International Conference, 19-21 September 2022

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

Session 7: Certificates of Suitability

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Former Director of the EDQM, Council of Europe

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

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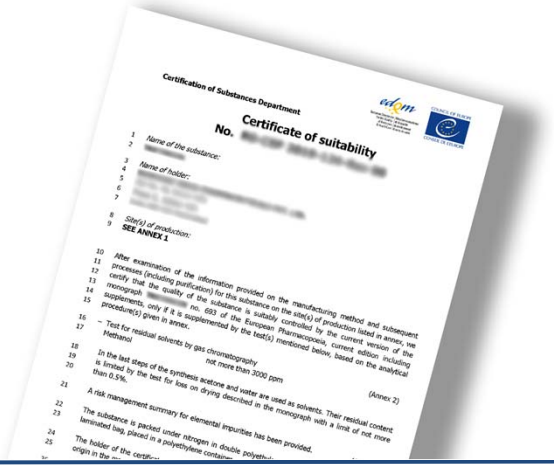
Recent updates regarding CEPs


Certification of Substances Department

Certificate of suitability

No.

Name of the substance:

Name of holder:

Site(s) of production:
SEE ANNEX 1

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph no. 693 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography
Methanol
not more than 3000 ppm
(Annex 2)

In the last steps of the synthesis acetone and water are used as solvents. Their residual content is limited by the test for loss on drying described in the monograph with a limit of not more than 0.5%.

A risk management summary for elemental impurities has been provided.

The substance is packed under nitrogen in double polyeth... laminated bag, placed in a polyethylene contain...

The holder of the certi... origin in the ...

Summary

- Quality update in the context of the CEP procedure
  - Nitrosamines: Approach, work done, information sharing
  - Azido impurities in Sartans: Brief recap. and actions taken by the EDQM
- Operational updates in the context of the CEP procedure
  - Timelines - Key figures
  - Documents recently published
  - CEP holders' responsibilities towards their customers
  - New process for CEP documents (public consultation)
  - New EDQM Inspection Tool: RTEMIS

Quality updates on the CEP procedure

General quality update

Nitrosamines in (**all**) active substances **covered** by CEPs

- EDQM has aligned with EU call for review in September 2019

  Stepwise approach for CEP holders:

Step 1
Risk evaluation
(31st July 2020)

- conduct a risk assessment to identify any risk of nitrosamine formation
- EDQM to be informed with a testing plan and timelines if risks identified

Step 2
Confirmatory testing
(26th September 2022)

- provide test results to EDQM, and if needed a corrective actions plan with timelines

Step 3
Update of CEP application

- implement additional controls or process changes
- send revision application to EDQM as needed
- **Deadline extended to 1st October 2023!!**

Nitrosamines in (**all**) active substances (2)

The work done so far..

Since January 2019 – Assessment of CEP applications

- ✓ Routine assessment by EDQM of risks for nitrosamines in the context of new dossiers, renewals, and in case of changes to routes of synthesis/ changes of suppliers
- ✓ Implementation of controls to prevent presence of nitrosamines when needed

Since 1st October 2020 – Applicants to include risk assessments

- ✓ In new CEP dossiers, renewals, and revisions where a risk of nitrosamine formation may be introduced (i.e. changes to the manufacturing process, change of suppliers of starting materials or intermediates, etc.)

The recommendations of the EMA document EMA/409815/2020 (Q&As) are **fully implemented** in the context of the Certification Procedure

Nitrosamines - information sharing & communication

The EDQM has been **co-operating continually with regulatory authorities at national, EU and international level**

Cooperation with other authorities worldwide:

✓ via the Nitrosamines International Strategic Group (NISG – chair Health Canada)

✓ via NISG's technical Group (NITWG)

Sharing information with international partners under confidentiality agreements:

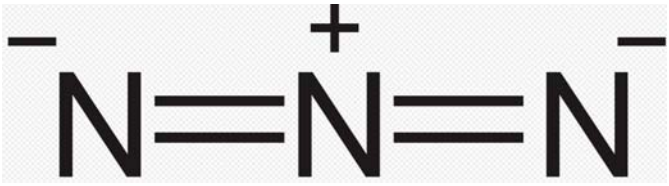
- Signals on presence of nitrosamines in sources of APIs & in medicinal products - trigger review of CEP dossiers if necessary
- Signals sent by the EDQM to partners
- Information on analytical methods and test results
- To trigger alignment of decisions

The EDQM shares the information and relies on **the Non-Clinical Working Party (EMA)** for the assessment of toxicological data provided for unknown nitrosamines by CEP holders.

The EDQM has also participated and contributed in the EU Sartans lessons learnt exercise.

General quality update

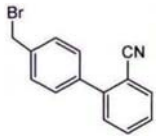
Azido impurities in sartans



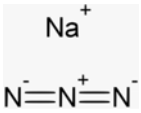
Azido impurities in Sartans

- September 2020: Information received concerning the presence of a potentially mutagenic impurity (AZBT) in **Irbesartan** at levels above the TTC
  - ✓Potential origin – Reaction between Sodium Azide and residual 4'-Bromomethyl-2-cyano-biphenyl (Br-OTBN).
  - ✓The process is similar for all Sartans with a tetrazole ring, so the risk is not only applicable to Irbesartan.

