6. To be fully optimised before transfer for validation of its characteristics such as accuracy, precision, sensitivity, ruggedness etc.

Note : (a) Method validation for a particular analytical problem may not always be applicable in other situations due to interference of other ingredients present in the formulation.
(b) The method so developed must discriminate between the available for which it is designed, process contamination, decomposition products, related substances.
(c) Before finally selecting a method for application in a given case, trial run of the proposed method is advisable.

Type of analytical problems

1. It may be essentially a problem already solved and the earlier validated analytical procedure may be directly applied such as compendial procedures.
2. It may be related to earlier problem and the existing validation procedure may be applicable with some judicious changes/modifications.
3. It may altogether be a new problem, one might not have encountered or solved before. It is here that the experience/skill/expertise of the analyst is called for and the options are :
   (a) Use personal experience and knowledge of analytical chemistry.
   (b) Try out well-established procedures.
   (c) Survey the literature; unfortunately in most of the reported methods, the knowledge/ information about various parameters of the method (LOD, LOQ, precision, accuracy, range, interference) is often inadequate, and some degree of optimization is required.

Data for analytical procedures

(Before finalising the method, it is preferable to enlist the proposed analytical specifications to be applied to a particular substance or its dosage form.)

1. Justification for proposing an analytical procedure with comparison to other possible alternatives should be described.
2. Scientific basis i.e. the principle involved in the proposed procedure should be elaborated. If the proposed method is intended to replace the existing procedure comparative laboratory data including merits/demerits should be made available.
3. List of all necessary reagents, test solutions with directions for their preparation. Unstable reagents be identified, their storage conditions and usable shelf life be specified.
4. List of instruments required along with their parameters such as instrument type, cell dimensions, GLC/HPLC columns, TLC plates and sensitivity required.
5. Detailed step by step procedure along with equilibration, extraction and centrifugation time, system suitability parameters if required, preparation of sample, standard, use of blank and other procedural details as required.
6. Detailed complete formulae for calculation of analytical results with all terms/symbols defined along with representative calculations for each parameter.
7. Precautions or any other unusual hazards in carrying out the method be indicated.
8. It must be specified whether the method is capable of detecting decomposition products/ impurities/related substances or not.
9. Whether the proposed method is stability indicating or not.

Note : The proposed method must provide comprehensive details as deemed necessary to allow reasonably trained analyst to perform it in a reliable and reproducible manner.

Analytical parameters to be validated

- Accuracy
- Precision

Analytical data required for assay validation

	Type of analysis			
	1	2		3
Parameters	Assay	QT	QL	Assay
Accuracy	Yes	Yes	—	—
Precision	Yes	Yes	No	Yes
Specificity	Yes	Yes	Yes	—
LOD	No	No	Yes	—
LOQ	No	Yes	No	—
Linearity	Yes	Yes	No	—
Range	Yes	Yes	—	—
Ruggedness	Yes	Yes	Yes	Yes

quantitatively with acceptable precision, accuracy and reliability by a given method under stated experimental conditions. The procedure usually followed is to analyse samples containing decreasing known quantity of the analyte and determine the lowest level at which acceptable level of accuracy/ precision is attained. However, it is preferable to validate the method at or near LOQ.

- Instrumental—Usually 10 times of standard deviation of blank response; 2-3 times higher than LOD.
- Non-instrumental—One has to establish the level experimentally depending on the method of analysis employed.

Ruggedness

Degree of reproducibility of test results obtained by analysing the same sample under variety of normal test conditions such as different

- Analysts
- Instruments
- Days
- Reagents
- Columns and TLC plates

i.e., lack of influence of environmental variables on the method. Comparison of reproducibility of test results to the precision of assay is the direct measure of ruggedness of the method.

Robustness

It is the measure of the capacity of the analytical method to remain unaffected by small but deliberate variations in procedure. It provides an indication about variability of the method during normal laboratory conditions.

Sensitivity

Capacity of the test procedure to record small variations in concentrations.

