EU-Kommission: Q&A „Regulatory expectations for medicinal products for human use during the COVID-19 pandemic“

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Q&A – Expectations during COVID-19 pandemic

- Revision 3 / 01 July 2020

https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf

- Kooperation von EC, CMDh, IWG, EMA
- Introduction
  - COVID-19 pandemic: considerable impact and unprecedented challenges
  - Operation under business continuity mode
  - Public health may require quick actions or re-prioritisation of operations
  - Appropriate measures to minimise risks of shortages while ensuring high standards are maintained
  - Guidance to MAHs
  - Queries not specifically addressed in this Q&A: MAH invited to address EMA or national CA
  - Ultimate responsibility for interpretation of EU legislation: European Court of Justice

Q&A – Expectations during COVID-19 pandemic

- Issues related to Marketing Authorisations, Marketing Authorisation Procedures:
  - Products intended for use in COVID-19 patients: marketing in absence of a MA?
    - Identify such communication with „CONCERNS COVID-19“
  - Postpone renewal application?
    - Contact EMA of national CA before the foreseen deadline for submission of renewal application with justified request to postpone
  - Sunset clause
    - Request exemption in view of exceptional circumstances

Q&A – Expectations during COVID-19 pandemic

- Manufacturing, importation of finished products and API and GMP and GDP issues:
  - Exceptional Change Management Process (ECMP) für kritische Arzneimittel für COVID-19 Patienten
    - NUR für „crucial medicines for use in COVID-19 patients“
    - NUR für „changes required to address supply chain/manufacturing challenges resulting from pandemic … ensure continuity of supplies“
    - ECMP can cease to be valid in case one or more of the commitments are not fulfilled
  - GMP-Certificate:
    - Site located in EEA:
      - Validity extended until end of 2021 (no action from holder); auch für befristete Zertifikate!
      - Achtung: Gilt nicht für Änderungen im Scope des GMP-Zertifikates (z.B. neues Produkt)
      - Für neue Betriebsstätten (noch nie inspiziert): „distant assessment“ möglich, Inspektion vor Ort sobald wieder möglich (Clock Stop bei negativem Ausgang des „distant assessment“)
    - Sites located outside EEA:
      - Validity extended until end of 2021 (no action from holder), unless authorities take any action affecting validity of the certificate
      - Achtung: Gilt nicht für Änderungen im Scope des GMP-Zertifikates (z.B. neues Produkt)
      - New sites in third countries, where there is no MRA (or scope not covered by MRA):“distant assessment“ möglich, Inspektion vor Ort sobald wieder möglich (Clock Stop bei negativem Ausgang)

Q&A – Expectations during COVID-19 pandemic

- Manufacturing, importation of finished products and API and GMP and GDP issues:
  - Inspections of plasma collection centers:
    - EEA or third country sites that have been previously inspected:
      - Supervisory authority will issue SONI (statement of next inspection)
    - EEA or third country sites that have not been previously inspected:
      - If parent company operates already centers under a PMF: distant assessment for individual centers
      - If distant assessment does not permit approval: clock-stop until on-site inspection
      - If parent company has never been inspected: on-site inspection required
  - GDP-Certificate:
    - Validity extended until end of 2021 (no action from holder); auch für befristete Zertifikate!
    - Achtung: Gilt nicht für Änderungen im Scope des Zertifikates!

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- Remote Batch Certification:
  - Erlaubt nach EU GMP, vorausgesetzt die QP hat Zugang zu allen erforderlichen Informationen
- Remote Audits der API-Herstellung:
  - „Paper-based audits“ und Inspektionen durch EEA-Behörden dürfen verwendet werden
  - Erwartung, dass die QP die erforderlichen Kontrollen und Rechtfertigung in einem produktspezifischen Risk-Assessment dokumentiert
- Batch Release of IMP imported from third countries:
  - „QP may rely on documents, where on-site inspections are not possible“
    - Batch records, including inprocess test reports and release reports
    - Validation status of facilities, processes and methods
    - Examination of finished packs
    - Results of any analyses or tests performed after importation
    - Stability reports
    - Source and verification of conditions of storage and shipment
    - Audit reports concerning the quality system of the manufacturer
    - Etc.
  - Aber: Verantwortung die Qualität der einzelnen Charge gemäß CTA und PSF und Herstellung gemäß einem Standard „at least equivalent“ zu EU-GMP **bleibt bei der QP unverändert**!

