THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

Top ten deficiencies in CEP applications

Igor Popovic,
Scientific officer/Assessor/ at Certification of Substances Department
EDQM/Council of Europe

15th ALIMS Symposium: Jubilee of cooperation in the interest of patients, October 2019

CEP Process Overview

Validation
- Administrative
- Technical

Evaluation 1
- CEP granted or
- Additional information requested

Evaluation 2
- CEP granted or
- Additional information requested

Evaluation 3
- CEP granted or
- Application closed without the CEP being granted

Technical validation at receipt

- Summarise the commercial history - what product containing THIS source of API is on the EUROPEAN market. Information on ASMF submitted for the same substance

- Give as much information as possible (companies, products names, countries, registration dates, marketing dates) → Impact on Qualification (limits) of impurities and applicability of guidelines

Applications are blocked when

- Reference is made to an old version of the Ph. Eur. monograph
- Use of Class I solvents without justification and control
- Unsuitable information on the impurity profile of the substance
- Sterile substances: absence of validation data on the sterilisation
- Absence of quantitative method to replace a non-specific TLC test of the monograph

Evaluation

- The EDQM has 5 months to complete the evaluation and inform the applicant of the outcome.
- Currently the deadlines are being respected.
- See monthly report published on www.edqm.eu

Deficiencies: How to avoid them?

Reference documents

PA/PH/CEP (04) 1 6R (December 2018)
"Content of the dossier for chemical purity and microbiological quality"

- **PA/PH/CEP (16) 58 (December 2016)**
- "Top Ten Deficiencies – New applications for certificates of suitability for chemical purity (2015-2016)"

  - Publicly available on the EDQM website
  - They describe what we expect to see in the dossier

The scheme is Certification of suitability to the monographs of the EUROPEAN Pharmacopoeia.

List of deficiencies

Mutagenic Impurities

Top 2

Fate and carryover of impurities from *starting materials*

Top 3

Manufacturing Process

Top 4

Redefinition of *starting materials*

Top 5

Quality of *starting materials*

Top 6

Analytical specifications for reagents and solvents

Top 7

Carryover of reagents and elemental impurities

Top 8

Quality of intermediates

Top 9

Fate and carryover of impurities from intermediates

Top 10

Information on *starting materials*

Starting materials

Top 2 Top 4 Top 5 Top 10

Definition of starting materials

- For synthetic processes the production of an API starts with the introduction of the starting materials (ICH Q7)
- The approved starting materials are the starting point for GMP and variations and must be representative of the overall synthetic process.

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

Reference documents: ICH Q11 and its Q&A document.

→ Relationship between risk and number of synthetic steps

Starting materials

Top 2 Top 4 Top 5 Top 10

- Quality of starting materials/Fate and carryover of impurities

1. The impurity profile of the starting material should be adequately characterised;

2. Analytical specifications with justified acceptance criteria should be proposed to control the impurity profile of starting materials.

3. Discussion on fate and carry-over of impurities.

Example of non-acceptable analytical specification

Chromatographic purity (By GC)	
Purity	Not less than 98.00 % (Including 4-Methoxy phenacyl chloride)
4-Methoxy acetophenone	Not more than 0.50%
Unknown single impurity	Not more than 1.00%
Total impurities	Not more than 2.00%

It is not clear what the major impurity is → risks of having uncontrolled impurities → risks for the quality of final API

Manufacturing Process

Top 3

The description of the manufacturing process in place from the introduction of starting materials should contain complete information on:

- Chemicals used and their quantities;
- Operations conducted with conditions adopted.

Absence of information related to the maximum batch size for the approved process

The maximum batch size for which the manufacturer has acquired experience with the defined process and which should correspond to batches referred to in the dossier, should be stated.

Quality of intermediates

Top 8 Top 9

Fate and carryover of impurities from intermediates

The proposed control strategy is evaluated keeping in mind the risk of having uncontrolled impurities in the final API above acceptable limits.

The impurity profile of isolated intermediates should be characterised and this becomes particularly important in case of:

- Intermediates which are isolated late in the process;
- Intermediates showing low purity;
- Related substances in the crude API are controlled by a method which is different comparing to the one adopted at release.

Quality of intermediates

Top 8 Top 9

Isolated intermediates are potentially contaminated by related substances that can lead to API-like impurities.

