



Impurities and Degradents

The unwanted Guests in Drug Substance

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References –

ICH Q 3 A (R2), Impurities in new Drug Substances

European Medicines Agency (EMA)

October 2006

Q 3 B (R2) Impurities in New Drug Products

US FDA Guidance for Industry

July 2006

ICH Q 3 C (R3), Impurities: Residual Solvents

European Medicines Agency (EMA)

March 1998

Genotoxic and Carcinogenic Impurities in Drug Substances and Products

US FDA Guidance for Industry

December 2008

Guidelines on limits of Genotoxic Impurities

European Medicines Agency (EMA)

January 2007

Guidelines for Limits for residues of Metal catalyst

European Medicines Agency (EMA)

January 2007

A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity

Lutz Muller et al , Regulatory Toxicology and Pharmacology

Volume 44, Issue 3, April 2006, Pages 198-211

Content of the presentation

1. Process chemistry
2. Source of Impurities
3. Process related
 1. Starting materials
 2. Side reactions
 3. Chiral Impurity
 4. Degradable
 5. Metabolites
4. Residual solvents
5. Genotoxic Impurities
6. Metal contamination
7. Extractable and leachables
8. Identification , isolation, Characterisation and quantification methodologies

The Art and Science of making a drug substance

Organic chemistry makes it possible to produce an Active pharmaceutical Ingredient (API) by several routes of manufacture using multiple stages in the process , with a combination of organic molecules , reagents and solvents

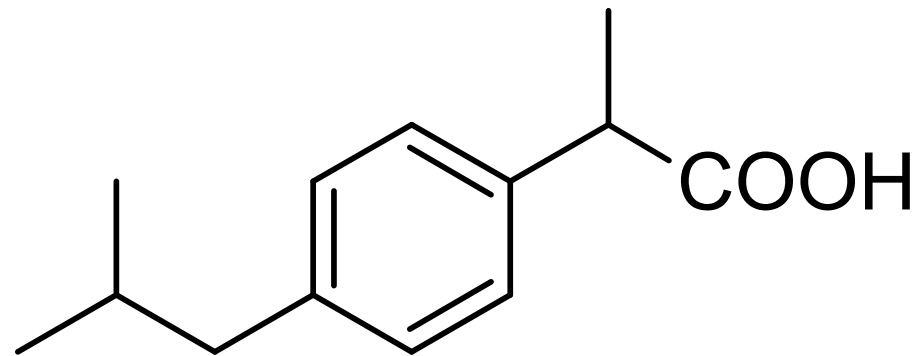
Even though the final molecule is same , the unwanted components appearing in the in the API can vary with the use of various organic molecules , reagents and solvents in the Process.

These unwanted components called as “ Impurities” can reduce the efficacy of the drug, or bring in side effects which can be dangerous to the human being.

The side effects could be noticed immediately, or over a period of extended use of the drug

