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

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

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The EDQM Certificate of Suitability (CEP) Procedure

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"The European Pharmacopoeia"
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EDQM Director

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EU legislation and certificates of suitability

- EU Directives 2001/83/EC and 2001/82/EC, as amended, on medicinal products require active substances (APIs) to comply with the Ph. Eur. monograph if there is one
  - Claiming compliance with a Ph. Eur. monograph is not enough
  - The applicant shall demonstrate the suitability of the Ph. Eur. monograph to control the quality of the API used

…"where the active substance is the subject of a monograph of the Ph. Eur., the applicant **can apply for a certificate of suitability** that, where granted by the EDQM, shall be presented in the relevant section of the CTD Module. Those certificates of suitability …are deemed to replace the relevant data of the corresponding sections described in the Module…"

The CEP procedure

- CEP = Certificate of Suitability to the monographs of the European Pharmacopoeia
- An international platform for:
  - ➢ Assessment of the quality of substances for pharmaceutical use (mainly APIs), with reference to monographs of the Ph. Eur.
  - ➢ Coordination and conduct of GMP inspections of API manufacturers
  - Source of information to update Ph. Eur. monographs
- Managed by the EDQM
- Open to any manufacturer of pharmaceutical substances regardless of geographical origin

The CEP procedure (2)

- CEPs are not mandatory
- In the EU, up to the applicant to choose the way to provide data on the quality of an active substance:
  - Certificate of suitability (requires a Ph. Eur. monograph, APIs and excipients)
  - Active substance Master File (ASMF) (For Ph. Eur. and non-Ph. Eur. APIs)
  - Full details of manufacture in marketing authorisation application (For Ph. Eur. and non-Ph. Eur. APIs)

The data to be submitted **are the same**, irrespective of the route selected

The CEP procedure provides

- Centralised assessment
- Easier management of marketing authorisation applications and respective variations: CEP replaces main part of 3.2.S of CTD
- CEPs are increasingly accepted worldwide

Save time and resources!

Scope

- Chemical substances, fermentation products, herbals, **covered by a monograph in the Ph. Eur.**
  - To demonstrate:
    - that the quality of a substance is suitably controlled by the Ph. Eur. monograph (with additional tests, if needed)
    - that the substance quality is in compliance with ICH & EU requirements (related substances, mutagenic impurities, residual solvents, elemental impurities, etc.)

  ➔"Chemical CEP" or "Herbal CEP"
- TSE (Transmissible Spongiform Encephalopathy) risk materials (with reference to the General Monograph "Products with TSE risk")
  - To guarantee compliance with the General Monograph

  ➔"TSE CEP"

Who is involved

- Steering Committee
  - 16 members, representing the main authorities & working groups in Europe and Ph. Eur. member states
  - Takes decisions on scope, makes links with regulatory groups and adopts EDQM guidelines
- Technical Advisory Boards (TAB)
  - Chemical, TSE, Herbals
  - Experienced assessors taking part in the procedure
  - Prepare policies, guidelines, take decisions on technical issues…

Who is involved (2)

- Assessors:

  from National competent authorities from Ph. Eur. member states, and international partners
  - Skilled in the relevant domain (chemical evaluation, TSE risk, herbal products, toxicologists…)
  - About 100 assessors from 25 countries, including Australia and Canada, and also from EDQM
  - Come regularly to EDQM premises for the evaluation of dossiers together with EDQM colleagues

Who is involved (3)

- Inspectors:

  # 30 inspectors from supervisory authorities from 16 EU/EEA countries + Switzerland

  - Perform inspections with EDQM
- EDQM Certification Department
  - located in Strasbourg, France
  - #45 people: assessors, inspectors, scientific and administrative staff
  - Run the procedure, coordinate the activities and communication

