Submission of data: ASMF or CEP?

ASMF: GMP perspective and regulatory compliance

from starting materials to API

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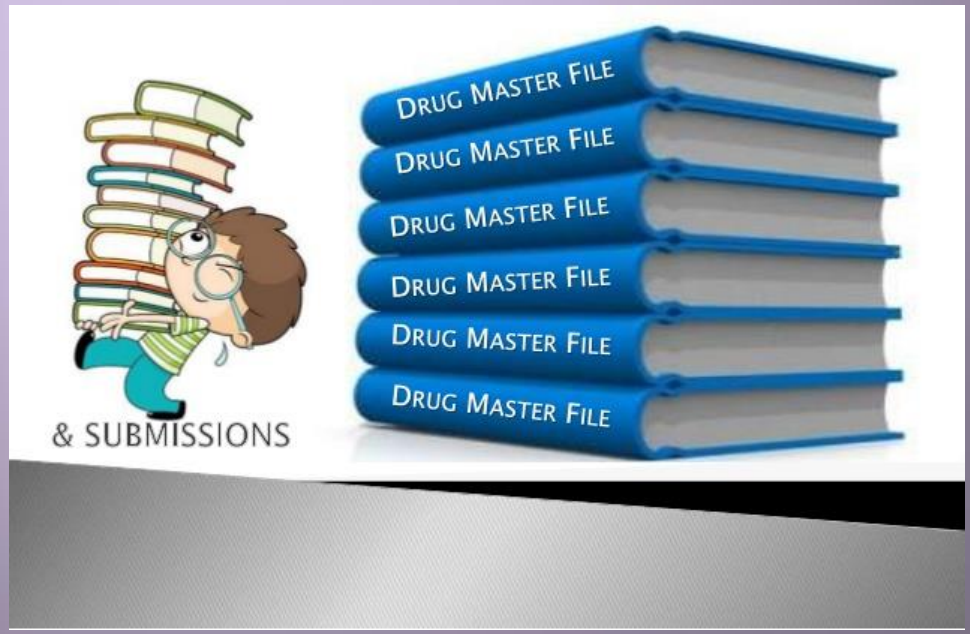
Drug Master File

Confidential intellectual property or «know-how» of the manufacturer of the active substance allowing the Applicant or Marketing Authorization Holder to take full responsibility for the medicinal product and the quality and quality control of the active substance



Back-ground

Thus National Competent Authorities /EMA have access to the complete information as necessary for an evaluation of the suitability to the intended use of the active substance in the medicinal product.

CEP (Certificate of Suitability to European Pharmacopoeia)

- Evaluation of the suitability of the monograph for the control of the chemical and microbiological quality of the substance
- Evaluation of the minimization of the TSE/BSE risk
- Evaluation of the suitability of the monograph for the control of herbal drugs and herbal drug preparations

ASMF (Active Substance Master File)

- New active substances
- Existing active substances not included in the European Pharmacopoeia (Ph.Eur.) or the pharmacopoeia of an EU Member State
- ASMF procedure cannot be used for biological active substance

Authority competent for the assessment

CEP

- European Directorate for the Quality of Medicines

ASMF

- European Medicines Agencies

Review

CEP

- Certification of Substances Department (DCEP)

ASMF

- National Competent Authority

Review procedures include:

Centralized Procedure

- Acceptance in all 27 EU member states
- Single application to place the product on the market throughout the European Union
- Scientific assessment done by EMA
- Authorisation granted by the European Commission, after consulting a committee of Member States
- Marketing authorisation, valid in all Member States
- Product name identical in all Member States
- Authorization managed by EMA/Commission