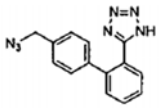
Br-OTBN



Sodium Azide

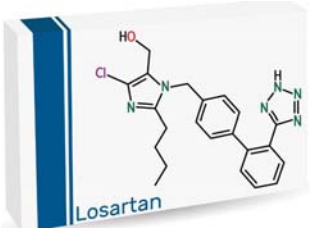


AZBT



Azido impurities in Sartans (2)

- April 2021: AZBT confirmed as Ames positive (EMA)
- June 2021: Information about the presence of "Losartan azido impurity" in Losartan potassium, potentially mutagenic, at levels above the TTC.
  - ✓August 2021: Information that "Losartan azido impurity" was Ames positive
  - ✓July 2022: In-vivo studies confirmed impurity is non-mutagenic



Azido impurities in Sartans – Actions by the EDQM

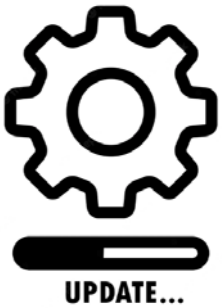
- All CEP holders for sartans with a tetrazole ring contacted by EDQM, companies requested to provide:
  - ✓a risk assessment for ALL Azido impurities
  - ✓batch data if a risk was identified
  - ✓corrective actions when appropriate (eg. additional controls, process change)
  - ✓For new applications, where a risk is identified, questions asked as needed.
- Several azido impurities may be generated, but main « candidates » more likely to be present are:
  - ✓ 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole, CAS 152708-24-2 (AZBT)
  - ✓ 4'-(Azidomethyl)-[1,1'-biphenyl]-2-carbonitrile, CAS 133690-91-2 (AZBC)
  - ✓ 5-[4'-[(5-(Azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl)methyl]-[1,1'-biphenyl]-2-yl]-1H-tetrazole, CAS 727718-93-6 (Losartan Azido impurity)
- Substances with highest risk: Irbesartan, Losartan, Valsartan

Azido impurities in Sartans – Actions by the EDQM (2)

- Data received and reviewed by EDQM
- TTC limits and ICH M7 principles applied for assessment
- In case of levels > TTC, mitigation of risk and implementation of corrective actions being assessed
  - ➔A number of CEPs revised
  - ➔ 4 CEP suspended by EDQM, some CEPs withdrawn by respective holders
- Analytical methods published by the OMCL (3 methods):

https://www.edqm.eu/en/ad-hoc-projects-omcl-network#AZBT

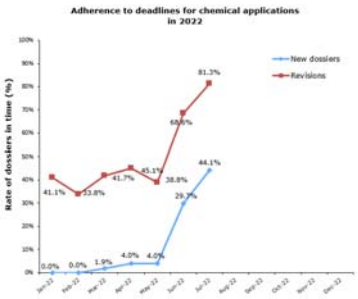
Operational updates on the CEP procedure

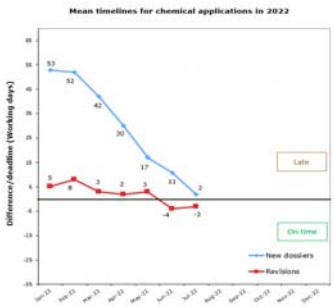


General operational updates to the CEP procedure

The Covid-19 pandemic impacted the CEP procedure

- ✓Significant increase in CEP applications received + lack of experts = **Delays** in treatment of dossiers → **Remote assessment**
- ✓No on-site GMP inspections → **RTEMIS**
- ✓May 2022 – Conditions favourable to start evaluation sessions in presence





The situation is improving..!

General operational updates to the CEP procedure (2)

Recent documents published:

- Revised policy for GPS coordinates for manufacturing sites (2022)
  - GPS coordinates expressed in Degrees to at least 5 decimal places
  - Removed requirement to provide DUNS number (when available).

- Revised application forms (2022) – for all kinds of applications
  - Introduction of recommendation to include **ORG_ID** and **LOC_ID** in line with the EMA **SPOR** data management services (see EMA website) – Facilitates the unique identification of organizations and locations involved in the API supply chain.

- Change of Contact details (2022)
- Revised guidance on management of CEP applications (2021)
- Use of « DCEP Sharing Tool » (2022)
- CEP holders responsibilities towards their customers (2022)

CEP holders responsibilities towards their costumers

In recent years it has been noticed that CEP holders often lack knowledge and awareness regarding the extent of their responsibilities towards their **costumers -** Marketing authorisation applicants / holders and sponsors that use CEPs

For that reason, additional **clarity** was needed and this document was created which in summary:

- ✓ Identifies regulatory frameworks containing the requirements supporting these responsibilities
- ✓ Defines that the overall responsibility with regards to the information contained on the CEP lies with its holder. The holder is also responsible for sharing the necessary information with their costumers so they fulfil their respective legal responsibilities
- ✓ Provides a non-exhaustive list of examples (e.g. provide MAH with most recent CEP version in a timely manner, transparency in case of GMP non-compliance, etc).

General operational updates to the CEP procedure (3)

- Upcoming updated process for CEP public documents/guidelines
  - Recently adopted by the Certification Steering Committee
  - Clear and transparent process which includes public consultation
  - Will be available via the EDQM website

- CEP of the future: Major ongoing project → Separate presentation today

Watch the space

EDQM Inspection programme - RTEMIS

Real **T**ime R**em**ote GMP **I**nspection**s** of API manufacturers in the frame of the CEP procedure

- Triggered by the Covid-19 pandemic and travel restrictions
- Before RTEMIS, the GMP compliance assessment tools available for inspectors were: On-site inspections and Documentation based GMP assessment
- Provides a possibility to evaluate the GMP compliance of a company, with real time interactions, when an on-site inspection cannot be performed