One API – Several routes

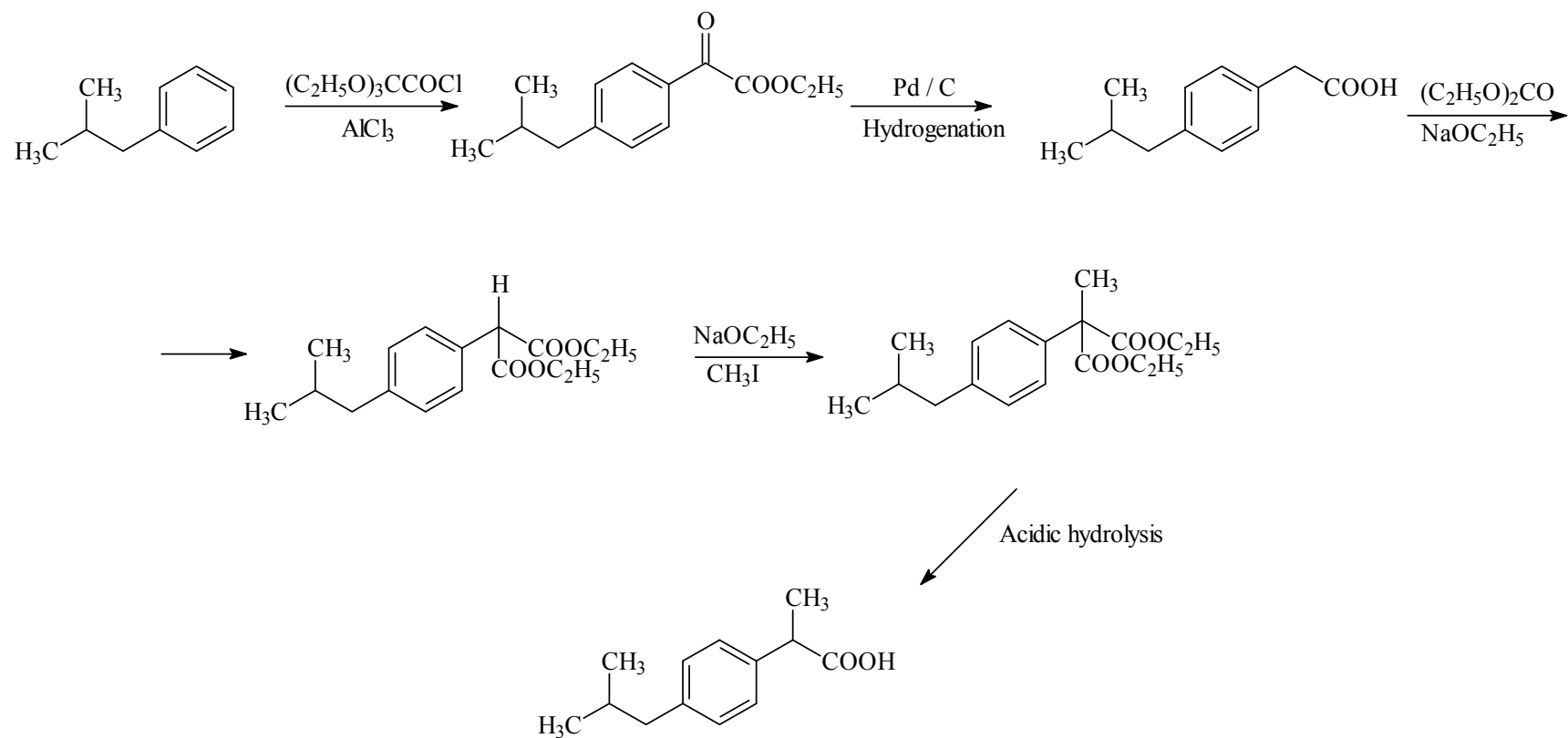
Ibuprofen



Analgesic, Anti-inflammatory

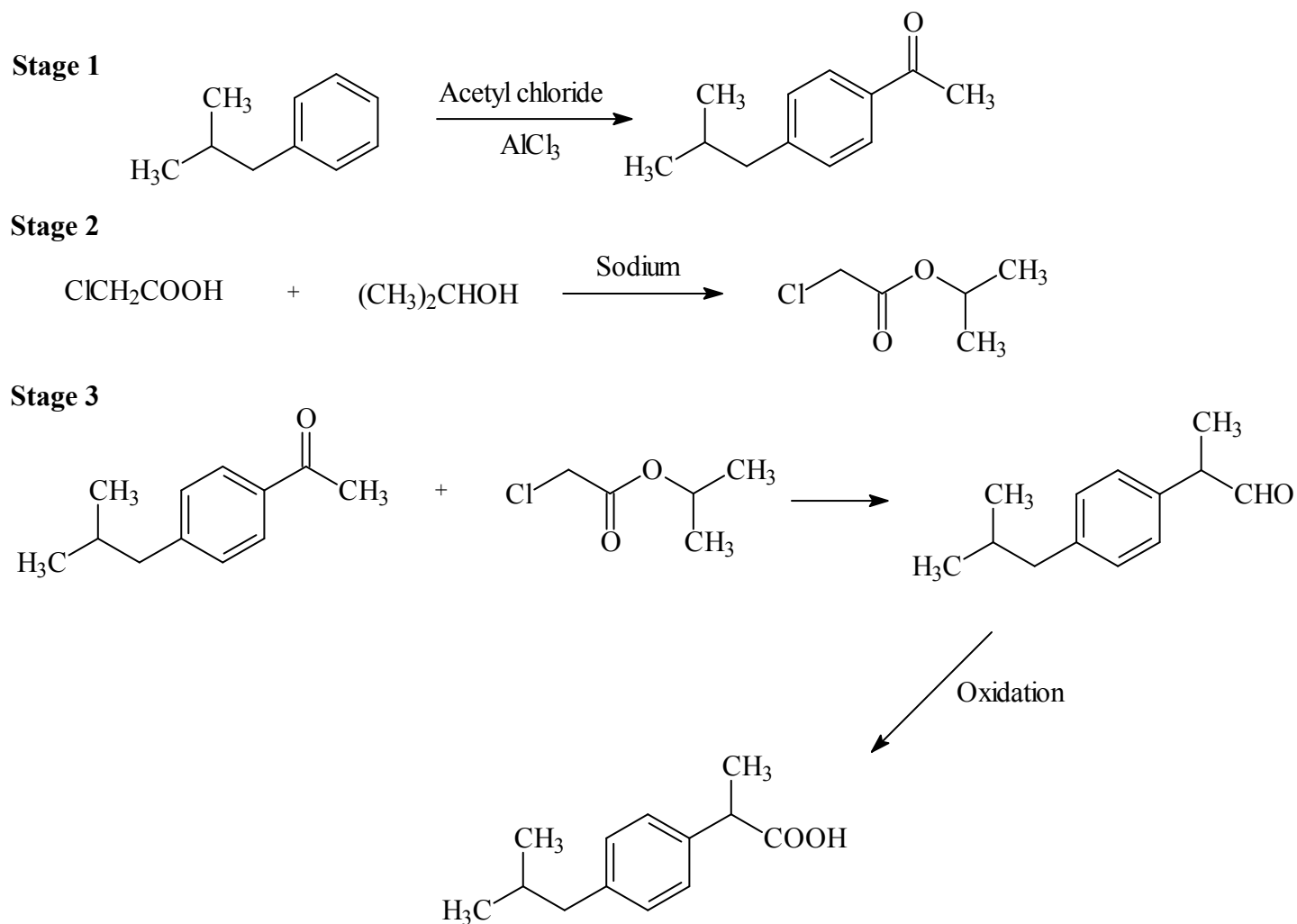
One API – Several routes

Ibuprofen – Process 1



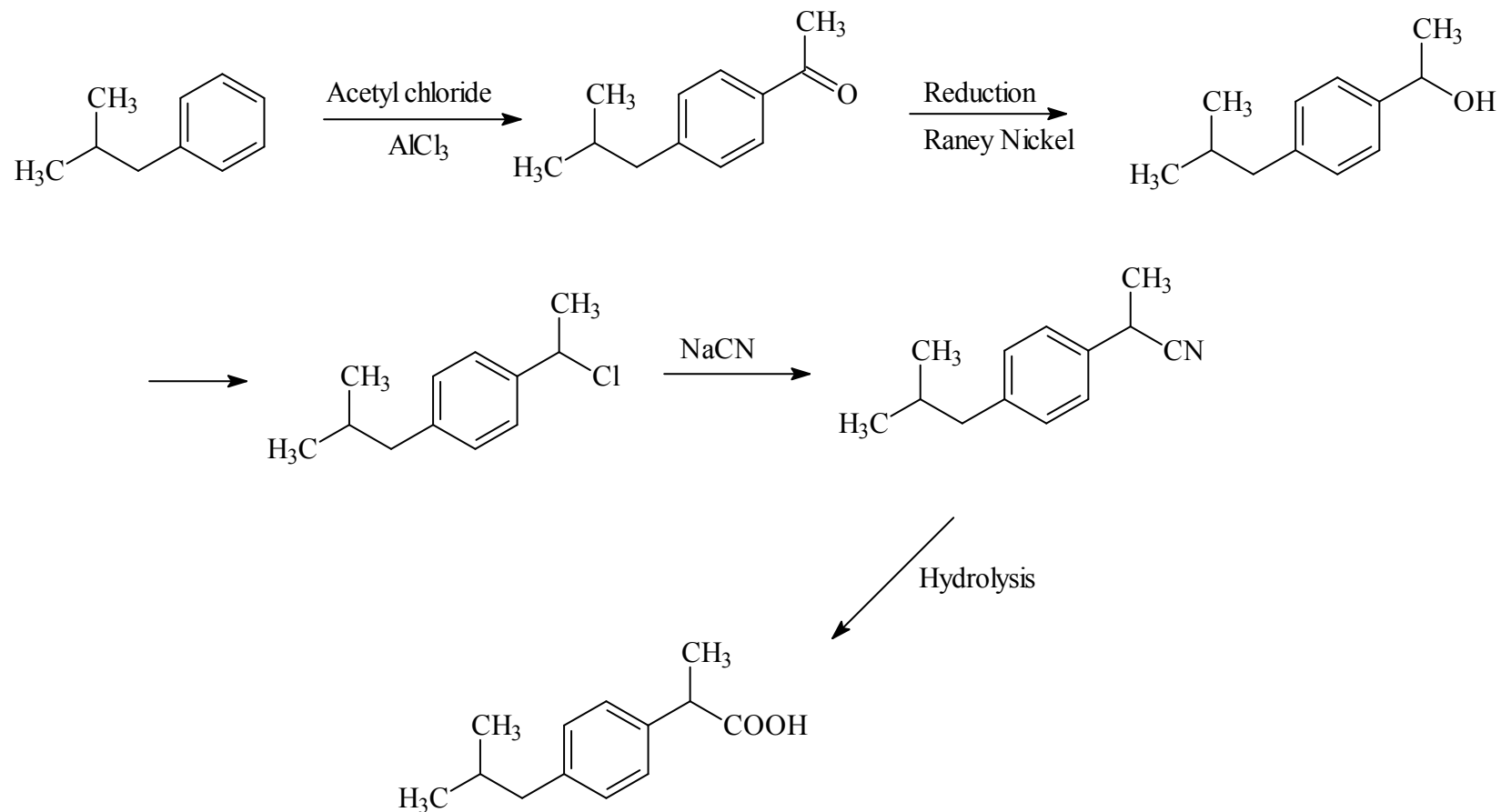
One API – Several routes

Ibuprofen – Process 2



One API – Several routes

Ibuprofen – Process 3



Ibuprofen as referred in the European Pharmacopoeia

Specifications as per EP 6.0

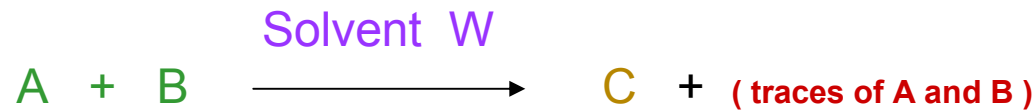
Any individual impurity : Not more than 0.3 %
Total Impurities : Not more than 0.7 %