Active substances eligible for Centralized Procedure

Mandatory

- Biotech
- AIDS
- Diabetes
- Cancer
- Orphan
- Neurodegenerative

Optional

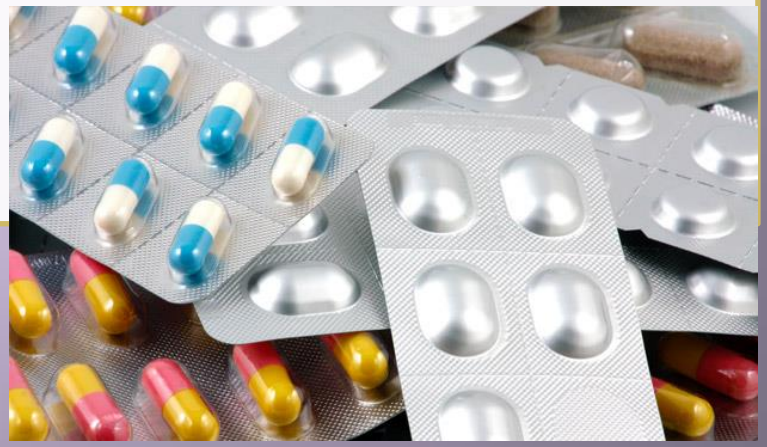
- Significant therapeutic, scientific or technical innovation

Decentralized Procedure

- No pre-existing marketing authorisation granted by one Member State
- Simultaneous application to a RMS (Reference Member State) and several CMS (Concerned Member State)
- Assessment by RMS and reactions by the CMS.

Mutual Recognition Procedure

- Starts from an already existing national marketing authorisation granted by one Member State – the Reference Member State (RMS)
- One or more Member States – the Concerned Member States (CMS) – are asked to recognize the authorization granted by the Reference Member State.



Submission

CEP

- Since June 2016 paper format has become obsolete and all submissions must be done electronically
- E-CTD format according with M4Q Quality and EDQM guidelines for electronic submission
- NeeS
- PDF: files bookmarked according to the relevant subsections

ASMF

- To be submitted in two separated parts, the Applicant part and the restricted part
- eCTD

ASMF Process

REQUEST OF MA APPLICATION

REQUEST OF ASMF REF. NUMBER

SUBMIT NO MORE THAN 2 WEEKS BEFORE THE INTENDED ASMF SUBMISSION

WITHIN 10 DAYS THE ASMF REF. NUMBER IS ISSUED

SUBMIT ASMF FORM, LOA AND COMPLETE ASMF TO AUTHORITIES

References

GUIDELINE ON SUMMARY OF REQUIREMENTS FOR ACTIVE SUBSTANCES IN THE QUALITY PART OF THE DOSSIER

EMEA CHMP/QWP/297/97rev.1 corr

CEP PROCEDURE (1)

- The active substance manufacturer submit the documentation to the European Pharmacopoeia Secretariat for the assessment of the suitability of the pharmacopoeial monograph in relation to the manufacturing method actually applied.
- The Applicant includes a copy of the CEP in the dossier together with a written assurance that no significant changes in the manufacturing method have taken place following the granting of the certificate or its latest revision

CEP PROCEDURE (2)

- With the CEP the Applicant supplies results of batch analysis demonstrating the compliance with the EP monograph and including any additional tests/limits included in the CEP (e.g. residual solvents, addtional testing for related impurities)

- The Applicant must provide additional data as stability studies to justify the retest period (if retest period is not in the CEP) or additional physico-chemical characteristics like particle size or polymorphism