Process flow for RTEMIS

- Preparation stage (more complex compared to on-site inspections)
  - Preparatory teleconference to explain approach
  - Agreement on technical solutions (software/hardware); connection trial, including connectivity in the manufacturing areas (speed test)
  - Review of many documents by inspectors prior to the inspection (QA SOPs, API specific information, etc.)
- During the inspection
  - Visual tours (e.g. storage / production / QC facilities)
  - Inspectors work in parallel when needed, using additional conferencing tools
  - Exchange and review of documents (via a secure Collaboration tool similar to Dropbox)
- Follow-up is the same as for on-site inspections
  - List of GMP deficiencies issued / CAPA submitted by company / Inspection report issued

During the inspection – visual feedback

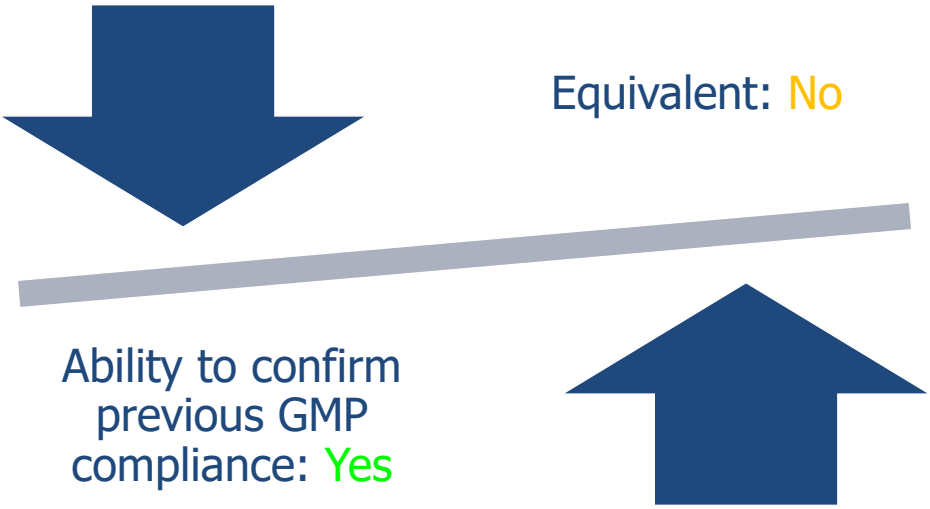
RTEMIs inspections performed in 2020-2022

- Twenty (20) manufacturing sites located in India and China
- Participation of EEA National Competent Authorities in most inspections (➔ GMP certificates granted)
  - Deficiencies were identified during all remote inspections
- Limitations / Challenges
  - Technical difficulties depending on area connectivity, staff's technical experience etc
  - Some inspection techniques that cannot be used remotely (e.g. element of surprise, body language, staff conversations, etc)
  - Time difference & language, in particular in China

RTEMIs inspections performed in 2020-2022 (2)

- Advantages:
  - Possibility to evaluate the GMP compliance of a company when an on-site inspection cannot be performed or is deemed of lower priority
  - Real time visual interaction with the company concerned
  - Saves resources (both for the EDQM and companies)
  - No travel: reduces carbon dioxide footprint, therefore beneficial for environment

RTEMIS equivalent to on-site inspections?



Equivalent: No

Ability to confirm previous GMP compliance: Yes

Real Time Remote Inspections

A new, third pillar for the supervision of the GMP compliance of pharmaceutical manufacturers

Thank you for your attention

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Nitrosamines in Active Substances

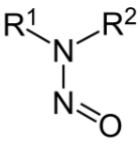
A Quality Assessor´s Point of View

Gernot Hirn

20.09.2022

Background

What are nitrosamines?



- Chemical compounds classified as **probable human carcinogens** on the basis of animal studies
  - Feature a nitroso group (NO) bonded to a deprotonated amine
- Subgroup of N-nitroso compounds, which belong to the `**cohort of concern´ (ICH M7)**
  - Mutagens that **can display extremely high carcinogenic potency**
  - Threshold of Toxicological Concern not applicable **(compound specific AI needed)**
- Nitrosamines can arise from reaction of **secondary- or tertiary amines and nitrosating agents** (oxidized nitrogen containing compounds, NOx)
  - Other generation pathways exist too (e.g. oxidation and reduction from hydrazine-type compounds and N-nitro derivatives)

Background

Brief Overview of Regulatory History of Nitrosamines - EMA

- **Mid 2018:** Nitrosamines found in `Sartans´ (starting with NDMA in Valsartan)
  - Article 31 referrral (*lessons learned exercise outcome published on EMA Homepage (HP)*)
- Nitrosamines also found in medicines containing other APIs
- **Sep 2019: Article 5(3) referral** (*AR and **Q&A document** published on EMA HP)*
  - CHMP recommendations on controlling nitrosamines (apply to all human medicinal products)
    - `presence of nitrosamines…shall be mitigated as much as possible and shall be at or below a limit based on ICH M7(R1) principles …considering a lifetime daily exposure.´
    - Risk evaluation / risk assessment (incl. confirmatory testing) required from MAHs / Applicants
- **Sep 2019: `Call for review´** (on-going)
  - MAHs to evaluate, mitigate and report the risk of presence of nitrosamines
  - Authorized human medicinal products containing chemically synthesized APIs or biological APIs
- API manufacturers should provide MAHs / Applicants with all information necessary for a comprehensive RE / RA (also applicable if a CEP is used)!

Background

Brief Overview of Regulatory History of Nitrosamines - EDQM

- `Call for review´ to CEP holders (completed)
- **Risk assessment required for new CEP applications, renewals and revisions**
- Revision of monographs for `Sartans´
  - Valsartan, Losartan potassium, Irbesartan, Candesarten cilexetil and Olmesartan medoximil
    - Initial: Interim limits for NDMA and NDEA in test section
    - Current: Paragraph on nitrosamines in production section
- General chapter 2.5.42 on the analysis of N-nitrosamine impurities in active substances
    - Validated for above `Sartans´
- **On-going: Revision of general monographs** (aligned to CHMP recommendations)
    - Substances for pharmaceutical use (2034)
    - Pharmaceutical preparations (2619)

Risk Evaluation

How should the RE look like?