Total number of specified impurities : 18

Labeled as : A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R

General process for the synthesis of an API

Stage 1



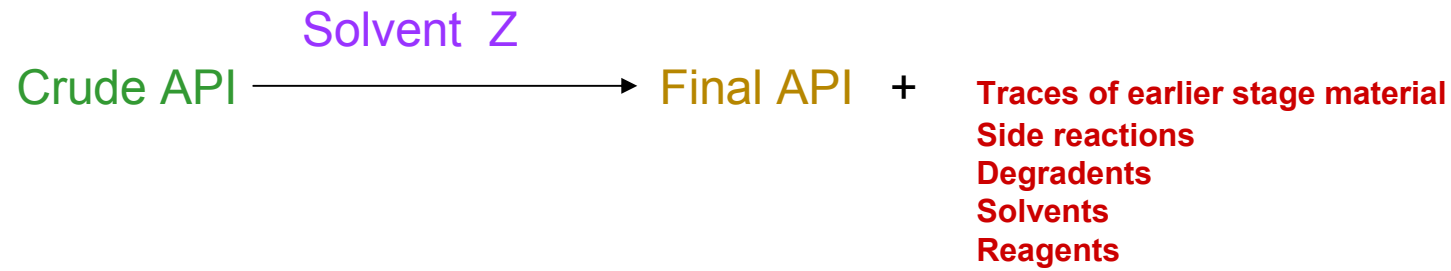
Stage 2



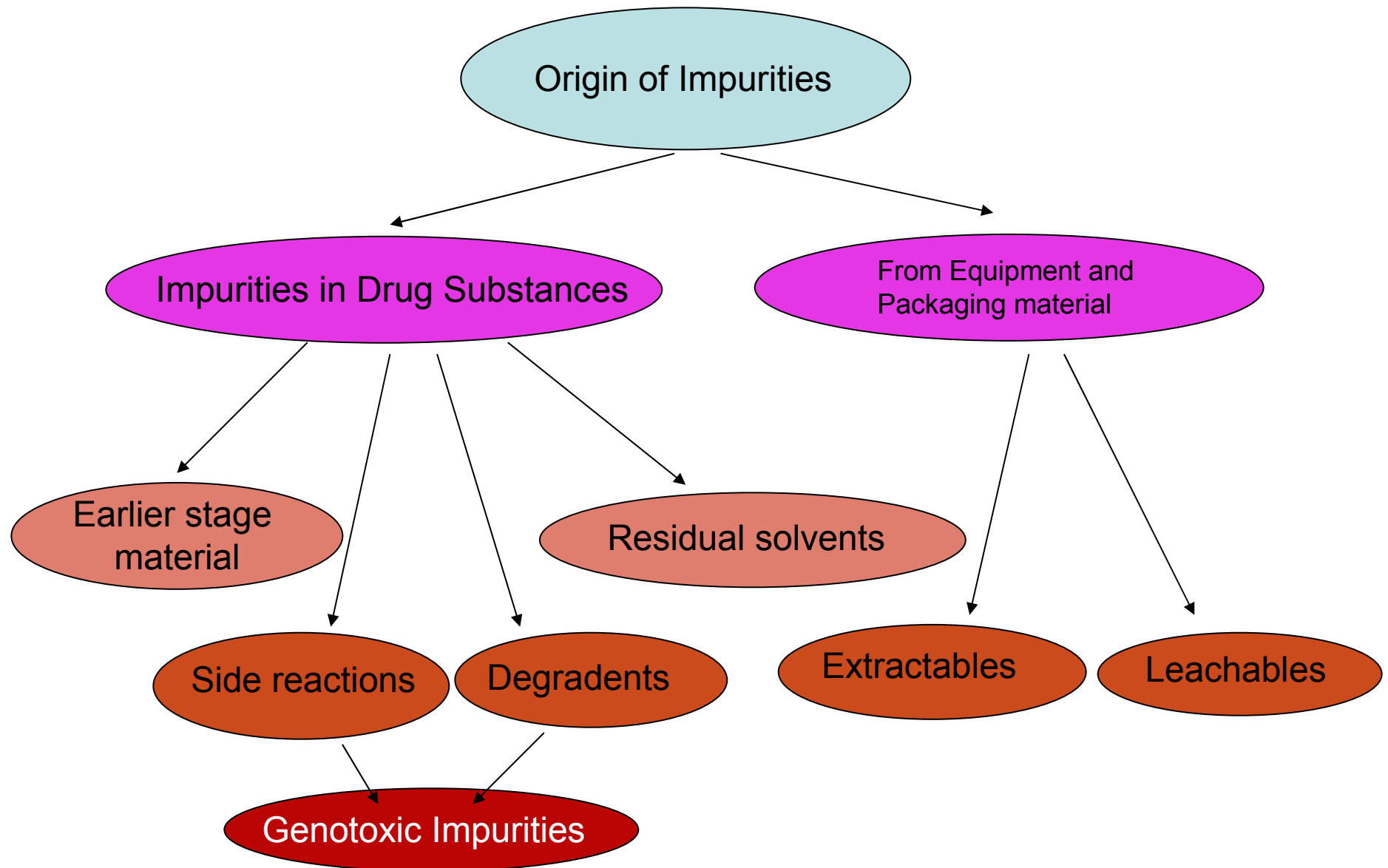
Stage 3



Stage 4



Source of Impurities in the Drug Substance



Side reactions and degradents in the synthesis process

1. Some times inevitable
2. Can be avoided by maintaining correct molar ratio of the reactants
3. Sequence of addition of the raw materials in the process
4. Targeting higher purity of Intermediate stages
5. Efficient workup process for the intermediate stage isolation
6. Optimising process parameters like reaction temperatures and time
7. Quantities of solvent in the process

The unwanted “ half ” – Chiral impurity

Organic molecules show a unique property of existing in various 3D structural forms, property commonly called as “ chirality ”

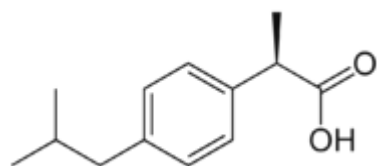
In a molecule, a carbon with four different substitutions can exist in two different space orientation , often called as isomers. Pair called as enantiomers

There are several cases in APIs , were one of the isomer is an active drug and the other isomer is inactive or in some cases has dangerous side effect !!

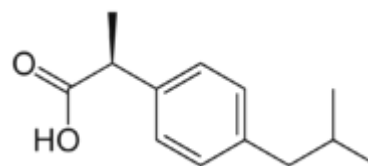
Chiral molecules

Ibuprofen

One chiral carbon, two isomers.