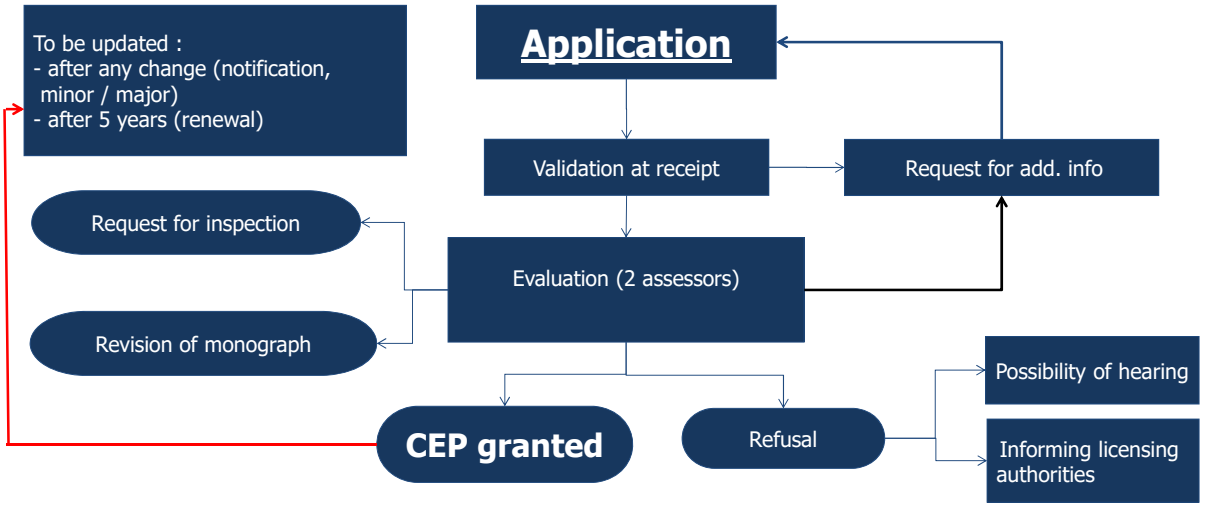
A great and successful example of international cooperation!

Evaluation of applications and granting CEPs

How to apply for a CEP

- Intended holder (substance manufacturer) to **send a Dossier to EDQM**
- Content in compliance with EDQM guidelines:
  - "Content of the Dossier for Chemical CEP": comparable to content of 3.2.S of CTD
  - "Content of the dossier for TSE risk"
  - "Content of the dossier for herbal drugs/herbal drug preparations"
  - All documents are available on the EDQM website (www.edqm.eu)
- Fees: currently 5000 euros for a new application

How does it work



Principles for assessment

- Performed against applicable monographs and chapters of the Ph. Eur., applicable ICH and EU guidelines (e.g. on quality of active substances) and applicable EDQM policies
- Science- and risk-based – focus on impurities and their control
- It is a requirement to show whether the monograph of the Ph. Eur. the substance refers to is suitable to control the quality of the source of the substance under evaluation and to propose appropriate additional specification(s), where relevant
- Outcome: **an official certificate granted by EDQM: CEP**

How long does it take ?

- "3-round policy":
  - Initial assessment
  - Letter of questions
  - Assessment of responses
  - 2nd request for information
  - Assessment of responses and decision to grant the CEP or to reject the application (or exceptionally a last request for information)
- Official deadlines for each milestone
- It takes min 5 months and max 1.5 year to get a CEP

Revisions of CEPs

Once a CEP has been granted it must be maintained throughout its lifetime!

Basic principles for revisions of CEPs

- Changes to CEP applications are handled by EDQM
- Any change must be reported to EDQM and approved, depending on the nature of the change
- Original CEP is valid 5 years
- Holder needs to apply for renewal on time
- After renewal, CEP valid for an unlimited period, provided the dossier is kept up-to-date
- CEP Holder should inform customers of any changes made
- If a revised CEP is issued, it has to be sent to customers and a variation to the marketing authorisation application(s) has to be submitted

Basic principles for revisions of CEPs (2)

- Based on EU Regulations on Variations to Marketing Authorisations
- Specific EDQM guideline for revisions of CEP (EDQM website)
- Timelines for approval depend on the type of changes

Types of revisions

- Notifications (Immediate (IN) or Annual (AN)) ➔ 'Do & tell'
- Minor revisions ➔ 'Tell & do'
- Major revisions ➔ 'Tell, get approval and do'
- Renewal after 5 years
- Update following revision of the monograph or following regulatory changes
- Sister File (separate application treated as a revision)

Type of changes

- Administrative changes (e.g. Change of names of companies)
- Quality changes:

  Changes could be made to any part of the application e.g.
  - Change in the manufacturing process of the substance
    - Minor changes e.g. adjustments to operating conditions, introduction of inert process aids OR
    - Major: substantial changes to the manufacturing process, e.g. change of solvents used for purification, change to synthetic route
  - Change in specification for the final substance e.g. changing limits for impurities (should remain within the limits of the Ph. Eur. / ICH-VICH guidelines), changing analytical method

Renewal process

- After 5 years, a way to confirm the original assessment and approved specification for the substance
  - Recent batch data to be submitted
- Assessment of renewal takes into account regulatory changes (e.g. ICH Q3D on elemental impurities)

Update following revision of monograph

- Ph. Eur. monographs are subject to regular updates and this has an impact on CEP applications and on the CEPs themselves
- Systematic process at EDQM to make sure that CEP applications are updated when monographs are revised
- When a revised Ph. Eur. monograph is published and an update is needed, the CEP Holder is requested by EDQM to provide data
- After assessment of the data, if needed a revised CEP is granted

Ensures that all CEPs refer to the current version of a Ph. Eur. monograph

When are CEPs revised?

- After any notification/minor revisions, update following implementation of a revised monograph, impacting the content of CEP
- After any major revision
- After renewal (renewed CEP)

- In the other cases, an approval letter is sent by EDQM

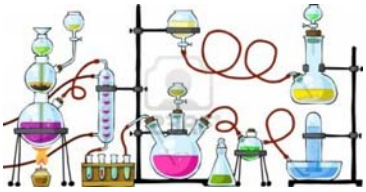
What to do after approval of a CEP revision?

- What to do with a revised CEP
  - Holder to provide copy to their customers
  - MAH to update relevant Marketing Authorisation Application(s) (variation) ➔Mandatory
- What to do when a change is approved but CEP is not revised
  - Holder to inform customers, but no variation of the Marketing Authorisation Application

  ➔Mandatory

Appropriate communication between the CEP holder and their customers is crucial!

Use of a CEP



Content of a CEP

- Each CEP has a **unique** reference number:

R1-CEP 2014-001-Rev 03

- **R1:** this CEP has been renewed once (5 years after issue)
- **2014-001:** CEP application number allocated by EDQM (the dossier was submitted in 2014)
- **Rev 03:** this CEP has been revised 3 times since its renewal
- Each CEP has a date of issue, which is also reported on the public database

Certification of Substances Division

Certificate of suitability
No. Reference CEP

Name of the substance:
SUBSTANCE NAME

Name of holder:
CEP HOLDER NAME
CEP Holder Address
Country name-Post code Town, State

Site(s) of production:
SEE ANNEX 1

After evaluation 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 **SUBSTANCE NAME** no. n° substance 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 related substances by liquid chromatography (Annex X)
Specified impurity V not more than XXX%
Any unspecified impurity not more than XXX%
Total impurities not more than XXX%

– Test for residual solvents by gas chromatography (Annex X)
Solvent not more than XXX ppm

The re-test period of the substance is XXX years if stored in XXX placed in XXX.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (07) 1] for a period of five years starting from **DD MMM YYY**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines. Delete Para Five Y

This certificate has XX (letters) annexes, the first of XX (figures) pages and the second of XX (figures) pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, DD MM YYYY

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

Name of holder, as holder of the certificate of suitability

Reference CEP for Substance Name

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of the version of the certificate.

Date and Signature *(of the CEP holder)*:

CEP in a marketing authorisation application in EU

• CEP (chemical purity) intended to be included in Part 3.2.S of the Marketing Authorisation Application:

- A complete copy of the CEP, with its annexes
- Specification of the active substance, **which should include the tests mentioned on the CEP**
- A CEP may **not** address all parameters relevant for the specific use in the finished product, e.g. specific physico-chemical characteristics, etc. ➔ API specification in the dossier may include additional tests to those of the monograph + the CEP
- Batch data in 3.2.S.4 demonstrating compliance with Ph. Eur. monograph and any additional tests on CEP (+ other tests if needed)
- If needed, stability data in 3.2.S.7 (NB. in the EU, stability data are not mandatory for substances described in the Ph. Eur., the substance may be tested immediately prior to use)