- Information should be given on the impact the quality of isolated intermediates can have on the quality of the final API. Hence:
- Fate and carryover of impurities from intermediates to the final API should be discussed;

- Absence of residues of intermediates (isolated and non-) in the final API should be demonstrated;

- The suitability of the monograph to control the quality of the final substance coming from the presented synthesis should be discussed.

Analytical specifications for reagents and solvents and their carry-over

Top 6

Top 7

- Specifications of reagents and solvents used to manufacture the substance from the introduction of the starting materials is needed. Purity should be defined and a reasonable mass balance should be observed;
- Specifications of recycled material before being re-introduced in the process should be given and justified;
- Particular attention should be paid to the quality of solvents (both fresh and recovered) used in the last steps;
- Carryover to the final API of reagents and solvents should be discussed, as applicable.

Mutagenic Impurities

Reference documents

ICH M7 (R1) (March 2017)

"Assessment and control of DNA reactive (mutagenic)

impurities in pharmaceuticals to limit potential carcinogenic risk"

- Hazard assessment in order to classify actual and potential impurities (class from 1 to 5)
- Guideline on how to develop an adequate control strategy according to the nature of the impurities
- Applies to new sources of active substances
- A specific discussion is expected in the dossier (section 3.2.S.3.2)

Mutagenic Impurities

Classification of impurities with respect to mutagenic and carcinogenic potential

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

Mutagenic Impurities

How to set an acceptable limit: application of the “less-than-lifetime” (LTL) concept

Scenario[1]	Acceptable Intake (µg/day)
Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice	120
Treatment duration of > 1-12 months: e.g., anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives)	20
Treatment duration of >1-10 years: e.g., stage of disease with short life expectancy (severe Alzheimer’s), non-genotoxic anticancer treatment being used in a patient population with longer term survival (breast cancer, chronic myelogenous leukemia), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms[2] (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV[3]	10
Treatment duration of >10 years to lifetime: e.g., chronic use indications with high likelihood for lifetime use across broader age range (hypertension, dyslipidemia, asthma, Alzheimer’s (except severe Alzheimer disease), hormone therapy (e.g., growth hormone, thyroid hormone, parathyroid hormone), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis	1.5

$$\frac{acceptable\ intake\ (\frac{\mu g}{day})}{MDD\ (\frac{g}{day})}$$

Nitrosamines are part of ICH M7 “cohort of concern”-extremely high carcinogenic potency

Acceptable amounts significantly lower than TTC level

-NDMA: 96,0 ng/day

-NDEA: 26,5 ng/day

Mutagenic Impurities

How to develop a control strategy of process-related impurities

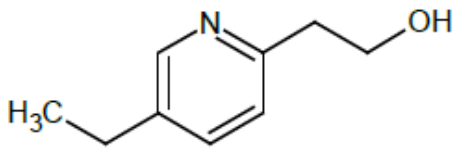
- **Option 1**: test the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit;
- **Option 2**: test the impurity in starting materials or intermediates or as an in-process control, with an acceptance criterion at or below the acceptable limit;
- **Option 3**: test the impurity in starting materials or intermediates or as an in-process control, with an acceptance criterion above the acceptable limit of the impurity in the drug substance. The control should be coupled with demonstrated understanding of fate and purge, without the need for any additional testing later in the process. This option can be justified when the level of the impurity in the drug substance is less than 30% of the acceptable limit;
- **Option 4**: Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity.

