IMPURITY PROFILE

Balaji College of Pharmacy

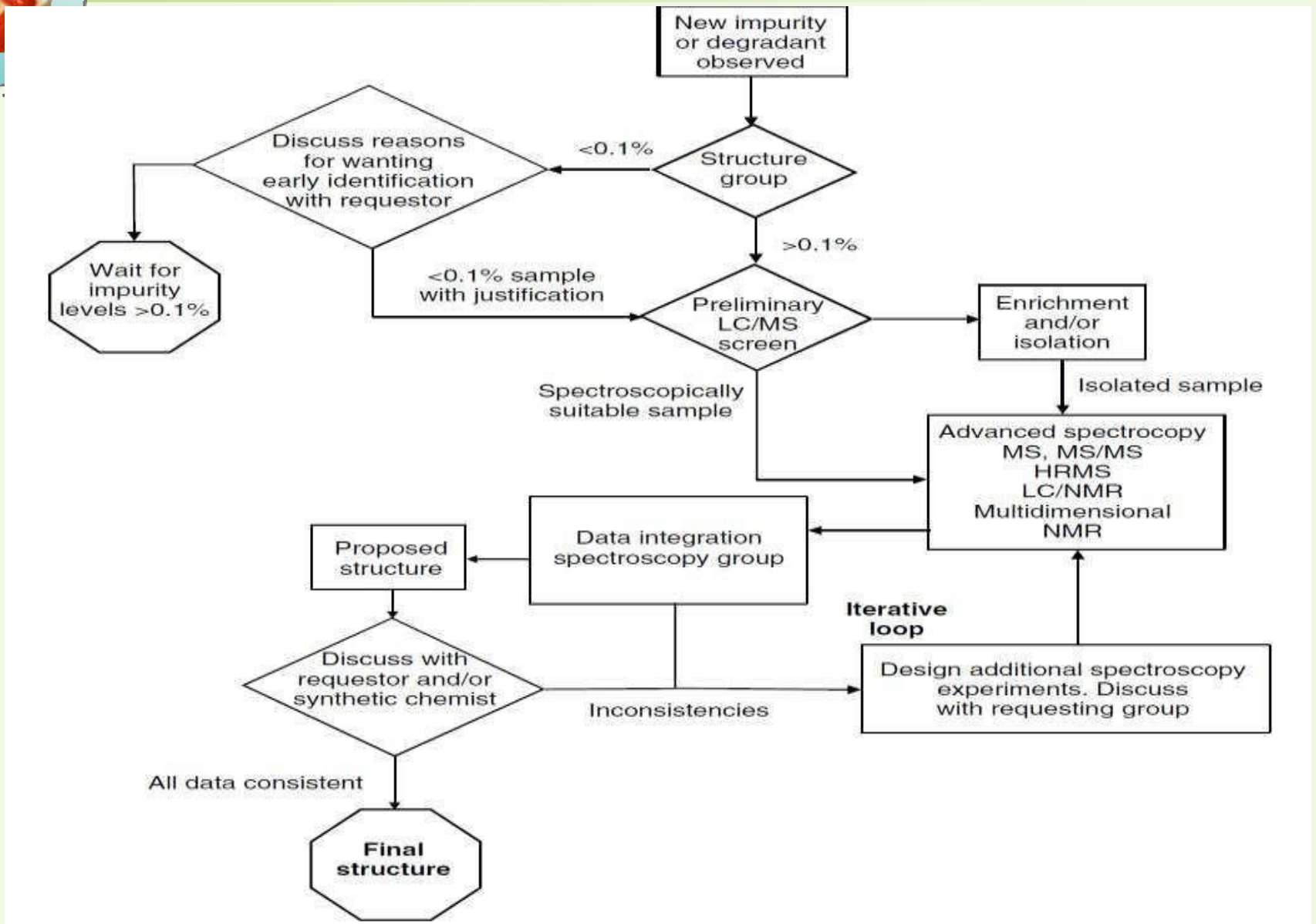
LOGO

Contents

Objective

- The objective of impurity profiling is to identify and quantitate impurities that are present in an API or drug product.
- Impurities may take the form of three broad classifications: (1) organic impurities, (2) inorganic impurities, and (3) residual solvent impurities.
- Organic impurities typically arise from the manufacturing process and may include unreacted starting materials, reaction intermediates, degradation products, and reaction by-products. Some of these impurities may even be genotoxic.
- Inorganic impurities include ligands and catalysts, heavy metals, inorganic salts, and filter aids. Residual solvents can be either organic or inorganic solvents used during manufacturing.

- Regulatory agencies require identification and quantitation of impurities above specific levels.
- Hence, conducting impurity profiling projects requires thorough documentation, robust data management, and the use of a variety of analytical techniques, e.g., LC/UV, LC-MS, and NMR, in order to provide prove that the impurities have been properly characterized.