ASMF PROCEDURE

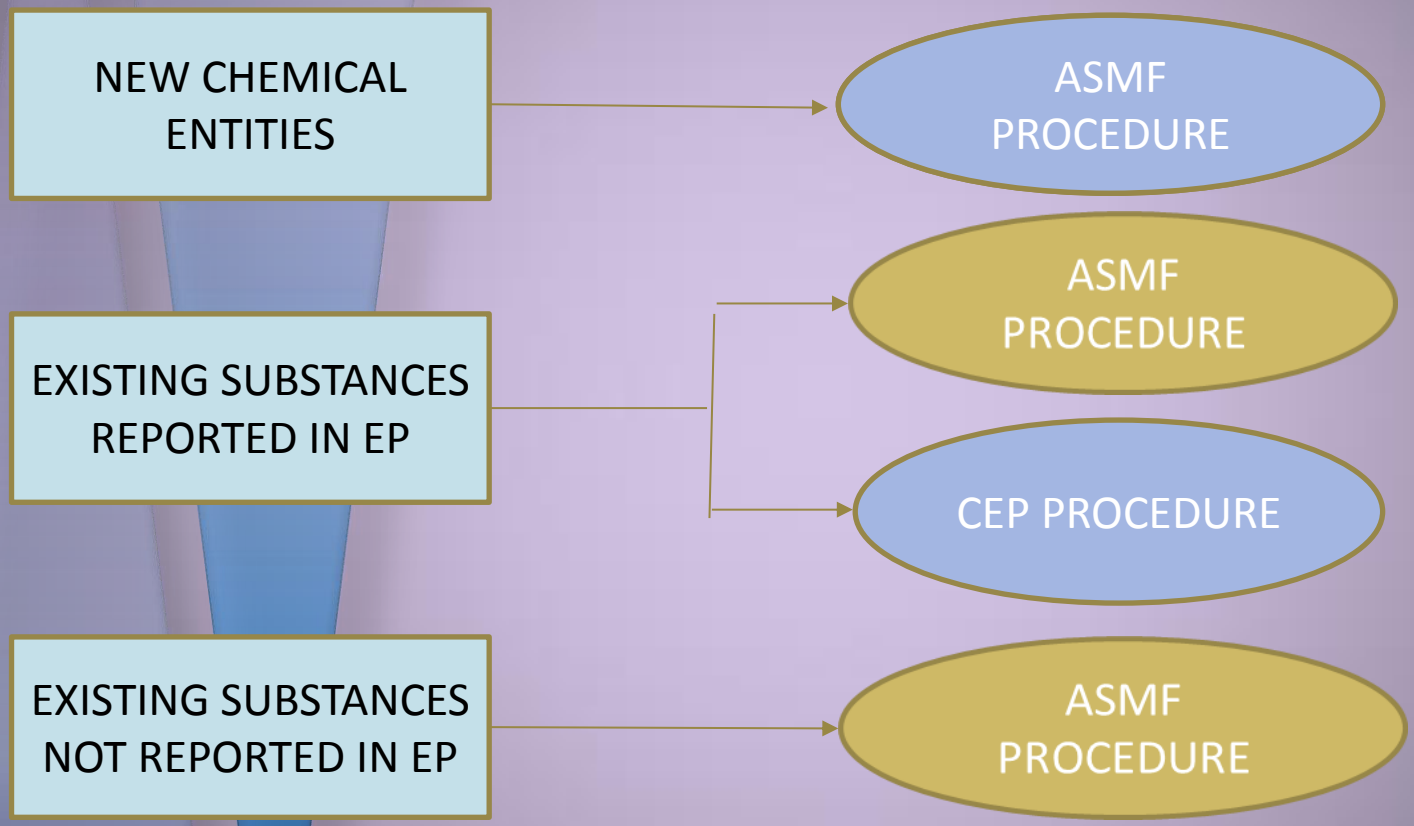
- Full details of chemistry, manufacturing process, quality controls during manufacture and process validation are submitted in the form of the ASMF as outlined in the guideline Active Master File Procedure (EMEA CPMP/QWP/227/02)
- The Applicant part needs to be included in the marketing authorization (MA) application
- The Applicant supplies other supportive data obtained from the active substance manufacturer