- Follow quality risk management principles, as outlined in ICH Q9 to identify, if API and/or FP could be at risk of presence of nitrosamine impurities
  - Risk factors related to the API could contribute to nitrosamine formation in the FP whether or not nitrosamine formation has occured in the API
- Summarize detailed enough to allow assessement of **appropriateness and completeness**
  - Considered **sources** of nitrosamines, vulnerable amines and nitrosating agents
    - RM (SM, reagents, solvents, catalysts) and impurities / degradation products thereof as well as IM, by-products, API and their degradation products
    - Different manufacturers of IM, SM or other RM
  - Considered **risk factors** (EMA/409815/2020 Q&A #4 and any additionally identified)
  - If applicable, **supportive data** like actual batch data or spike / purge studies
    - Theoretically calculated purge factors without supportive data are **not** sufficient
  - Any **assumptions, calculations and rationales** made (if applicable, include supportive literature)

Risk Evaluation

How should the RE look like?

- Conclude on identified risks
  - **Nitrosamine formation during synthesis or storage of API**
    - Confirmatory testing required
  - **Carry over of vulnerable amines and / or nitrosating agents into FP**
    - Confirmatory testing only required, if RE identifies risk of nitrosamine formation during manufacture and / or storage of the FP
    - Also the API itself can exhibit amine- and / or nitro-functionalities (increasing numbers of nitroso APIs are reported)
- API manufacturers should provide MAHs / Applicants with all information necessary for a comprehensive risk evaluation (also applicable if a CEP is used)!
- MAHs together with API- (and FP) manufacturers are expected to reevaluate the RE as and when new information becomes available!

Risk Assessment

How should confirmatory tests be conducted?

- **Generally confirmatory testing is to be carried out on FP**
- Still, testing of API (or IM, SM and RM) is recommended to support root cause analysis
  - If risk is only linked to API manufacturing process -> **API and IM may act as surrogates for FP**
    - Justification needed -> **no additional risk factors in the FP (or API)**
- **Testing strategy should be justified** -> tested (number of) batches representative?
  - Is the source of risk well-understood -> can impurity levels be expected to be consistent?
  - Is formation during manufacturing and storage considered (aged batches tested)?
  - Are different manufacturers and / or mfg. processes considered (API, IM, SM or RM)?
  - Is the batch size representative (production scale vs. pilot scale)?
- If despite extensive efforts nitrosamine cannot be synthesized -> no confirmatory testing
  - Thorough justification needed
- Apply appropriately sensitive methods

Risk Mitigation

Presence of nitrosamines…shall be mitigated as much as possible…

- MAH/ Applicants shall design their mfg. processes and controls to prevent if possible or mitigate as much as possible the presence of nitrosamines in their API and FP, e.g.
  - Change manufacturing process
  - Change RM quality
  - Introduce appropriate specifications (and methods)
- **If nitrosamine levels are at or above 10% of acceptable limit -> specify** (usually in FP)
  - If source of nitrosamine is only in the active substance manufacturing process ICH M7 control options 1 – 3 can be used (i.e. specification in API, IM, RM, SM or as IPC)
    - **The control point should be justified** (w.r.t. the identified root cause / source of risk)
  - If levels of a single nitrosamine are consistently below 30% of the acceptable limit -> skip testing could be acceptable

Limits and Control Options

Which limits apply for nitrosamines?

- Nitrosamines belong to `cohort of concern´ (ICH M7)
  - Compound specific acceptable intakes (AI) need to be calulcated
  - `Less than lifetime approach´ should not be applied (except as temporary measure agreed by CA)
- EMA/409815/2020 Q&A #10
  - Established AIs
  - Calculation of limits
    - Single nitrosamines
    - More than one nitrosamine
    - Genotoxic (mutagenic, clastogenic and / or aneugenic) APIs

Limits and Control Options

Acceptable Intakes

N-Nitrosamine (CAS number)	ng/day[1,*]	Source[2]
N-Nitrosodimethylamine, NDMA[3,4] (62-75-9)	96.0	
N-Nitrosodiethylamine, NDEA[3,4] (55-18-5)	26.5	
N-Nitrosoethylisopropylamine, EIPNA[3,5] (16339-04-1)	26.5	
N-Nitrosodiisopropylamine, DIPNA[3,5] (601-77-4)	26.5	
***N*-Nitrosamine (CAS number)**	**ng/day[1,*]**	**Source[2]**
N-Nitroso-*N*-methyl-4-aminobutyric acid, NMBA[3,6] (61445-55-4)	96.0	
1-Methyl-4-nitrosopiperazine, MeNP[3] (16339-07-4)	26.5	Rifampicin
N-Nitroso-di-*n*-butylamine, NDBA[3,5] (924-16-3)	26.5	
N-Nitroso-*N*-methylaniline, NMPA[3,4] (614-00-6)	34.3	
N-Nitrosomorpholine, NMOR[3,7] (59-89-2)	127	
N-Nitrosovarenicline, NNV[8]	37.0	Varenicline
N-Nitrosodipropylamine, NDPA (621-64-7)[3,5]	26.5	
N-Nitrosomethylphenidate[9], NMPH, (55557-03-4)	1300	Methylphenidate
N-Nitrosopiperidine[3] (100-75-4)	1300	
N-Nitrosorasagiline[10]	18	Rasagiline
7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3- a]pyrazine[11]	37	Sitagliptin
N-Nitroso-1,2,3,6-tetrahydropyridine, NTHP[3] (55556-92-8)	37	
N-Nitrosonortriptyline[12]	8	Amitriptyline, nortryptyline
N-Methyl-*N*-nitrosophenethylamine, NMPEA[3] (13256-11-6)	8	
N-Nitrosodabigatran[10]	18	Dabigatran