How to develop a control strategy

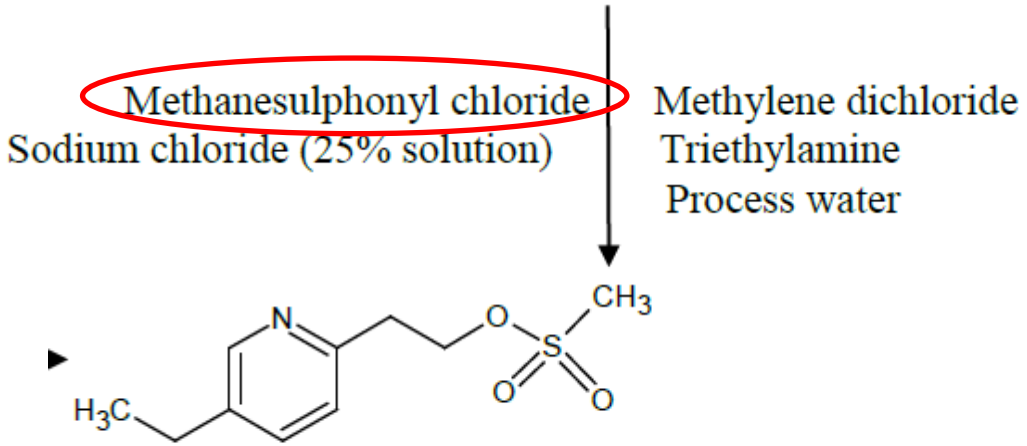
Pioglitazone, antidiabetic. MDD= 45 mg

Methanesulphonyl chloride
- Washing step with water?