R - isomer



S - isomer

Studies showed that the S - isomer is active

However the R – isomer gets converted to S - isomer in vivo, hence the need to separate the two isomers is not required

Thalidomide

During 1960's this drug was used by pregnant women in Europe and Canada to treat morning sickness

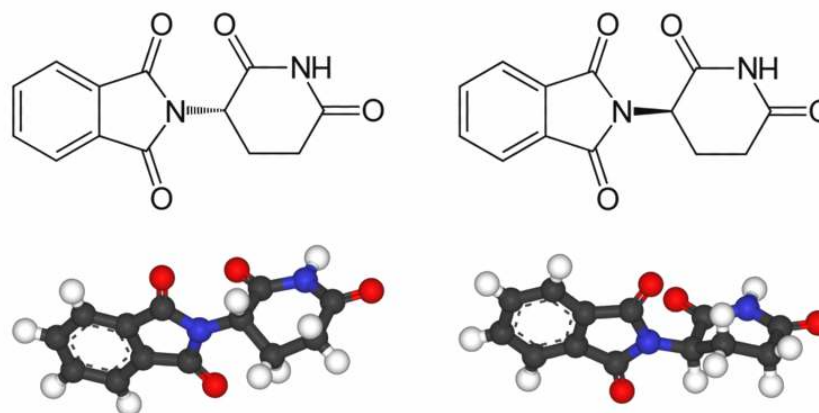
Women who took the drug in early pregnancy gave birth to children with severe birth defects such as missing or shortened limbs.

Shortly after the birth defects were observed, thalidomide was banned worldwide.

Chiral molecules

Thalidomide

The side effect associated with use of Thalidomide was attributed to one of the isomer



In 1962, US FDA refused to authorise Thalidomide for marketing in the USA due to concerns about the drug safety

Thalidomide

Interestingly, the study on Thalidomide as a drug continued in several countries and now its known and confirmed that it's an effective drug against Leprosy, Arthritis, Spondylitis, Cancer and AIDS.

The drug was approved by US FDA in the yr 1998 for the treatment of Leprosy

The prescription is under control by the doctors and patients are educated on the side effects associated with the drug and its history

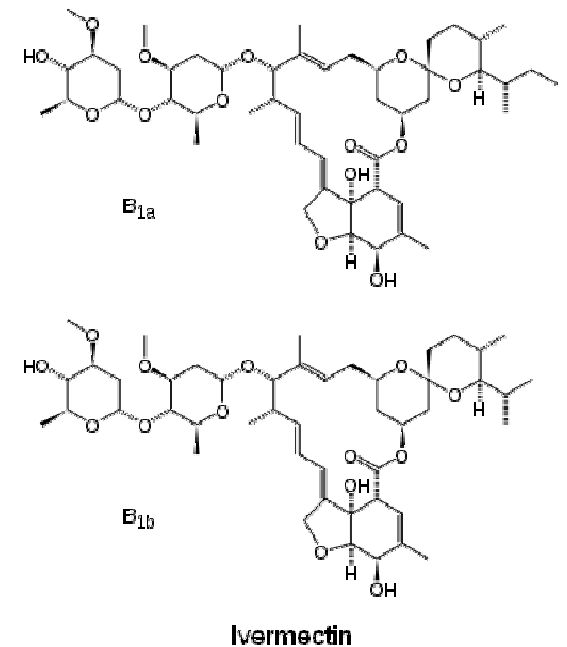
Chiral Impurity

Ivermectin

(22,23-dihydroavermectin B1a + 22,23-dihydroavermectin B1b)

a broad-spectrum antiparasitic medication, traditionally used against worms

- Ivermectin has 20 chiral centres
- The possible diastereomers will be 2^{20}
- Approx 1,048,576 potential diastereomeric impurities !!!!
- Which ones are important to monitor and control ??



Metal contamination

Contamination due to usage of metal catalyst for API synthesis

Limits recommended by EMEA guidelines

Classification	Oral Exposure		Parenteral Exposure	
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)
Class 1A: Pt, Pd	100	10	10*	1*
Class 1B: Ir, Rh, Ru, Os	100**	10**	10**	1**
Class 1C: Mo, Ni, Cr, V Metals of significant safety concern	300	30	30*	3*
Class 2: Cu, Mn Metals with low safety concern	2500	250	250	25
Class 3: Fe, Zn Metals with minimal safety concern	13000	1300	1300	130

Residual Solvents

Integral part of an organic synthesis process for an API

ICH Q3 C classifies the level of residual solvents allowed in the API

Class 1 Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane

Class 2 Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

Genotoxic Impurities

Compounds that have been demonstrated to induce -

1. genetic mutations
2. chromosomal breaks, and/or
3. chromosomal rearrangements

are considered genotoxic and have the potential to cause cancer in humans

Exposure to even low levels of these impurities may be of significant concern

Genotoxic Impurities

Compounds that fall into this category are those

that interact with DNA either directly or indirectly,

E.g.. alkylating agents, intercalating agents, or agents that can generate free radicals.

Since any exposure to these agents can convey some level of carcinogenic risk, and since complete elimination of genotoxic impurities from drug substances is often unachievable, the presence of a concerning impurity requires the implementation of a concept of an acceptable risk level.

Limits of Genotoxic Impurities – US FDA guidelines

For genotoxic impurities without sufficient evidence for a threshold-related mechanism,

the US FDA guideline proposes a policy of controlling levels to –

“as low as reasonably practicable” (called the *ALARP principle*).

The ALARP approach specifies that –

every effort should be made to prevent the formation of such impurities during drug substance synthesis, if that is not possible, technical effort should be made post-synthesis to reduce impurities (e.g., purification steps).

