Impact of COVID-19 pandemic on Pharma: GMP and Regulatory Flexibility

Part one

Are you aware that a few interesting measures were introduced to ensure the supply chain during COVID-19 pandemic? This enables the MAH to act quickly and provides regulatory relief. Here are a few examples:

- **Fast Implementation of Changes (Variations)**
  - Changes for crucial medicines for treatment of COVID-19 patients can be implemented using an **exceptional change management process (ECMP)**. This means that for these medicines, the MAH may exceptionally use alternative suppliers of starting materials, reagents, intermediates or active substances as well as manufacturing and control sites which are not mentioned in the dossier (MAA) in order to mitigate shortages of supplies in the EU.
  - The MAH informs the Authority **within 48 h after implementation of the change** and commits to submit the **variation within 6 months** after implementation. Please consider that the MAH is responsible to ensure the quality of the API and finished product from these alternative sources.
  - However, for changes of control tests (e.g. due to difficulties to perform all QC-tests as mentioned in the MAA), the MAH should contact the Authorities and present the adapted control scheme (risk-adapted). Then this should be submitted as variation and marked accordingly ("concerns COVID-19") to get prompt assessment.
- **GMP-Certificates and Authorisations**
  - GMP certificates and time-limited manufacturing and import authorisations are **automatically extended until the end of 2021**.
  - For new sites there will be a **distant assessment**, followed by an on-site assessment later.
  - Once COVID-19 restrictions are lifted, there will be again pre-approval and routine inspections (risk-based-approach).
- **QP-Release**
  - **Remote batch certification** (e.g. from home-office) is possible, if the QP has access to all the necessary information.
  - **Remote audits of API-manufacturers** can be done as long as sufficient information is available to ensure quality, efficacy and safety of the drug product.
  - **Batch release of IMPs (Investigational Medicinal Products) from 3rd countries** is possible without on-site inspection after review of the relevant documents.
- **Deadlines for Renewals**
  - If the MAH has difficulties in meeting these deadlines due to COVID-19 pandemic, the MAH can contact the corresponding authority or EMA with a justified request to postpone the submission deadline.

- **Sunset Clause**
  - If you have not placed your product on the market within 3 years after having received the marketing authorisation, the authorisation will cease to be valid. However, now during pandemic, you might request an exemption based on exceptional circumstances and on public health grounds.
- **Product Information and Labelling**
  - To ensure availability of medicines there are regulatory flexibilities, i.e. exemptions in severe cases, such as no translation of product information into the official language of the relevant country or use of different presentations.

There are many more examples. You will find further information here:
https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf

- **Development of vaccines or drugs for treatment of COVID-19:**
  - If you want to speed up your development for these vaccines or drugs, you should consider that there are accelerated procedures in place, such as rapid scientific advice (free of charge), rolling reviews, and accelerated assessment. You might also like to consider the PRIME-scheme, procedures for conditional marketing authorisation and compassionate use programmes. **Further details will be discussed in the next newsletter (COVID-19 - part 2).**

Would you like to know more or do you need specific support for your development, then please feel free to contact us. We know the details and guide you through the process.

Part two

Are you developing drugs for treatment of COVID-19 or vaccines? If you want to speed up your development you should consider that there are faster and flexible regulatory procedures in place, such as rapid scientific advice (free of charge), rolling reviews and accelerated assessment leading to shorter timelines for approval of your drug product. You might also like to consider the PRIME-scheme, procedures for conditional marketing authorisation and compassionate use programmes.

Up to now 125 potential COVID-19 treatments and 33 potential COVID-19 vaccines have been discussed with the EMA. Potential COVID-19 treatments used in clinical trials are *remdesivir* (originally developed for Ebola) as well as marketed products, such as *lopinavir/ritonavir*, *chloroquine* and *hydroxychloroquine*, *interferon beta* and monoclonal antibodies. Many others are under development.

If you are currently developing drugs and vaccines and you want to ensure that these treatments and vaccines are rapidly available for COVID-19 patients, the following new rapid regulatory procedures will help you.