- Only applicable, if <u>single</u> nitrosamine is present
- Convert to specification limit in ppm (or ppb)
  - **AI [ng/d] / MDD [mg] = AI limit [ppm / ppb]**
  - MDD of spec. medicinal product acc. to SmPC
- **Class specific TTC: 18ng/d** (default option)
- Control according to ICH Q3A / Q3B
  - Advanced cancer indication (ICH S9)
  - Mutagenic / clastogenic API (therapeutic conc.)
    - Not applicable for aneugenic APIs
- Nitroso APIs are indicated (`source´)
  - Only if AI has been established
  - Others, e.g. Quinapril, HCT, Sotalol, Paroxetine, Amitriptylene (and APIs with related structures)

Limits and Control Options

Multiple Nitrosamines

- **Option 1**
  - Specify limit for **total nitrosamines** according to the most potent nitrosamine present at or above 10% of its AI limit
    - Limits for individual nitrosamines can be defined but are not necessarily needed
    - Clearly state which nitrosamines are included
  - **Pro:** very easy to set limit
  - **Con:** very conservative
    - OOS result might occur even if total (excess cancer) risk level of 1 in 100,000 is not exceeded
- **Option 2**
  - Limits for nitrosamines should ensure a total (excess cancer) risk level of NMT 1 in 100,000
    - **`Fixed approach´**
    - **`Flexible approach´**

Limits and Control Options

Fixed Approach

- Specify each nitrosamine present at or above 10% of its AI limit individually
- Set specified limits for each nitrosamine at an appropriate percentage of AI limit [ppm/ppb]
  - e.g. based on the ratio of nitrosamines found during confirmatory testing and their AI limits
- Sum of % AI limits of all specified nitrosamines should not exceed 100%
  - = total risk level of 1 in 100,000
- No limit for total nitrosamines
- **Pro:** Less conservative than option 1
- **Con:** Little flexibility
  - Variability in nitrosamine levels could cause OOS results for individual nitrosamines even if total risk level does not exceed 1 in 100,000

Limits and Control Options

Flexible Approach

- Specify each nitrosamine present at or above 10% of its AI limit
- Set specified limit for each nitrosamine at AI limit [ppm/ppb], i.e.
  - Each nitrosamine is specified at 100% AI limit (= 1 in 100,000 total risk level)
    - Sum of nitrosamines could exceed total risk level of 1 in 100,000 without exceeding ind. limits
- Need to additionally **specify total nitrosamines (sum of % AI limits = NMT 100%)**
  - Convert actual amount of each specified nitrosamine to percentage of its respective AI limit
  - Sum of % AI limits of specified nitrosamines should not exceed 100%
    - = total risk level of 1 in 100,000
- **Pro:** Less conservative than option 1 and more flexible than fixed approach
  - Variability in ind. nitrosamine levels is no problem as long as total risk level is NMT 1 in 100,000
- **Con:** Reporting of results is more complex than in option 1 / Option 2 - fixed approach

Limits and Control Options

How could a specification look like?

- NDMA and NDEA at or above 10% of AI limit in DS (1000mg MDD) – no add. risk in FP
  - AI limit NDMA: 96.0[ng/d] / 1000[mg] = 0.0960ppm (96ppb) -> 10% = 9.60ppb
  - AI limit NDEA: 26.5[ng/d] / 1000[mg] = 0.0265ppm (26.5ppb) -> 10% = 2.65ppb (most potent)
- NDMA / NDEA levels found during confirmatory testing (10% of all batches)
  - NDMA: 9.6 – 14.4ppb (10% - 15% of AI limit)
  - NDEA: 17.2ppb – 18.5ppb (~ 65% - 70% of AI limit)
- **DS specification** (examplary)

	Option 1	Option 2 – Fixed	Option 2 - Flexible
NDMA	Not needed	19ppb (20% AI limit)	96ppb (100% AI limit)
NDEA	Not needed	21ppb (80% AI limit)	26.5ppb (100% AI limit)
Total Nitrosamines	26.5ppb	Not needed	NMT 100% (Sum of AI limits)[1]

[1]Calculation of result: (ppb NDMA / 96ppb + ppb NDEA / 26.5ppb) * 100% (= total risk level of 1 in 100,000)

Limits and Control Options

Potential consequences of applied control option / approach

	Batch X	Option 1	Option 2 – Fixed	Option 2 - Flexible
NDMA	10ppb	Not needed	19ppb (20% AI limit)	96ppb (100% AI limit)
NDEA	18ppb	Not needed	21ppb (80% AI limit)	26.5ppb (100% AI limit)
Total Nitrosamines	28ppb (78%[1])	26.5ppb	Not needed	NMT 100%[1]

	Batch Y	Option 1	Option 2 – Fixed	Option 2 - Flexible
NDMA	10ppb	Not needed	19ppb (20% AI limit)	96ppb (100% AI limit)
NDEA	23ppb	Not needed	21ppb (80% AI limit)	26.5ppb (100% AI limit)
Total Nitrosamines	33ppb (97%[1])	26.5ppb	Not needed	NMT 100%[1]

	Batch Z	Option 1	Option 2 – Fixed	Option 2 - Flexible
NDMA	19ppb	Not needed	19ppb (20% AI limit)	96ppb (100% AI limit)
NDEA	25ppb	Not needed	21ppb (80% AI limit)	26.5ppb (100% AI limit)
Total Nitrosamines	44ppb (114%[1])	26.5ppb	Not needed	NMT 100%[1]

[1]Sum of % AI limits; calculated as follows: (ppb NDMA / 96ppb + ppb NDEA / 26.5ppb) * 100%

Analytical Methods

Appropriately sensitive methods should be used!