Limits of Genotoxic Impurities – EMEA guidelines

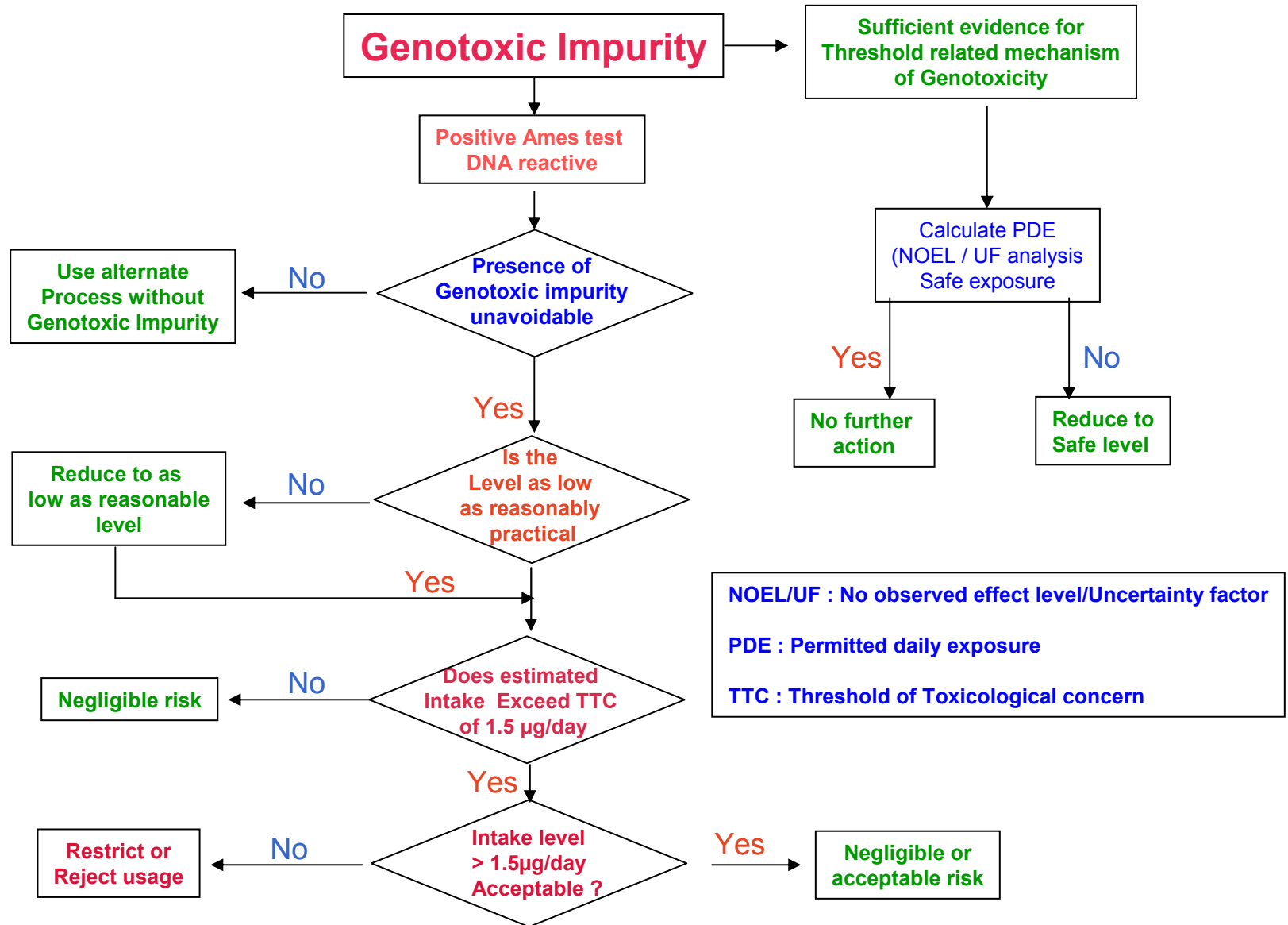
The EMEA guideline proposes the use of a “threshold of toxicological concern” (TTC) for genotoxic impurities.

The TTC refers to a threshold exposure level to compounds that does not pose a significant risk for carcinogenicity or other toxic effects.

The EMEA guideline recommends a TTC of 1.5 µg per day for all but a highly potent subset of compounds. This is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals.

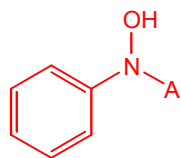
From this threshold value, a permitted level in the active substance can be calculated based on the expected daily dose. Higher limits may be justified under certain conditions such as short-term exposure periods.

Decision Tree for Assessment of Acceptability of Genotoxic Impurities

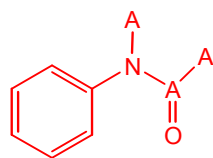


Genotoxic Impurities – Classification Functional group wise

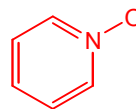
Aromatic Groups



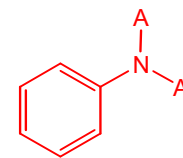
N-Hydroxyaryls



N-Acylated Aminoaryls

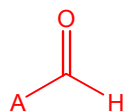


Aza-Aryl N-oxides

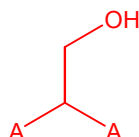


Alkylated Aminoaryls

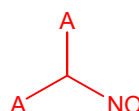
Alkyl and Aryl Groups



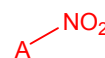
Aldehydes



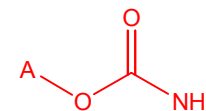
N-Methylols



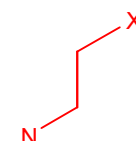
N-Nitrosoamines



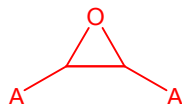
Nitro Compounds



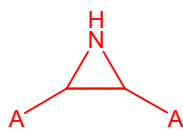
Carbamates



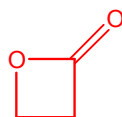
S or N Mustards
(Beta Haloethyl)