Theoretical impurity
Option 4



HEEP *(2-(5-Ethyl-pyridin-2-yl)-ethanol)*



PGL-1 *(2-(5-ethylpyridin-2-yl)ethyl methanesulfonate)*

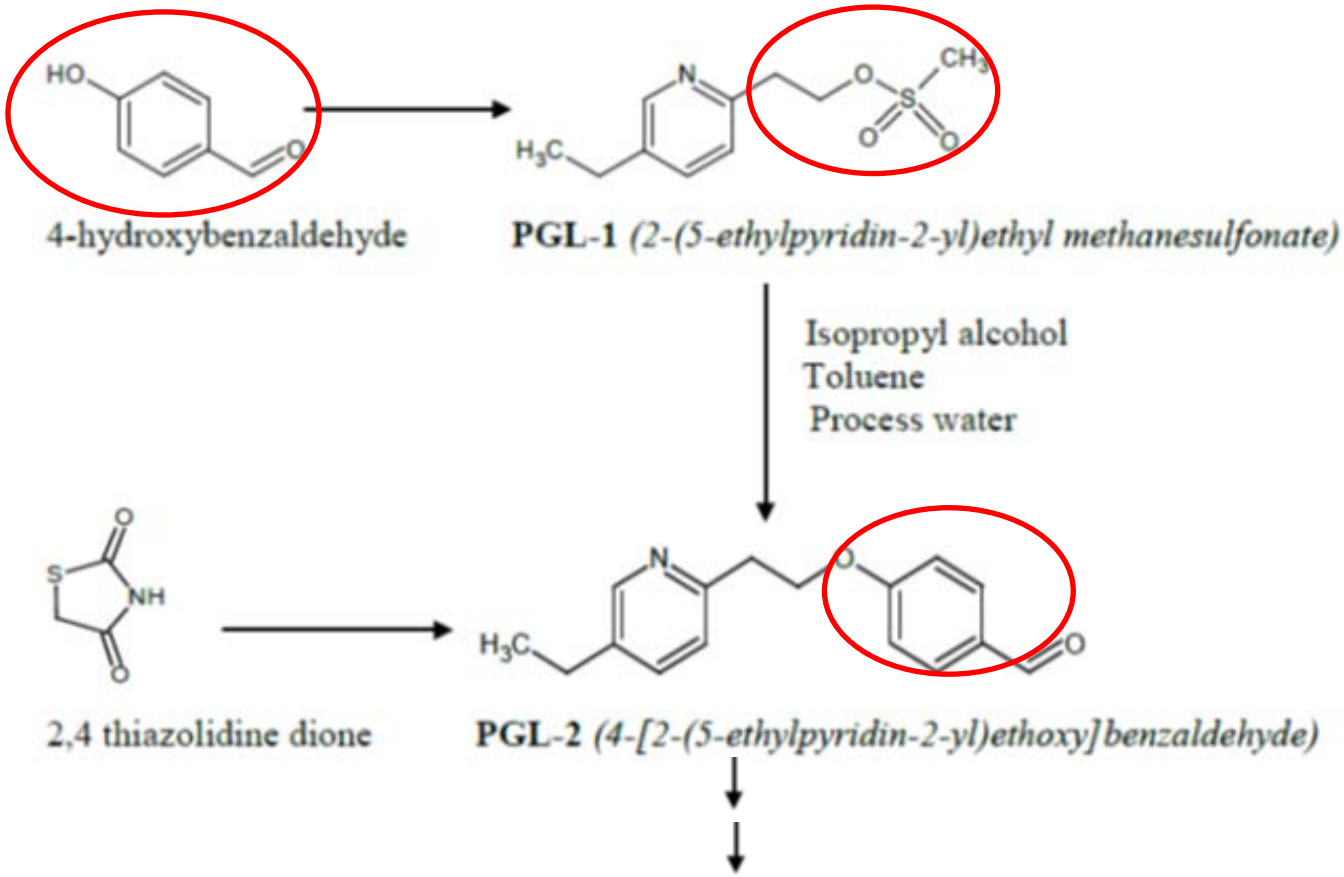
How to develop a control strategy

4-HB: aromatic aldehyde

PGL-1: mesilate

PGL-2: aromatic aldehyde

Options 2 or 3

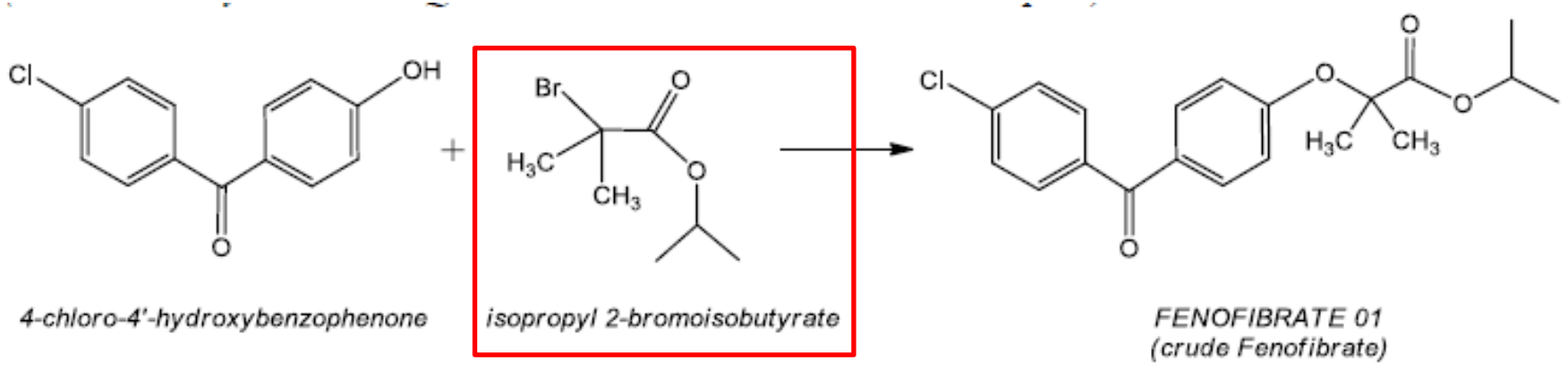


Final API

Mutagenic Impurities

How to develop a control strategy

Fenofibrate, lipid regulation drug



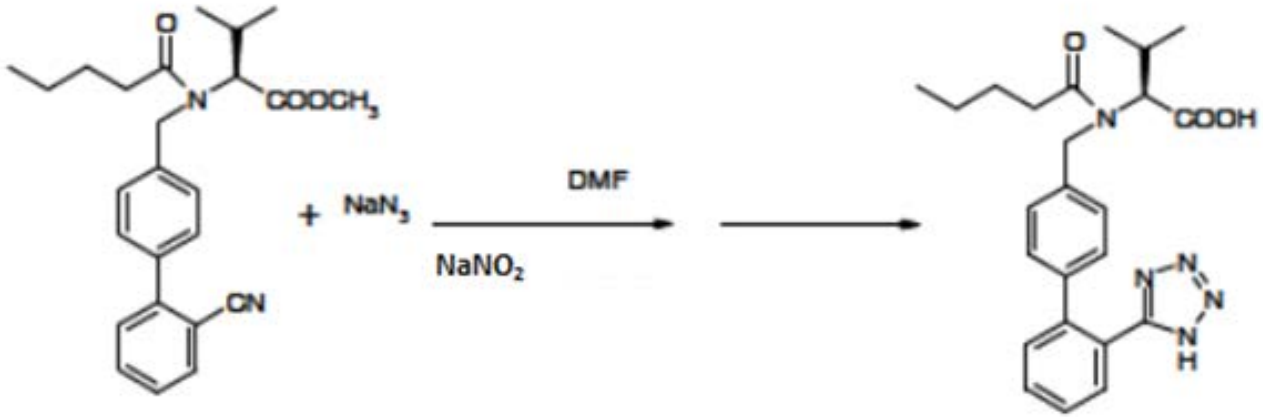
According to ECHA website: mutagenic compound both in vivo and in vitro