- LoQ should be used for impurity testing and decision making
  - Quantitative testing as a routine control -> LoQ at or below AI limit
  - Quantitative testing to justify skip testing -> LoQ at or below 30% of AI limit
  - Quantitative testing to justify omission of specification -> LoQ at or below 10% of AI limit
- Potential exceptions (high MDD, multiple nitrosamines) – case by case
- Method description and validation data to be included in RA or S.4 (routine control)
  - If the same analytical method is used for multiple nitrosamines, then selectivity of the method should be demonstrated for each nitrosamine

Active Substances for Veterinary Use Only

Not in the scope of Art. 5(3) referral

- No specific guidance for nitrosamines in APIs and FPs for veterinary use only (yet)
- Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (EMA/CVMP/SWP/377245/2016)
  - `Cohort of concern´ (incl. nitrosamines):
    `Intakes even below the TTC are theoretically associated with a potential for a significant carcinogenic risk and a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should be developed to justify acceptable intakes for authorised VMPs. Principally, these substances should not occur as an impurity of an API or a VMP, due to their extremely high carcinogenic potency.´

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

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"CEP of the Future" project

Background for the project

- No significant changes to the CEP document since its creation in 1992-1994 but slight evolutions (increasing amount of information)
- Increasing use of CEPs within Europe and worldwide
- Evolving environment: globalisation of manufacture of APIs, evolution of regulatory requirements, scientific and technological developments
- Feedback received regularly from various stakeholders on needs/opportunities to improve CEPs
- Time to prepare the "CEP of the Future" and better meet the stakeholders' needs.

Goals of the project

- Meet the most recent needs of stakeholders: CEP holders/API manufacturers, drug product manufacturers, regulatory agencies (worldwide) including quality assessors
- Ease the registration activities linked to the use of CEPs
- Increase the acceptance of CEPs

Public consultation

- Wide public consultation 2020 via an on-line survey, publicly available via EDQM website
- Sent to targeted groups (assessors from national authorities, EMA WPs, authorities outside Ph. Eur. using CEPs, Industry Associations, main CEP holders)
- Questions on various aspects connected to CEPs and open for free suggestions
- About 550 responses, of which 150 complete
- Compilation of comments and feedback received in 2021

Review of feedback

- Lack of knowledge and understanding of
  - Duties of CEP holders/API manufacturers vs MAH/Drug product manufacturers
  - Current regulations, EDQM policies on the content of the CEP and how to use CEPs
- Expectation for more information on CEPs to increase transparency and clarity for users
- Requests to reduce revisions of CEPs
- Enhance use of the public database and IT tools

➔ More details on the outcome of this public consultation can be found here

Work areas

- Review information to be stated on the CEP
- Reduce revisions of CEPs and facilitate handling of changes
- Enhance digital tools and public databases
- Foster information sharing between CEP holders and medicines manufacturers
- Train users on content and use of CEP

The "CEP of the future"

- The CEP remains a « document », with a layout similar to the current one.
- Electronic document with a digital signature.
- Downloadable as a pdf or printed by CEP holders to share with their customers, for inclusion in MAA.
- No declaration of access box in the CEP document anymore
  - replaced by a template (available on the EDQM website).

The "CEP of the future"

- Technical information such as additional controls for impurities or solvents will be replaced by full specification including methods appended to the CEP
- Sentence on "animal or human origin material" will be mentioned ONLY if there is use of such materials (i.e. no text in case no animal/human origin material is used).

Changes regarding assessment

- CEP dossier (modules 2 and 3) will reflect the assessment performed and the approved specification
  - if no grade claimed, related info to be removed from the file regarding the specification and the process description (e.g. particle size)
- Encouragement to claim re-test period and inclusion of stability data

Open points

- Replacement of company details (name and address) for the CEP holder and manufacturing sites by SPOR/OMS Loc Id. and details regarding sites
- Details regarding solvents used in the last steps of the process
- Extension of assessment (e.g. microbiological controls if proposed by applicants, stability data in additional climatic zones if proposed by applicants)
- Inclusion on the CEP of information on MDD, route of administration and treatment duration used as basis for assessment of the CEP application.

Databases

- On-line Certification database (publicly available database)
  - Expand the current database to provide more information on dossier lifecycle (e.g. history of procedures, types, outcomes etc).

- Authorities database (dedicated to NCAs)
  - Expand the current database to provide more information on dossier lifecycle (e.g. access to the CEP document associated to a specific procedure)
  - Considerations for the future: possible extension of access to regulatory authorities beyond Ph. Eur. as part of worldwide acceptance of CEPs under suitable confidentiality agreements and MoU.

Foster information sharing CEP holders & MAH

Step-wise approach, **step 1**:

- CEP holder shall provide information to their customers in addition to the CEP
  - Up to CEP holder and MAH to agree on information shared and format.
- In January 2022 publication on the EDQM website of the document "CEP holders responsibilities towards their customers" as a reminder to CEP holders (here)
  - This aspect is checked during EDQM GMP inspections.