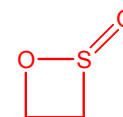
Epoxides



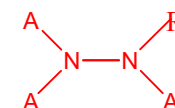
Aziridines



Propiolactones



Propiosultones

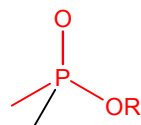


Hydrazines and Azo compounds

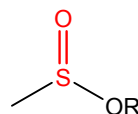
Heteroatomic Groups



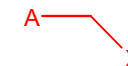
Michael Reactive Acceptors
R : Electron withdrawing group



Alkyl esters of
Phosphonates or Sulfonates



Halo - Alkenes

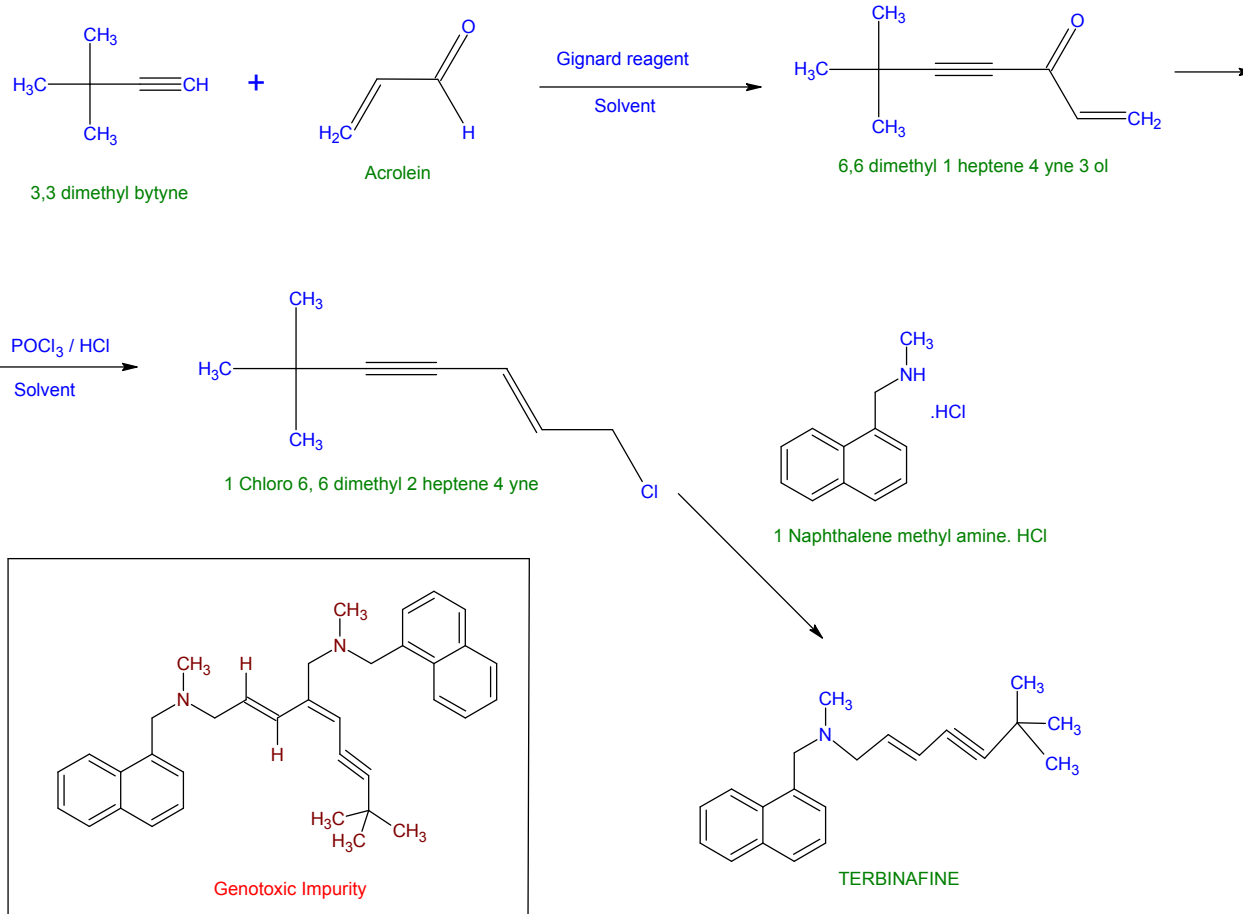


Primary Halides
(Alkyl and Aryl - CH₂)

X : Halogens ; A : Alkyl , Aryl or H

Terbinafine and its Genotoxic Impurity

Synthesis of Terbinafine



Genotoxic Impurity now added to the existing monograph as Impurity E, with a limit of Not more than 500 ppm

Packaging material

Pharmaceutical packaging is important to maintain the integrity of a drug, containing and preserving product ingredients at their specified concentration until the expiration date, maintaining the original purity of the drug, and delivering and dispensing the drug.

However, the rubber and plastic components used in Pharmaceutical products can also pose a serious threat to patient safety as they have the potential to interact with the API and dosage form.

In recent years there has been an increasing importance placed on the examination of leachables and extractables that may arise from primary container and closure systems, self-adhesive labels or secondary packaging materials.

