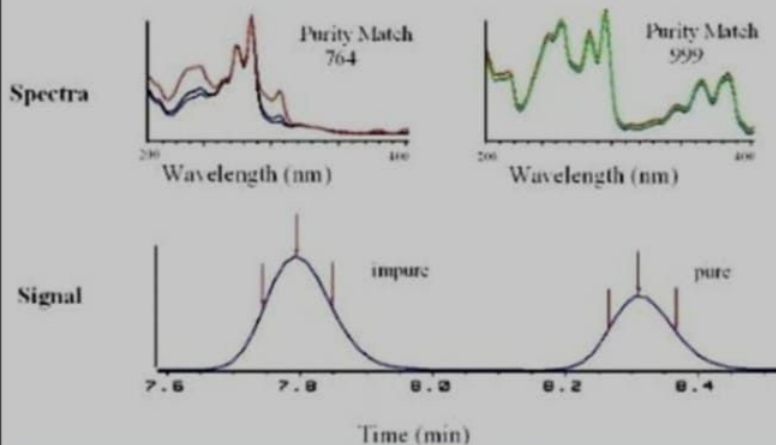
- **USP** monograph defines selectivity of an analytical method as its ability to *measure accurately an analyte in the presence of interference*, such as synthetic precursors, excipients, enantiomers & known (or likely) degradation products that are expected to be present in sample matrix.
- *Selectivity 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*.

www.dulomix.com is the best place to find the best quality control materials for your laboratory.

## 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.

## 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 percent** can be detected.

|| meet.google.com is sharing yo

## SELECTIVITY/SPECIFICITY<sub>CONTD..</sub>

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<sub>CONTD..</sub>

### 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.*

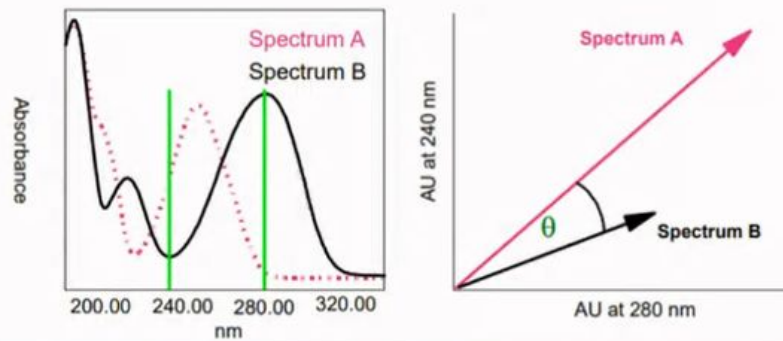
meet.google.com

|| meet.google.com | sharing your screen. Stop sharing Hide

Meeting details ^



## SELECTIVITY/SPECIFICITY<sub>CONTD..</sub>



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

meet.google.com is sharing your screen. Stop sharing Hide

Meeting details ^

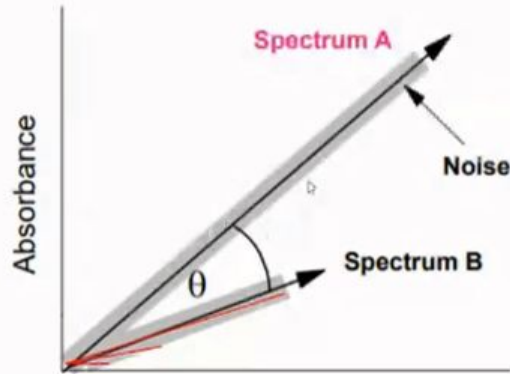


## SELECTIVITY/SPECIFICITY CONTD.

*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.

meet.google.com is sharing your screen. Stop sharing HIDE

Meeting details ^



## SELECTIVITY/SPECIFICITY<sub>CONTD..</sub>

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.



## PRECISION AND REPRODUCIBILITY

- **Precision** is the extent to which individual test results of multiple injections of a series of standards agree.
- Measured standard deviation is subdivided into 3 categories: *repeatability, intermediate precision and reproducibility*.

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## PRECISION AND REPRODUCIBILITY

- **Repeatability** is obtained when the analysis is carried out in a laboratory by an operator using a piece of equipment over a relatively **short time span**.
- At least six determinations of three different matrices at 2 or 3 different concentrations should be performed.
- Expressed as **%RSD** (calculated as  $SD \times 100 / \text{mean}$ )
- **ICH**: Results from at least 6 replications to be measured at 100% of test target concentration or at least 9 replications covering complete specified range. e.g., results can be obtained at 3 concns. with 3 injections at each concentration on same day (***intra-day precision***) and 3 consecutive days (***inter-day precision***)

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## PRECISION AND REPRODUCIBILITY

- **Acceptance criteria** for precision depend very much on the type of analysis.
- **Pharmaceutical QC precision** of **<1 % RSD** is easily achieved for compound analysis.
- Precision for **biological samples** lesser: **15%** at the concentration limits and **10%** at other concentration levels.
- **Environmental and food samples:** Precision is largely dependent on sample matrix, the concentration of the analyte, the performance of the equipment and the analysis technique. It can vary **between 2% and > 20%**.

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## Estimated Precision & Analyte Concentration

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

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## PRECISION AND REPRODUCIBILITY

- **Intermediate precision** is a term that has been defined by ICH as the **long-term variability** of the measurement process.
- **Objective** is to verify that *in same laboratory*, method will provide same results once the development phase is over.
- Determined by comparing results of a method run within a single laboratory over a **number of weeks**.
- Intermediate precision may reflect discrepancies in results obtained..
  - *from different operators,*
  - *from inconsistent working practice (thoroughness) of the same operator,*
  - *from different instruments,*
  - *with standards and reagents from different suppliers,*
  - *with columns from different batches or*
  - *a combination of these.*

meet.google.com is sharing your screen. Stop sharing Hide

Meeting details ^





## PRECISION AND REPRODUCIBILITY

- **Reproducibility** as defined by the ICH, represents the precision obtained *between different laboratories*.
- **Objective** is to verify that the method will provide the same results *in different laboratories*.
- Determined by analyzing aliquots from homogeneous lots in **different laboratories** with **different analysts**, and by using **operational and environmental conditions** that may differ from, but are still within, the specified parameters of the method (inter-laboratory tests).
- Validation of reproducibility is important if the method is to be used in different laboratories.

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## Typical variations affecting a method's reproducibility

- Differences in **room temperature and humidity**
- **Operators** with different experience and thoroughness
- **Equipment** with different characteristics, e.g. delay volume of an HPLC system
- Variations in **material and instrument conditions**, e.g. in HPLC, mobile phases composition, pH, flow rate of mobile phase
- Variation in experimental details not specified by the method
- Equipment and consumables of different ages
- Columns from **different suppliers or different batches**
- **Solvents, reagents** and other material with varying quality

|| meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^



## 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

meet.google.com is sharing your screen. [Stop sharing](#) [Hide](#)

Meeting details ^