Rapid Scientific Advice

- Instead of the fixed monthly deadlines, there are no pre-specified submission deadlines. The total review time from start to final scientific advice letter is reduced to 20 days (instead of the 40/70 days) or may even be shorter. There is flexibility for the briefing book and the scientific advice is free of charge. If you are not ready for a formal scientific advice, i.e. you are in a very early phase and you have only preliminary development plans, then you can still get feed-back by the EMA and COVID-ETF (COVID-19 EMA pandemic Task Force).

- **Rapid Agreement on PIP (Paediatric Investigation Plan**)
  - There are also no pre-specified submission deadlines. The review is faster and is reduced to min. 20 days (instead of up to 120 days). After the PDCO (Paediatric Committee) opinion, the decision of the EMA is adopted within 2 days (instead of 10 days). Please consider that an early interaction with the Authorities and quick response to questions are essential for a fast process.
  - Furthermore, the PIP in EU and iPSP (initial pediatric study plan) in the US can also be submitted simultaneously as described in the joint document from the EMA and FDA (June 2, 2020).

- **Rolling Review**
  - With this new procedure the applicant can provide data to the EMA on an ongoing basis without waiting for submission until the dossier is completed. The EMA will assess data as they become available with review times of approx. 14 days for each review cycle. This early exchange of questions from the Authority and responses from the applicant is essential to speed up the final evaluation of the dossier later. Once the dossier is complete, the applicant submits the formal MAA which will be reviewed faster. This will reduce the standard timeline of 210 days tremendously. The timeline depends on how much data have already been evaluated during the rolling review. If you want to use this procedure, agreement with the COVID-ETF is needed upfront.

- **Accelerated Assessment**
  - With this procedure the EMA will review MAAs which are of major interest for public health in a shorter time, i.e. within 150 days or even shorter (instead of 210 days). This would be used, if the rolling review is not possible for the applicant. But this also means that the review only starts once the dossier is complete. Therefore, rolling submission would be the preferred option for a fast evaluation.

- **Line Extensions**
  - If marketed products are intended to be authorised for treatment of COVID-19, shorter review times will apply at the EMA. Furthermore, the details as described for new submissions, such as e.g. rapid scientific advice, rolling submissions, rapid agreement on PIP apply. Please start early interaction with the EMA.

- **Compassionate use**
  - If no marketing authorisation is available, development products for treatment of COVID-19 may be used under the compassionate use programme as set up in the individual EU-member states. Please consider that applicants cannot request

the EMA (CHMP) directly for a scientific opinion on the compassionate use programme, but need to contact their national Authorities who can initiate a CHMP-opinion.

- **PRIME Scheme (Priority Medicines Scheme)**
  - For the sake of completeness, the PRIME scheme is mentioned here which should be considered for early phases of development. It is not new and was once developed for medicines with unmet medical need and is based on early dialogue with the Authorities and eligibility for accelerated assessment. However, for COVID-19 treatments or vaccines you can benefit most using the rapid scientific advice and rolling submission procedure as described above.

- **First COVID-19 MAA under Evaluation at EMA (Remdesivir)**
  - As an example, for the use of the rapid procedure you might like to consider the antiviral medicine *remdesivir* including the opinion of the CHMP on compassionate use of *remdesivir* in the EU.
  - The application for conditional authorisation of the first COVID-19 treatment i.e. *remdesivir* is currently being evaluated at the CHMP. The rolling review started on 30 April 2020 with quality and manufacturing data, preliminary data from clinical trials and supportive data from compassionate use programmes. In parallel the PRAC (Pharmacovigilance Risk Assessment Committee) assessed the preliminary risk management plan and the PDCO (Paediatric Committee) evaluated the PIP (paediatric investigation plan). If data are sufficient, the fast-track decision making process will lead to a fast approval of *remdesivir*.

Please feel free to contact us, if you would you like to know more on how to use fast-track procedures or if you need specific support for your development to deliver COVID-19 treatments or vaccines rapidly to patients. We know the details and guide you through the process.