New impurity or degradant observed
Structure group
<0.1%
Discuss reasons for wanting early identification with requestor
Wait for impurity levels >0.1%
<0.1% sample with justification
>0.1%
Preliminary LC/MS screen
Enrichment and/or isolation
Isolated sample
Spectroscopically suitable sample
Advanced spectrocopy
MS, MS/MS
HRMS
LC/NMR
Multidimensional NMR
Data integration spectroscopy group
Proposed structure
Iterative loop
Discuss with requestor and/or synthetic chemist
Inconsistencies
Design additional spectroscopy experiments. Discuss with requesting group
All data consistent
Final structure

What to be done after separation ??

- Purified and sample should be split into aliquots for MS,NMR, and vibrational spectroscopy
- Repetition of MS of sample is required

✓ 1st confirm that molecular weight of sample corresponds to initial LC/MS data

✓ 2nd determine fragmentation pathway from MS/MS data

- Empirical formula of HRMS is useful, if impurity is unknown and unrelated with drug
- In this case, by FT-IR,FT-Raman or both, functional groups are identified
- Structure is eluted by MS and NMR (Homo and hetero nuclear direct
- and long range chemical shift correlation experiments)

Samples to be profiled

Impurity profiling should be done for the following samples:

- Active ingredient
- Process check (synthesis or formulation)
- Final product.

Components seen in a profile

Ideally, an impurity profile should show the following:

- Synthesis-related impurities
- Formulation-related impurities
- Degradation products
- Interaction products.

Isolating impurities

- It is often necessary to isolate impurities because the instrumental methods that were mentioned earlier for directly characterizing impurities without isolating them are not available or when the authentic material is needed for further confirmation of the structure or its toxicity.
- Isolation should be initiated based on simple extraction or partition methods.
- It may be possible to extract impurities selectively on the basis of acidity, basicity, or neutrality.
- The extraction process usually involves liquid–liquid extraction, where one phase is an aqueous solution and the other is an organic phase that is nonpolar.
- By appropriate adjustment of the pH of the aqueous solution, one can extract acidic, basic, or neutral impurities.

Characterization of impurities

- Once an impurity has been detected, it becomes necessary to estimate its content.
- Detectability frequently means that a given component provides a signal at least twice that of background noise or the baseline.
- Initial estimations are generally done against the parent compound because in most cases the authentic sample of impurity is not available.
- It is important that the authentic sample should be used for estimations, when it is available. If the estimations indicate that a given impurity content is greater than 0.1%, then it must be characterized as per the FDA requirements

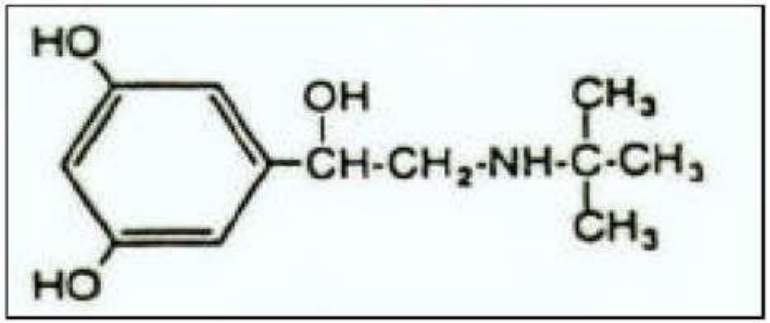
The characterization of impurities is generally achieved by the following means:

- Matching retention data
- UV
- IR
- NMR
- MS

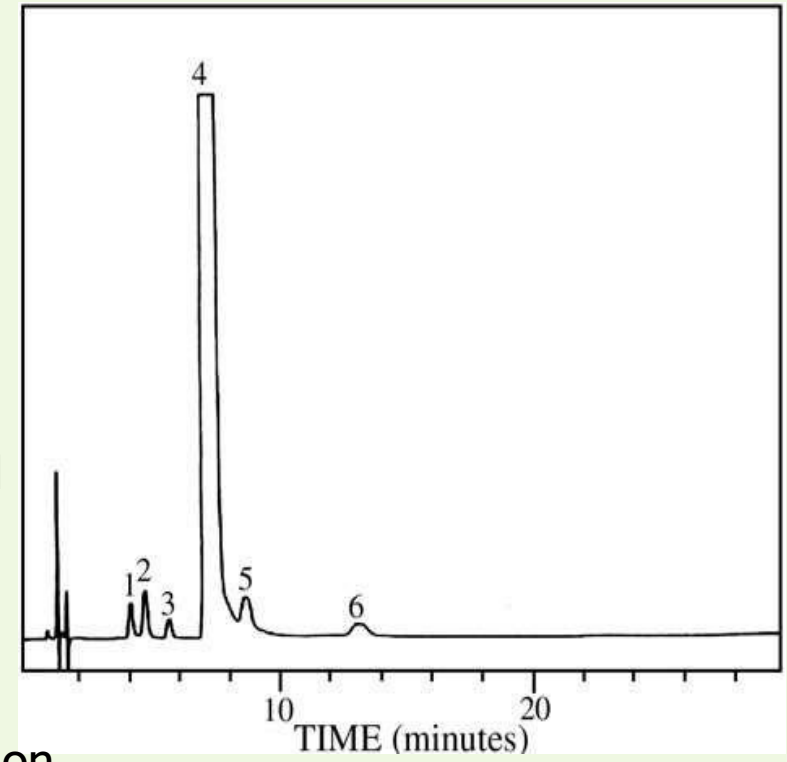
Hyphenated methods such as gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectromety (LC-MS)

Case study

A case study is presented below relating to monitoring impurities in terbutaline sulfate (it is sold as a racemate).