Extractables and Leachables

Extractables

Chemical components that can be extracted from container / closure / packaging materials under forced and appropriate solvent, temperature and time conditions

Leachables

Chemical components that migrate from the container /closure system of the drug under normal storage conditions

Packaging material

US FDA acknowledges the importance of drug substance and product design, including the selection of Equipment for production and of container and closure system for packaging materials.

The evaluation of extractables and leachables has become an important aspect in the Quality by design (QbD) initiative of US FDA

Analysis of Extractables and leachables

The materials under investigation are extracted with solvents of various polarities, using various extraction techniques like Soxlet extractions, Sonication, Microwave, Supercritical solvent extraction, etc.

The resulting extractions then are evaluated by Analytical techniques like HPLC , GC , MS, ICP/MS, IR , IC , TGA , etc

Once the level of extractables and leachables have been determined then a toxicological assessment can be made.

Identification is important or atleast the class of compound

Forecasting the Impurities in the API

Understanding of the process chemistry and forecasting the probable impurities is an important activity to be taken up by R&D synthesis team during the Process development of an API

This will help in developing an analytical method which is capable of Identifying and quantifying the impurities at the desired level

Isolation of impurities

Once its established that a certain impurity is bound to get retained in the drug substance, its important to obtain the impurity in as pure form as possible, characterise it and determine its response with reference to the drug substance for correct quantification.

Impurities can be obtained by –

- 1 Producing the impurity by a separate synthesis route
- 2 Isolation for the existing process by Preparative LC
Crude products , Intermediates and MLs are a good source
- 3 Degrading the drug substance to enrich the impurity for ease of isolation

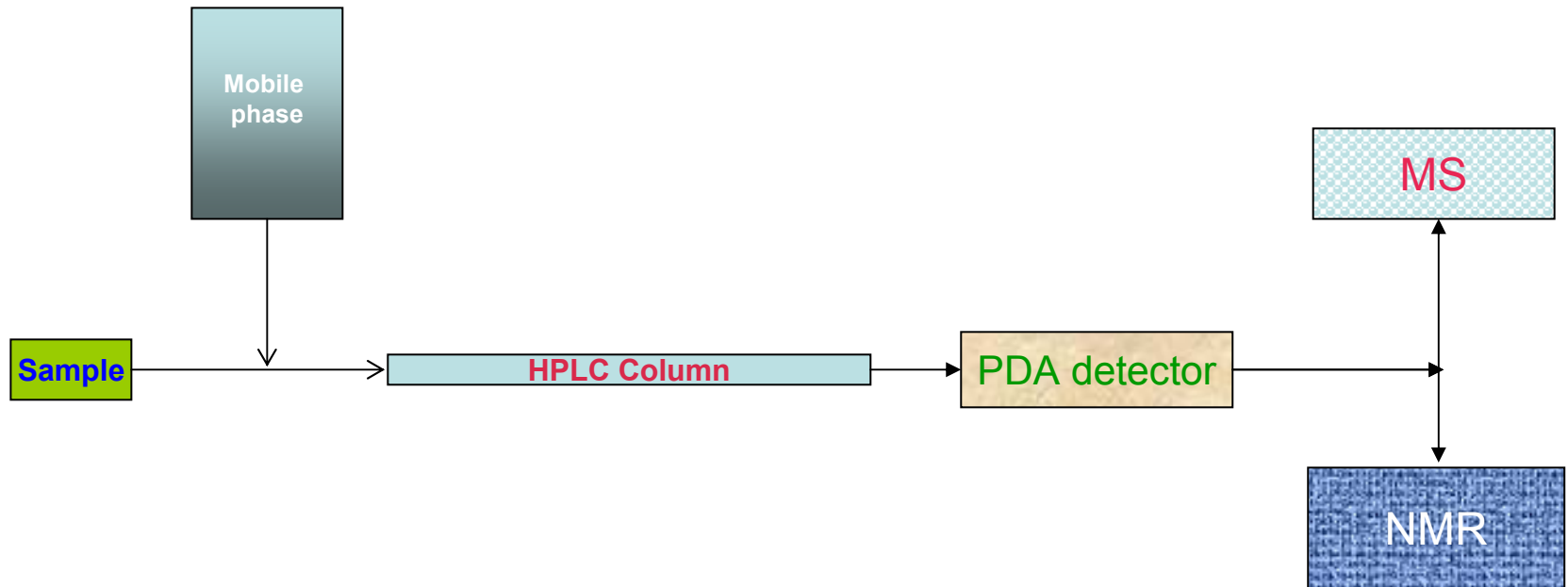
Analytical Methods for Detection and quantification of Impurities

Detection levels	Instruments which can be used
0.10% 1000 ppm	HPLC with PDA, UV, Fluorescence, ELSD
0.01% 100 ppm	NMR
0.001 % 10 ppm	GC with FID
0.0001% 1 ppm	LC - MS , GC – MS , ICP, AAS

Analytical techniques like NMR, Mass, C¹³ NMR, IR , UV, and elemental analysis can be used to characterise the impurities

Analytical Methods for Detection and quantification of Impurities

Coupled Chromatography - Spectroscopy



Challenges

1. Byproducts and degradation products are difficult to anticipate
2. Difficult to synthesis all potential impurities and hence to set up analytical methods to identify and quantify
3. Difficult to synthesis / isolate chiral molecules
3. Variation in the quality of Raw materials used in the process
4. Batch process are manual operations, difficult to maintain consistency
5. Impurities can show variation in the response factor in a typical chromatography analysis. Error in quantification
6. Lowering of specification Limits , Reproducibility in the analysis

Thank you