3. All the critical variables and their effect on the results must have been determined and the need and the way for their control must be emphasized.
4. The method should provide full written details by the leader of the team and preferably tested by junior analyst or an analyst who does not have background of the method.
5. All the reagents, equipments including unusual ones should be located and available from common supplier to make collaborating laboratories to procure the same. Alternatively sufficient quantity should be procured and supplied to the collaborating laboratories.
6. The samples must be identical and homogeneous to keep sampling error to minimum.
7. For inter-laboratory collaborative studies, at least 8 laboratories should participate to analyse sufficient samples to generate minimum of 40 point data.
8. Samples must be stable to withstand stress and strain of transport/storage.
9. Reserve samples (to replace lost sample or for re-analysis of sample—to evaluate the cause in case of abnormal results).
10. Instructions for carrying out collaborative studies should be clear and reviewed by personnel not associated with study.
11. If the analyte is not very stable, all participants should start analysis at the same time.
12. Practice samples to be provided for establishing recovery, repeatability of the methodology.

Advantages

1. Regulatory credibility for method validation.
2. Best estimate for reproducibility.
3. Best way to test that the method works as written.
4. Well-defined guidelines.

Disadvantages

1. Time and resources required for conducting the study.
2. Employment of highly qualified and experienced personnel.
3. Usually large number (8) of laboratories are required to obtain a good reproducibility estimate.

Collaborative study design

1. Triplicate samples (distinct lots)
2. Six replicates
3. Single analyst
4. Single day
5. Analyst to analyst
6. Day to day
7. Lot to lot.

Documentation

"DO AS WRITTEN & WRITE AS DONE."

Good documentation is an essential part of CGMP/CGLP. Its aim is to define the specification for all the materials and method of analysis and control, so that all personnel concerned with quality control know what to do and when to do, so that authorized persons have all the information necessary to decide whether or not to release a batch for sale, to provide an audit tract that to permit investigation of history of any suspected defective batch. The design and use of documents depends on the manufacturer.

General information

1. The document should be designed, prepared, reviewed and distributed with care. They shall comply with relevant part of the manufacturing process (manufacture, QC, marketing authorization).

5. Services of a referral laboratory may be obtained for post-testing audit.
6. Corrective action based on validation report.

Common problems for successful validation

1. Failure to include sample of critical impurity, degradation product or internal standard necessary to assess the adequacy of the method.
2. Failure to list complete specifications of the method.
3. Selection of unsuitable specifications such as those which do not account for assay building.
4. Failure to provide sufficient details of reagent preparation or equipment parameters.
5. Use of arbitrary arithmetic correction.
6. Use of single source of equipment or reagent without full specifications.
7. Use of specialized tools, equipments not commercially available.
8. Use of internal standard or any other reagent which is not commercially available.
9. Failure to provide fully characterized reference standard.
10. Failure to submit complete, legible data and labelled chromatographs and spectra.

Future of validation

In spite of the advances in analytical technology offering newer methods of analysis which are more accurate and precise, the need for validation shall always remain.

It is better to do modest amount of validation work on as many assays/products as possible rather than do an exhaustive job for few and no work on others.

As quality control process is not static, some form of validation/verification should continue till the validated procedure is in use. It should not be a concept that once the method is initially developed and validated, it is forgotten.

Responsibility

For validation work, one may require personnel with specialized training/qualifications beyond that usually required for routine quality control. Such personnel should not only bear the responsibility but should have personally to cope with the responsibility in term of emotion, experience and knowledge for which individual needs to have appropriate character i.e. education, commitment, leadership and empowerment.

It is advisable to get this work done from consultants under contractual obligations instead of hiring specialized personnel and facilities.

Consultant

Consultants are individuals or a group of persons hired by a company or organisation on a contractual basis. The advantages and disadvantages of having a work performed by consultants are the same in any given situation.

Consultants are able to review the present protocols and are in a position to apply experience gained in other organisations and field to problems that the personnel within the hiring company might not have anticipated. This has definite advantages as the hiring company need not go through potentially time-consuming and arduous task of recruiting technical personnel with specialized talent for particular job. This is more economically viable as work is taken up under contractual agreement with pre-determined cost and completion schedule.

Precaution : Since such works are time and cost bound, the initial contract must clearly spell completion schedule of the project and the overall cost.