Structure of Terbutaline



The first step in this process was to review all potential
sources of impurities in terbutaline.
Synthesis: starting materials, solvents used, intermediates, theorize potential by-products.
Formulation: solvents used, potential interaction products, any potential degradation products.
Stability: potential degradation products or reaction products that may be produced because of thermal, hydrolytic, oxidation,
or photochemical reactions.

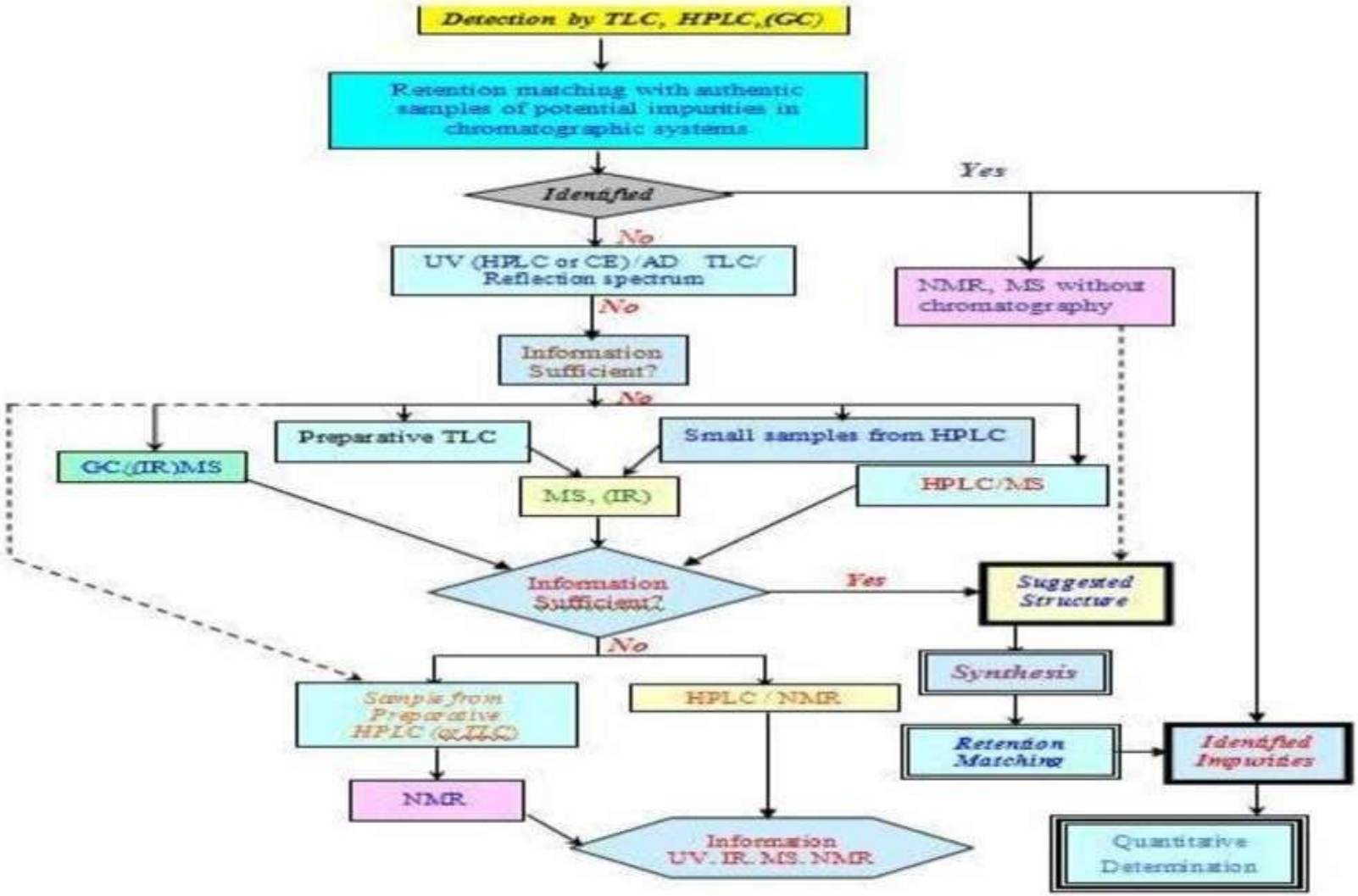


Figure 1: General Scheme for Drug Impurity Profiling