Introduced in the last synthetic step → **Option 1** (control in the final API)

Mutagenic Impurities

The nitrosamine risk assessment

Preparation of Valsartan



NDMA risk factors:

-DMF decomposition to dimethylamine (DMA) and sodium nitrite presence

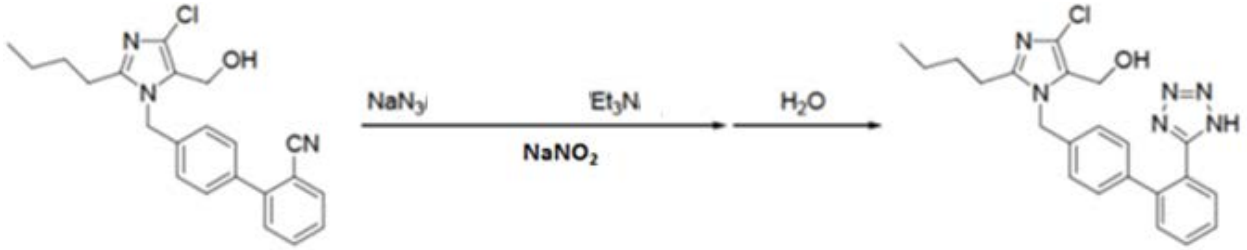
-the recovery of solvents/materials (sodium nitrite for azide quenching)

-solvents interchangeability between different processes for the same substance

Mutagenic Impurities

The nitrosamine risk assessment

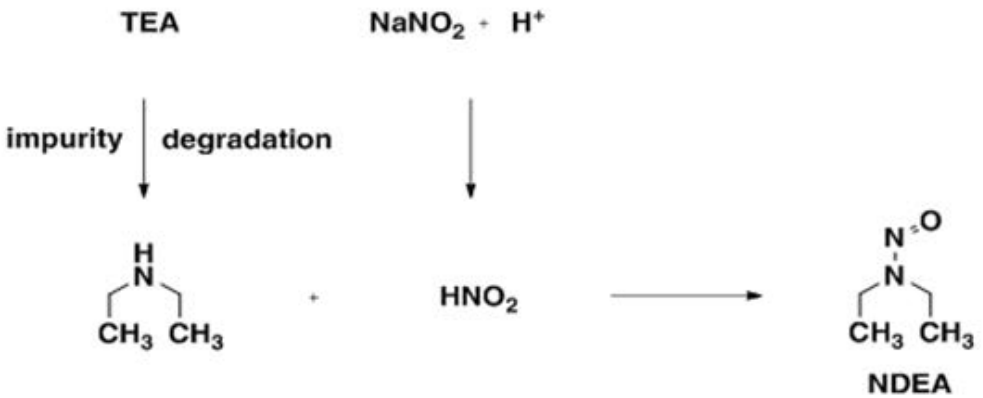
Preparation of Losartan



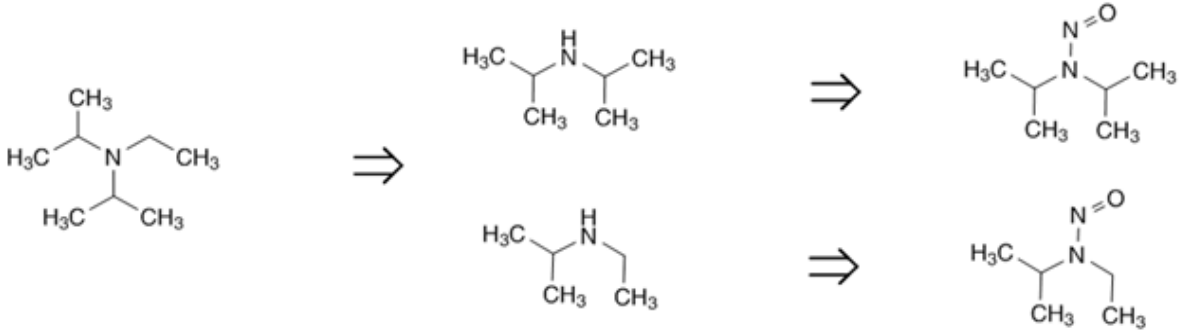
NDEA risk factors:

-TEA and sodium nitrite presence during tetrazole ring formation

-the usage of recovered solvents (sodium nitrate used azide removal)



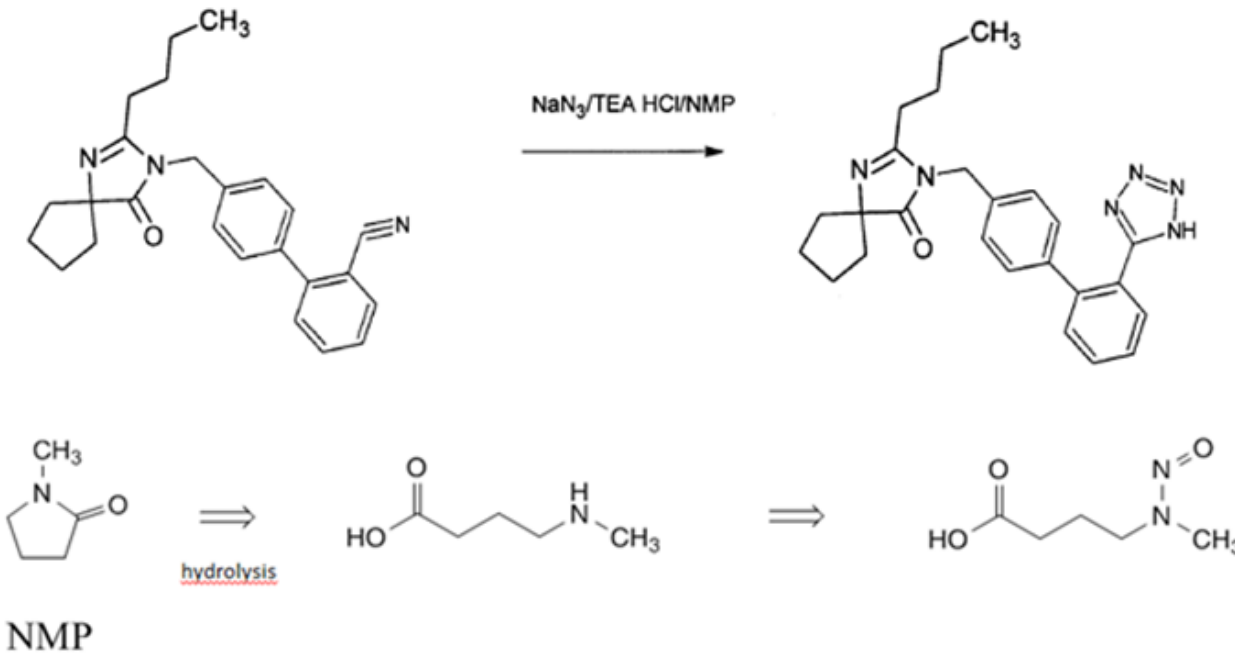
-DIPEA used instead of TEA as secondary amine source leads to formation of NDIPA (N-Nitroso-diisopropyl amine) and NIPEA (N-Nitroso-isopropyl ethyl amine)



Mutagenic Impurities

The nitrosamine risk assessment

Preparation of Irbesartan



NDEA/NMBA risk factors:

NMP

-NMP degradation to secondary amine

-TEA presence during tetrazole formation

-the usage of recovered solvents

(sodium nitrite for azide removal during recovery procedures)

Conclusions: how to avoid deficiencies?

- Build up your Dossier taking into account applicable policies and addressing the requirements discussed.

- With your Dossier you should give assurance on the ability of the process to remove impurities and to reduce the risk of having uncontrolled impurities above acceptable limits. Hence:
  - do not build up your Dossier on your purest batches of starting materials, intermediates and final API. This would just lead to questions;
  - include in the Dossier any relevant (recent and non-) analytical results and studies in support, even though performed during development phase.

- Suitability of the specific monograph to control the quality of your substance should be demonstrated.

- Deficient Dossiers delay the granting of your CEP and might lead to the closure of application without the CEP being granted.

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**

© 2019 EDQM, Council of Europe. All rights reserved.