- Reinforcement of this responsibility in 2023 through
  - A commitment as part of the application form for a CEP
  - A specific sentence on this obligation in the CEP document
  - Publication of history of procedures in the public certification database, so users are aware of changes and can ask details from the CEP holders.

Foster information sharing CEP holders & MAH

Step 2, to be considered as part of the upcoming new EU pharma legislation :

- Implementation of a "CEP summary"/"open part" for the CEP
- To be shared by CEP holders with their customers/CEP users

➔Major impact on CEP holders, EDQM, MAHs, possibly regulatory authorities.

Reduction of revisions of CEPs

- No revision of CEPs for changes not impacting their content even in case of major revisions
- Stop releasing a "renewed" CEP following the renewal procedure (the renewal process will be kept), except if the content is impacted ➔ impact on the CEP numbering
- Avoid revision of CEPs in case of administrative changes to details for CEP holders and manufacturing sites (name and address)

NB. Appending specification to the CEP may trigger more revisions.

Challenges and difficulties

- Evolving environment, digitalisation, many projects on-going in parallel at EU level ➔ need to coordinate, adapt and design the "CEP of the future" at the same time and have a step wise approach.

- Balance between
  - increasing transparency in CEPs and reducing number of revisions of CEPs
  - information included in the CEP document and information accessible via others channels/tools.

- Open points still to be addressed in a short period of time.

Next steps

- **September 2022**: Targeted consultations with Industry and Authorities
- **Q4 2022:** Final decisions concerning topics addressed in the workshops and validation by the CEP Steering Committee.
- **Q1 2023:**
  - Wide communication about new expectations regarding CEP dossiers (new applications, renewals etc)
  - Communication about changes to the CEP document
  - Start of development of IT tools (databases).
- **May 2023:** implementation of the « new look » CEP.

Impact of changes

- The project will have a major impact for all users (CEP holders, MAH, authorities and EDQM)
- Implementation of changes by CEP holders in their submissions (on-going and new applications)
- Technically not possible to update all existing CEPs to the "new look" at the implementation time ➔ coexistence of "old look" and "new look" CEPs for some time
- Communication and training will be key.

Thank you for your attention

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The CEP of the future
API manufacturers' perspective

Marieke van Dalen for APIC
Strassbourg, September 2022

Overview of this presentation

- Introduction
- CEP optimization (APIC points)
- Outlook to the future
- Current developments

Introduction

- Marieke van Dalen
- Working for Aspen Oss B.V. in the Netherlands, an API producing site, holding 23 active CEPs.
- Over 35 years of experience in the regulatory field
- Board member of APIC, a Technical European Industry Association, based in Brussels, with focus on APIs from a quality and regulatory perspective.
- APIC is the API observer in the ICH and is a recognized discussion partner for many authorities including Anvisa, EDQM, EMA and the PMDA.

Introduction

- APIC working group on “CEP optimization”
- Not all APIC members are solely producing APIs, meaning that their ideas were also brought into the meetings.
- The working group in the end drafted an APIC position which was approved by the APIC board and submitted to the EDQM.
- In the APIC position, proposals were made towards improvement of the current system , but also some wishful thinking towards the future.

CEP optimization

- First of all : APIC fully supports and promotes the use of CEPs, allthough the fact that it is “used” in many countries outside the EU is also complicating matters.
- There is clear guidance on the information to be submitted to obtain a CEP, and EDQM is usually quite fast in publishing guidance when changes need to be incorporated (e.g. implementation of ICH Q3D, nitrosamines).
- But (of course?) we also found some room for improvement.

CEP optimization

- Some of the administrative data is recurrent: for each and every CEP requested by a single company, the same details (on e.g. the contact person, the home office address) need to be provided per CEP in the application form. This could in our view be simplified by means of a database. This would prevent quite a number of changes, e.g. when the contact person is changed or when there is an administrative change to the holders’ address.

CEP optimization

- When a grouped notification for an administrative change (name or address) is submitted, EDQM requires documentation (statement, declarations e.g. GMP) for each dossier, this is quite a lot of work with not much added value; our proposal would be to provide only once the administrative package which would be applicable for all dossiers impacted by the administrative change.

CEP optimization

- We feel there is still some guidance/training needed from EDQM (even in the EU), on what type of information is being assessed by EDQM, and on the possibility to access the assessment report by the Health Authorities, as too often questions are still raised on topics that are already dealt with at EDQM. It seems in such cases that the assessment reports are not accessed at all.

CEP optimization

- Retest date for different climate zones (e.g. IVB studies).
  We suggest to add retest dates based on stability testing of different climate zones, including III and IV, when requested. This would be very helpful, as CEPs get more and more accepted all around the world.

CEP optimization

- Solvents listed on CEP “selected” by EDQM.
  We feel the phrasing should be amended to reflect that this is the minimum required by EDQM. Often companies have included more solvents in their specification (and thus on the Certificates of Analysis) and this gives rise to questions from Health Authorities as they seem to think that information was then withheld from EDQM.

CEP optimization

- GPS coordinates instead of address
  We propose to change the information regarding production site addresses on the CEP, as in omitting detailed postal addresses (which sometimes change for administrative reasons) and instead include the GPS coordinates and the country of the production site. An alternative is provided under the heading outlook to the future.

CEP optimization

- Include information on genotoxic/mutagenic impurities on the certificate.
  We suggest to always include on the CEP a statement regarding evaluation of mutagenic impurities, for example: Control of (potentially) mutagenic impurities has been established in-line with the ICH M7(R1) guideline, EMA "Guideline on the Limits of Genotoxic Impurities" / Nitrosamines Article 5(3) etc.