The EDQM inspection programme

The EDQM inspection programme

- Integral part of the Certification Procedure
- For manufacturing sites for APIs involved in CEP applications
- Establishment of an annual programme, by combination of:
  - On-site GMP inspections
  - Getting information from GMP inspections carried out by EU/EEA inspectorates and international partners

Inspections carried out by EDQM

- Performed before or after the CEP is granted
- **Selection of sites** eligible to be inspected by EDQM
  - In line with EU legislation for GMP compliance of API manufacturers
  - According to a **risk-based approach**
- Inspections mostly in Asia
- Aim: to verify compliance with
  - submitted CEP dossier and Ph. Eur.
  - EU GMP Part II (ICH Q7) & any applicable annex such as 1 for sterile substances, 11 for computerised systems etc.

EDQM inspections

- Inspections performed by team composed of 1 EDQM inspector and 1 inspector from an EU/EEA/MRA authority
- Joint inspections may be performed, e.g. with WHO, TGA, USFDA
- Last generally 3 days
- An initial inspection report is issued by EDQM
- The company should reply to the deficiencies found within 1 month from the receipt of the inspection report
- A final report is issued by EDQM

➔Immediate actions regarding the validity of the CEPs are taken in case of major or critical deficiencies (generally before the report is issued)

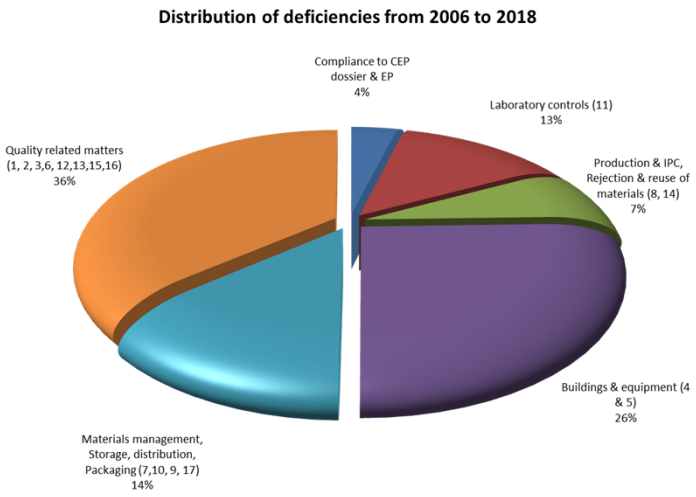
- Companies are subject to re-inspection programme

Possible outcomes

- Positive outcome:
  - An inspection attestation is delivered by EDQM, stating compliance with the CEP and with GMP
  - An EU GMP Certificate is issued by the EU/EEA participating Inspectorate in the EUDRA GMDP database (http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do)
- Negative outcome:
  - In case of critical/major deficiencies to GMP and/or the CEP dossier
  - Actions taken on the CEPs held by the company (suspension/cancellation, etc)
  - An EU Non-Compliance Statement is issued by the EU/EEA participating Inspectorate in the EUDRA GMDP database

Frequent GMP deficiencies

Quality related matters: Quality management, Personnel, Documentation, Validation, Change control, Complaints and recalls, Contract manufacturers



Getting information from inspectorates

- Different sources of information:
  - GMP certificates from EU/EEA/MRA authorities
  - Statement of GMP non-compliance issued by EU/EEA inspectorates
  - Inspection reports obtained from international partners
  - Desktop GMP assessment in the frame of the re-inspection programme

An important activity to ensure/increase supervision of manufacturing sites without duplicating work!

Non-compliance with the CEP procedure

when things go wrong…

Non-compliance with the CEP procedure

- ….. may be linked to:
  - GMP non-compliance, following inspection carried out by EDQM or by an EU inspectorate
  - Refusal to accept an EDQM inspection (after a notification of inspection is sent)
  - Failure to update the CEP application in line with a revised Ph. Eur. Monograph or a regulatory change
  - Major quality problem (e.g. nitrosamines in sartans)

➔ Need to consider risk for public health and actions to be taken on CEPs and CEP applications

Actions and decisions

- Possible actions to be taken:
  - Suspension of CEP
  - Withdrawal (cancellation) of CEP
  - Rejection of on-going new applications
  - Manufacturer removed from list of approved sites in an application
  - May affect one single CEP or all the CEP applications of a site

Suspension of CEPs

- CEPs are suspended for a period of 2 years
- Company is requested to bring corrective actions within this timeframe (they may ask for an extension if justified)
- Lifting the suspension can only be done if the conditions are met (e.g. re-inspection demonstrating GMP and CEP compliance as well as full implementation of the CAPA)

Suspension or withdrawal ?