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- Quality Variations:
  - Can Quality Requirements be waived/adapted for medicines for COVID-19 patients?
    - Quality Requirements in MA should be complied with!
    - Jede Abweichung davon: „Contact competent authorities“ as a variation! („CONCERNS COVID-19“)
- Pharmacovigilance, Adverse Reactions Reporting:
  - Falls aufgrund der Pandemie nicht anders möglich:
    - Vorübergehend Priorisierung der Meldungen möglich
    - Aber: Serious ICSRs (Individual Case Safety Reports) within 15 days!
    - Meldungen aus „Compassionate use or named patient“ unverändert erforderlich!
    - Wenn Priorisierung genutzt werden soll: „put a note in the Pharmacovigilance System Master File“
    - Justified reasons to prioritise activities for CAPA during the pandemic should be duly recorded
    - Flexibility for Pharmacovigilance System Audits: risk based approach, decision clearly justified and duly documented -> remote audits may need to be considered
- Product Information and Labelling:
  - Flexibilität bei Verpackung möglich
  - During the COVID-19 pandemic … crucial medicines for use in COVID-19 patients
  - Notify relevant national competent authority in advance (link to a website where product information in relevant official lanugage may be obtained)
  - Further guidance will be developed by CMDh

Q&A – Expectations during COVID-19 pandemic

- Additional Temporary GMP and GDP Flexibility:
  - National legislation and derogations cannot be superseded
  - **New lines or re-purposed facilities** to ensure continuous availability of **crucial medicines for COVID-19** treatment:
    - Limited prospective qualification may be possible
    - Application of Quality Risk Management
    - Risk Mitigation measures
    - All decisions documented within PQS and approved by authorised personnel, **including the QP**
    - Regular qualification tasks resumed as soon as COVID-19 restrictions are lifted
    - Results of limited qualification reviewed against expectations of routine qualification
    - Perform concurrent validation of manufacturing process (**approved by the QP**)
    - Sufficient data to support conclusion that any given batch is uniform and meets defined acceptance criteria
    - Processes that assure sterility must be prospectively validated (terminally sterilised product, aseptic processing and aseptic process simulations)
    - Full compliance with details as approved under the Marketing Authorisation

Q&A – Expectations during COVID-19 pandemic

- Additional Temporary GMP and GDP Flexibility:
  - **Temporary Changes** to free resources for continuous supply of **crucial medicines for COVID-19** treatment:
    - Where necessary, provided they do not adversely impact quality, efficacy and safety of any medicinal products
    - Managed transparently (within PQS)
    - Documented according to GMP (Chapter 4)
    - Quality Risk Management should be employed
    - **QP** should be made aware
    - **Changes CANNOT be used** to facilitate certification of batches affected by non-compliance with registered specifications

Q&A – Expectations during COVID-19 pandemic

- Additional Temporary GMP and GDP Flexibility:
  - Temporary flexibility to address imminent shortage of imported medicines, crucial for COVID-19 treatment:
    - Postponing or waiving testing in third country: **QP** may waive, but record this as a deviation
    - Postponing certain testing in EEA: in order to prevent shortage of crucial medicines for COVID-19 treatment, the **QP may give consideration** to certification based on testing performed in a third country
      - Product is crucial treatment of COVID-19 patients
      - All release tests have been performed in third country and results comply with specifications
      - All testing performed in facilities GMP-certified by EEA or MRA partner
      - Review of testing history shows results consistent with EU test results
      - Identitity testing of ALL active substances for each batch carried out in the EEA
      - Biological products: specialist analyses continued to be performed in the EEA before batch certification
      - Decision to certify batches recorded as deviation
      - Any postponed tests should be carried out in the EU after certification (any OOS to be notified immediately to supervisory authority)
      - **Any decision to postpone importation testing in the EEA should be notified in advance to the supervisory authority**

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- Additional Temporary GMP and GDP Flexibility:
  - Adaptations to the work of the RP considering travelling, absenteeism and other restrictions arising from COVID-19 pandemic:
    - Remote working of the RP (timely access to all information necessary)
    - Delegation of duties and responsibilities of the RP (a RP may temporarily take over, with prior approval by the competent authority. Risk Assessment, Job Description)
    - Delegation of duties of the RP to a person who is not a RP (acceptable to delegate duties, but responsibilites remain with the RP)
    - Replacement of RP at short notice (agreement of Competent Authoritiy should be sought, prior notification is necessary)
  - Use new equipment or newly authorised premises for storage and distribution of medicinal product with limited prospective qualification:
    - If necessary to meet demand within timeframe of COVID-19 pandemic
    - Compensated by sufficient ongoing monitoring
    - Employ principles of Quality Risk Management
    - Approach approved by the RP
    - Agreement of Competent Authority should be sought before using new premises for wholesaling activities
    - Full qualification and validation completed without delay

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- Additional Temporary GMP and GDP Flexibility:
  - Introduce planned deviations / temporary changes
    - When documented within quality system, approved by RP and assessed in accordance with Quality Risk Management, temporary flexibility can be introduced as follows:
      - Documentation (extension of routine review of SOPs)
      - Audits (paper-based audits and audits by third parties or inspection results)
      - Internal Audits (schedule can be adapted, however, each situation assessed, documented and authorised on a risk based approach)
      - Non-conformities and CAPA (implementation of CAPA and investigations into minor events can be deferred, following a risk assessment approved by the RP. Activities resumes once pandemic restrictions are lifted)
      - Change management in relation to CAPA implementation can be postponed
      - Training (routine retraining of experienced personnel may be adapted

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Fragen???