CEP optimization

- Statements of compliance to e.g. ICH Q3D
  We propose to change the information regarding elemental impurities on the CEP certificate, namely, risk assessment in line with Q3D has been performed. There is no need to control any elemental impurity / or …. needs to be limited at a level of …ppm, based on a … grams per day dosage (oral).
  We propose to omit the Risk Management Summary as Appendix to the CEP.
  A similar approach could be used for nitrosamines, genotoxic/mutagenic impurities etc.

CEP optimization

- Access box – abuse of CEPs.
  Although the access box was included on the CEP to address a concern raised by the API industry it did not take away the concern, as there is no direct contact between the CEP holder and the relevant Health Authority, and abuse of a CEP will thus not be noticed by the CEP holder.
  This could be covered by the introduction of an electronic portal for CEPs (see outlook to the future).

CEP optimization

- Major revision of a CEP automatically leading to a revised CEP
  This has been introduced upon request of the QWP, so that both the MA holders and the Health Authorities would be aware that a major change had been made. Between the CEP holder and the MA holder this is normally arranged in the Quality Agreements. Major changes should obviously never be introduced without informing the MA holder. The idea behind the awareness of the Health Authorities was that they could then have a look at the EDQM assessment report to get more information on the change. As this is however, hardly being done in practice, we would like EDQM to reconsider this “automatic” issuance of a revised CEP.

CEP optimization

- Obviously, if the text on the CEP is affected, a revision is a logical consequence.
  Another solution for this issue would be that a mere notification of the MA holder towards the Health Authorities would suffice (no variation with accompanying costs and administrative burden), or that a separate type of variation without costs and administrative burden (both at the MA holder and the HAs) would be implemented.

CEP optimization

APIC members also mentioned some things they would NOT like to see:

- Database: Customers should not be able to see other customers' names using the same CEP, nor should a copy of the CEP be available online.
- GMP aspects: communication on changes should be covered in Quality Agreements between the CEP holder and the MAH. The CEP should not be "abused" to enforce this communication, as this is part of the GMP based Quality systems of the companies.

Outlook to the future

APIC made a proposal for a searchable database, with different components:

- Portal page
  similar to the current certification database on the EDQM Website: this public page allows for looking up the following information on CEPs: substance, CEP holder, certificate number, issue date, status, end date and type.

Outlook to the future

- A repository where the actual CEP content can be reviewed:
  - ❖ the information in this part would be owned/updated by EDQM
  - ❖ the information in this part is visible to EDQM, the CEP holder, all signatories of the convention
  - ❖ the information in this part could additionally be made available to the MAH referring to this CEP and its revisions as well as any HA outside of the convention, when access is granted by the CEP holder

Outlook to the future

- Access for “other” parties
  a portion of the database where the CEP holder can manage access to its CEP for optional parties (being Health Authorities not being EDQM and the signatories of the convention).
  - The CEP holder can assign a MAH to its CEP.
  - Optionally, the CEP holder can upload the relevant MAA numbers for which the CEP can be used.
  - The CEP holder can assign additional HA to its CEP.
  - In case the CEP holders name is (administratively) changed, this can be updated by the CEP holder in this part of the database with a notification (no revision and thus no variation).

Outlook to the future

- PDF printer feature
  Here, the actual CEP can be printed, by default including the "access box data": CEP holder name, MAH name, territory and (optionally) the MAA numbers to generate a printed CEP in case a hard copy is needed for any HA (often outside of the EU legalized/apostilled/wet signature versions are required). The MAH can NOT print a blanc version of the CEP, they need to indicate the territory for which the printed CEP is needed and the CEP holder needs to approve that.

Outlook to the future

- Site addresses
  Our suggestion would be to include the addresses of the manufacturing sites in the database and to remove these from the CEP itself (there only keep the name and country of API manufacturing). This will allow administrative changes to the addresses without revising the CEPs, while ensuring that EDQM, the MAH and the HA have access to this information at all times.

Current developments

At the time EDQM published the outcome of the public consultation it became clear that there is quite some common ground in the reactions they received and 5 major topics were taken by EDQM to further elaborate on.

1. Information to be reported on the CEP
2. Reduce revisions of CEPs and facilitate handling of changes
3. Enhance digital tools and public databases
4. Foster information sharing between CEP holders & medicines manufacturers
5. Train users on content and use of CEPs

Current developments

On point 4, *foster information sharing between CEP holders & medicines manufacturers*, EDQM has already published a guidance entitled “CEP holders responsibilities towards their customers”.
In this guidance there is strong emphasis on the fact the CEP system should not be used as a way to avoid providing the MAH with relevant information (in the ASMF system this is verified through the Applicants Part).
Although APIC acknowledges the need for such a document we have some doubts about some strong wording used.

Current developments

On the other points there are no official publications yet, and in the days to come we will have a meeting between industry organizations and EDQM to discuss further proposals.

We are happy to see the speed with which EDQM moves forward.

Already APIC did get some preliminary feedback from EDQM which shows that serious steps are planned to be taken to decrease the amount of revised CEPs.

Current developments

APIC also took note that there is the intention to append full specifications and analytical methods to the CEP.
We do not know why this is deemed necessary, but we do foresee problems there:

- Changes in specifications or analytical methods are then always leading to a revised CEP, which means probably more variations than the ones “saved” by the decrease in relation to major revisions and addresses
- Agreement on specifications is not the same between all MAAs, espescially when you take into account the many countries outside of the EU where the CEPs are being used.
- As an example: my own company has one CEP with over 1500 MAAs linked to it.

Current developments

You can imagine we are very curious to see what will happen in the next days when the meetings between Industry and EDQM will take place on the CEP of the future.

We are happy to see again the openness with which EDQM takes up a project like the CEP of the future.