- **Suspension**: A temporary cancellation
  - CEP may be restored
- **Withdrawal**: A definitive cancellation, decided:
  - When no corrective actions are deemed possible
  - For extensive cases of falsification of data
  - After repeated GMP non-compliance

  If the company is still interested in having a CEP➔ new dossier to be submitted (in addition EDQM checks that corrective actions have been made – e.g. re-inspection of the site)

Actions and decisions

- Decision making process at EDQM:
  - Discussion of the issue and impact within the Certification Department
  - Decision by the EDQM AdHoc Committee
  - Holder/manufacturer notified of the decision (possibility of hearing within 14 days from notification)
  - Implementation of decision
- Information to stakeholders:
  - Information about suspension/withdrawal published on the EDQM website (CEP database and Certification webpages)
  - Information via letter to Ph. Eur. Member States & International Partners, as well as local inspectorate in case of GMP issue

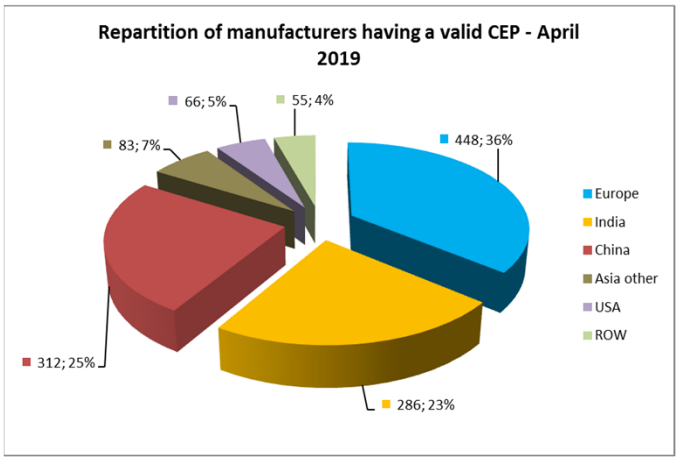
Key figures

Key figures

- More than 7000 CEP applications received for 850 different substances
  - About 300 new applications every year (mostly for chemical purity)
  - About 1800 requests for revision every year
- More than 95% of applications treated within official deadlines ➔ performance published on a monthly basis
- More than 5000 valid CEPs
- More than 1200 manufacturers from 50 different countries

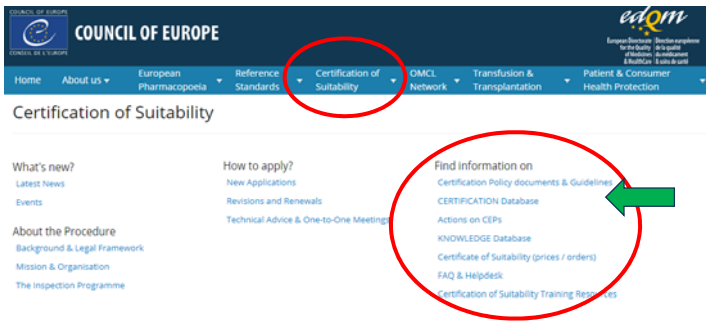
- About 70 sites/year covered by the EDQM inspection programme (50% inspections, 50% exchange of information)
- To date, GMP compliance checked for about 50% of sites located outside Europe

Repartition of API manufacturers



Keep up-to-date with CEP activities

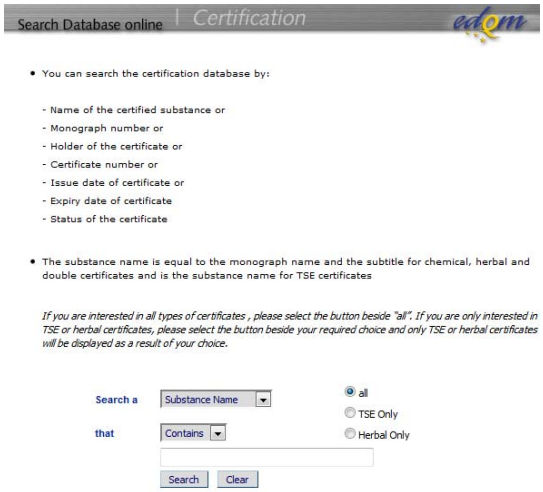
- EDQM Website (www.edqm.eu) – Certification of Suitability