New chemical substances

Existing substances included in EP phrmacopoeia

Existing substances not included in any pharmacopoeia

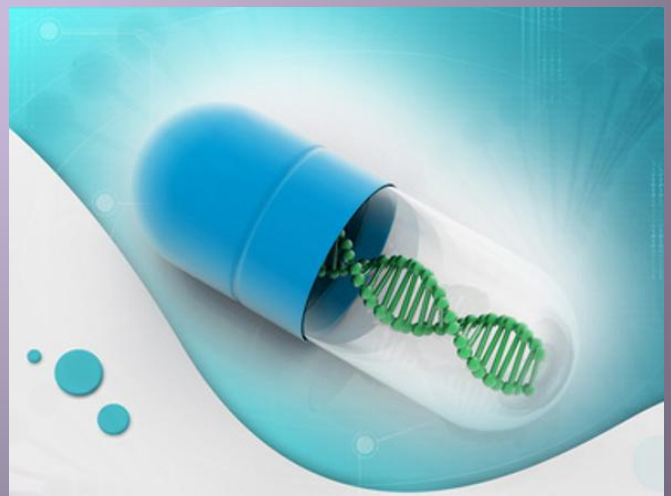
Summarising



Precisazioni relativamente ai medicinali biologici: CEP, ASMF e Modulo 3

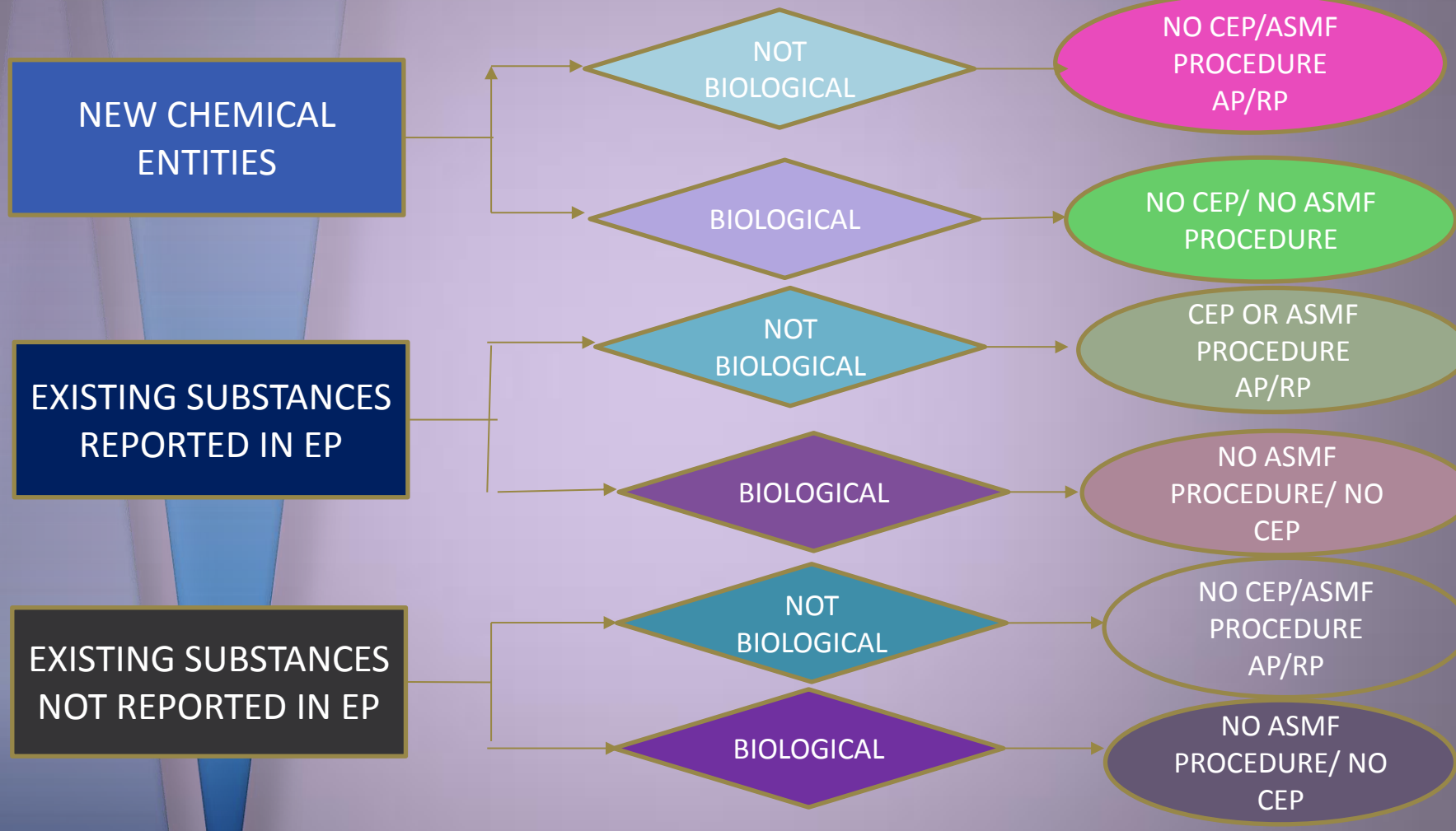
Il CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human), nelle sedute di novembre 2009 e novembre 2010, ha deliberato alcune raccomandazioni riguardo l'uso di CEP (Certificate of Suitability European Pharmacopoeia) e ASMF (Active Substance Master File) nell'ambito del Modulo 3 di dossier di medicinali contenenti principi attivi biologici di origine non ricombinante. In tale contesto, è stata definita una lista di prodotti biologici, che non deve essere considerata esaustiva, ma può essere ampliata anche per analogia con altri principi attivi.