Part three

Do you know how you can speed up your process if you produce drugs or vaccines which may be crucial for COVID-19 patients? GMP and regulatory flexibility was introduced to ensure continuous availability for these drugs. Consider latest details for process validation and changes.

- **Process Validation/Qualification**
  - **Concurrent process validation** instead of prospective process validation is possible for these drugs. Consider GMP Annex 15 and risk management principles (ICH Q9), and document it within the pharmaceutical quality system (PQS). Get signatures from authorised people incl. QP. Ensure that you have sufficient information to guarantee consistent quality. Use qualified equipment and validated methods.
  - However, concurrent validation is not possible for sterile products, including sterilisation processes, aseptic processing and media-fills.

- **Qualification:** Limited prospective qualification is possible under certain conditions for new premises and new lines to ensure availability during increased demands.
- *Further details on process validation will be discussed in the upcoming training course on Process validation in the online Seminar on 25.08.20, see https://www.forum-institut.de/seminar/2008272-prozessvalidierung-anforderungen-an-cmc-daten*

- **Temporary Changes**
  - **Routine Tasks:** Due to resource issues, temporary changes for certain routine quality-related tasks may be introduced to ensure the supply chain, but they need to be appropriately documented including QP-involvement. Examples are maintenance, requalification, revalidation, recalibration, periodic review of documents, audits, trainings and even stability testing. These activities may be delayed, if adequately justified and if no impact on quality, efficacy and safety is expected.
  - **Testing in 3rd countries:** If adequately justified, testing in 3rd countries prior to import may be omitted. This means that the product will be received under quarantine without CoA (deviation) and full testing is done in EU.
  - **Import Testing:** Vice-versa import-testing may be waived to avoid shortages. Reliance is on testing (batch data) in third countries. However, the supervisory authority needs to be informed upfront. Furthermore, a series of conditions need to be met, i.e. shortage of supply has to be confirmed by the authority, testing has to be done in GMP-certified facility (EEA inspected or with MRA), compliance with drug product specs has to be shown, deviation has to be documented, tests have to be done later and reported to the authority, if OOS. Consider that specific requirements will still exist for biologics.
- **Changes/Variations (Exceptional Change Management Process)**
  - Further details were defined for applying the **exceptional change management process (ECMP)**. This can be used for a fast implementation of specific changes for crucial medicines for treatment of COVID-19 patients. The step-wise approach covers 4 steps:
    - **Step 1**: MAH notifies authority about the intent to use the ECMP.
    - **Step 2**: Authority checks request within 2 working days and informs applicant, if the ECMP can be used. If no answer is received the ECMP can be used.
    - **Step 3**: MAH implements change and informs authority within 48 hours.
    - **Step 4**: MAH submits variation within 6 months after implementation.
  - Consider that the ECMP can only be used for products which are crucial for COVID-19 patients and only for certain types of changes, such as alternative suppliers of starting materials, reagents, intermediates or active substances and changes of drug product manufacturing, packaging and control sites.
  - The ECMP cannot be used for changes of specs, manufacturing changes etc. which need to be submitted as variations.
  - Include a statement why the drug product is crucial for use in COVID-19 patients.
  - Use the corresponding templates for your submission of the ECMP. You find them at the EMA and CMDh page.

- Keep your commitments (e.g. same quality, GMP, information of the authority within 48 h after implementation and submission of variation within 6 months of implementation).

Further details on changes will be discussed in the upcoming training course on Project Management in Regulatory Affairs on 10./11.12.20, see http://www.forum-institut.de/seminar/2012233-projektmanagement-in-regulatory-affairs

Please feel free to contact us, if you would you like to know more about GMP and regulatory flexibilities. We know the details and guide you through the process.

Author

Dr. Hiltrud Horn
HORN Pharmaceutical Consulting
Am Alten Schloß 1
D 76646 Bruchsal

Tel.: +49 7251 305 527
Mobile: +49 160 5834 213
e-mail: hiltrud.horn@horn-pharma.de
www.horn-pharma.de