- Several pages dealing with :
  - Procedure, news, etc.
  - **A page with actions on CEPs**
  - A page with the list of Certification Policy documents and Guidelines

Is a CEP valid…

Possibility to check on the « Certification database » on the EDQM website



Is a CEP valid…

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
721	Ibuprofen	Doctors Organic Chemicals Ltd IN 534 215 Tanuku (Po)	R0-CEP 2003-244-Rev 00	19/05/2005	EXPIRED	19/05/2010	Chemistry
721	Ibuprofen	PIRAMAL ENTERPRISES LIMITED IN 500 063 Hyderabad	R1-CEP 1998-012-Rev 08	24/05/2017	VALID		Chemistry
721	Ibuprofen	DR. REDDY'S LABORATORIES LIMITED IN 500 016 Hyderabad	R1-CEP 1997-082-Rev 01	17/07/2008	WITHDRAWN BY HOLDER	10/08/2011	Chemistry
721	Ibuprofen	SHANDONG XINHUA PHARMACEUTICAL CO., LTD. CN 255 086 Zibo	R1-CEP 2004-023-Rev 04	24/08/2015	VALID		Chemistry
721	Ibuprofen	IOL CHEMICALS AND PHARMACEUTICALS LTD IN 141 003 Ludhiana	R1-CEP 2008-316-Rev 00	01/10/2015	VALID		Chemistry
721	Ibuprofen	ARCH PHARMALABS LIMITED IN 400 072 Mumbai	R1-CEP 2000-114-Rev 03	15/04/2014	VALID		Chemistry
721	Ibuprofen	BASF Corporation US 78343 Bishop	R1-CEP 2000-087-Rev 02	04/08/2011	VALID		Chemistry
721	Ibuprofen	SI GROUP, INC. US 12301 Schenectady	R1-CEP 1996-058-Rev 05	02/10/2014	VALID		Chemistry
721	Ibuprofen "S250"; "S380"; "S500"; "SN"; "SHD"	STRIDES SHASUN LIMITED IN 600 032 Chennai	R1-CEP 1996-061-Rev 11	17/03/2016	VALID		Chemistry
721	Ibuprofen	HUBEI BIOCAUSE HEILEN PHARMACEUTICAL CO., LTD. CN 448 000 Jingmen City	R1-CEP 2002-099-Rev 03	01/12/2016	VALID		Chemistry

CEPs & international collaboration worldwide

Use of CEPs worldwide

- An increasing number of health authorities worldwide have decided to accept CEPs
  - e.g. Australia, Canada, Morocco, Singapore, South Africa, TFDA, WHO etc.
  - CEP often accepted with additional documents. National requirements apply, a number of countries have published guidance on how to use CEPs
- Signature of confidentiality agreements/MOUs, to share confidential information, including assessment reports and inspection reports
  - Regular information on non-compliances with CEP procedure (GMP non-compliance, quality issues etc.)
  - Sending assessment reports or inspection reports upon request
    - For assessment reports, prior agreement of CEP holder is needed
  - Sharing information in case of quality issues (e.g. nitrosamines)

Conclusion

- The CEP procedure, as a platform for assessment and GMP inspections, is a powerful and helpful tool
- CEPs should be used in an informed way:
  - A chemical or a herbal CEP **certifies** that the quality of the substance is suitably controlled by the Ph. Eur. monograph with addition of tests, if necessary (mentioned on the CEP)
  - A TSE CEP **certifies** that the substance complies with the Ph. Eur. General Monograph on Products with TSE risk only
  - A CEP **does not** replace testing and is not a certificate of analysis
  - A CEP **is not** a GMP certificate
  - A CEP **is not** a "carte blanche"
- Communication between the CEP holder and the drug product manufacturer is key!

More info on CEP activities:

www.edqm.eu

Thank you for your attention

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Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**