- In seguito alla decisione dell'EDQM del 22.10.2009 di escludere tali prodotti dalla Procedura di Certificazione, è stato stabilito che, in merito ai CEP già esistenti, i richiedenti devono presentare i dati completi nel Modulo 3 per le nuove domande di AIC per i medicinali contenenti tali sostanze biologiche. I CEP esistenti per queste sostanze possono essere inclusi nei relativi dossier, ma non possono essere usati in sostituzione dei dati pertinenti nelle sezioni corrispondenti del Modulo 3.



- Tale impostazione è basata sulla considerazione generale che per i prodotti biologici la caratterizzazione e la determinazione della qualità di questi prodotti richiede, non solo una serie di controlli finali chimico-fisici e biologici, ma anche una conoscenza approfondita da parte del titolare di AIC del processo di produzione e dei relativi controlli iniziali e in corso di processo.
- Pertanto, la procedura di deposito di ASMF (Active Substance Master File) non trova applicazione per i medicinali di origine biologica (si veda quanto riportato sul sito web CMDh), come chiaramente definito anche nella relativa linea-guida EMEA/CVMP/134/02 Rev 1 - CPMP/QWP/227/02 Rev 1.

Summarising



AMENDMENT/POST APPROVAL SUBMISSION OF CEP

- It is valid five years from the date when the original certificate was granted
- Regarless of any revision treated in the meantime, its renewal must be asked for at least six months before its expiry
- Revisions can be done, classified as:

  a) annual notification

  b) immediate notification

  c) major notification

  d) minor notification

AMENDMENT/POST APPROVAL SUBMISSION OF ASMF

- ASMF holders shall not modify the contents of their ASMF (e.g. manufacturing process or specifications) without informing each Applicant/MA Holder and each competent Authority. This obligation remains valid until the LoA has been withdrawn by the ASMF holder
- Any change to the ASMF should be reported by every MA holder to the Competent Authority by means an appropriate variation procedure

Acceptability

- CEPS are accepted by the signatory parties of the Convention on the Elaboration of the European Pharmacopoeia, i.e. all the member States of the European Union. Other countries accept CEP, e.g. Canada, Australia, New Zealand.....

- ASMF: accepted across all the EU members depending on the route of application

GRAZIE PER L'ATTENZIONE