Dear Sir or Madam,

Today we would like to inform you about the following topics:

Best regards

The DiaMed team

1 FINAL HMA ESUBMISSION ROADMAP

In February 2017, the HMA approved revision 2.0 of the eSubmission roadmap.

From the third quarter of 2018 onwards, purely **national marketing authorization applications** should therefore **only be submitted in eCTD format**. For **follow-up procedures** (e.g. variations, renewal applications) of purely national procedures, this is applicable **from the first quarter of 2019** onwards.

This also means that marketing authorisation holders of purely national marketing authorisations have to switch their dossiers to eCTD by the end of 2018 at the latest.

According to eSubmission roadmap version 1.0, the eCTD obligation for **DCP/MRP** will already be **valid from 2018 onwards**.

2 MUTUAL RECOGNITION AGREEMENT (MRA) ON GMP INSPECTIONS OF MEDICINES MANUFACTURERS BETWEEN THE EUROPEAN UNION AND THE USA

The EU and the USA signed an mutual recognition agreement (MRA) on GMP inspections in February 2017, which enters into force on November 1st 2017. With this agreement the regulatory authorities agreed to mutually rely on inspections of manufacturing sites for human medicines so that - unless under exceptional circumstances - there is no need for an EU authority to inspect a site located in the USA. This is also applicable vice versa, provided that the respective EU authority was already assessed by the FDA (see below).

The MRA is based on the collaborative work of the EU commission, FDA and EU authorities since May 2014, demonstrating that both sides have comparable regulatory and procedural requirements for inspections of manufacturers of human medicines.

With entering into force on November 1st 2017, the EU will have completed its assessment of the FDA and the FDA is expected to have completed its assessment of at least eight EU member states. The assessment of further member states will be gradually expanded. For detailed information, please refer to the website of the European Commission's Directorate General for Trade.

3 UPDATE ON THE FALSIFIED MEDICINES DIRECTIVE

With publication of the delegated regulation (EU) 2016/161 on February 9th, 2016 the detailed rules for the safety features appearing on the packaging of medicinal products for human use were announced and implemented into national law. This regulation will come into force on February 9th 2019.

3.1 Technical testing phase of the German national repository

The national verification system in Germany, established by the organization securPharm e.V., is currently performing a technical testing phase: There already are serialized medicinal products that and can be queried in certain pharmacies upon dispensing. If a negative response is received, the package may still be dispensed. This is not possible anymore from February 2019 on. By participating in this testing phase, pharmaceutical companies can check their internal processes and data management, in order to identify possible sources of error.

3.2 Application of the serial numbers

Besides the inline serialization, during which the individual serial numbers are printed on the carton in the packaging line, the serialization of the cartons by the manufacturer of the packaging materials is also an option. With respect to this, it should be kept in mind to design the artwork including the anti-tampering device and the field for serialization so that no information is covered accidentally.

3.3 Release

So far, there is no legal provision whether the release of the finished product by the qualified person (QP) may be performed before or after the upload of the serial numbers. The associations of the pharmaceutical companies have divergent views on this: Some argue that the upload of the data though a legal requirement is not part of the marketing authorization and that therefore a release before the upload is permissible, provided that the release includes a check whether the code is present on the packaging. The serial number could then be uploaded close to distribution or shipping. Others consider the successful upload to be a prerequisite for release, as the legal provisions are only fully complied with after this.

3.4 Provisions in the participating states

Each state participating in the system can decide on national level whether the unique identifier should be applied to other medicinal products than those listed in the directive. Although so far, no national deviations from the directive have been decided, there are participating states who are considering this.

Despite the transitional period of 6 years granted for Belgium, Greece and Italy, as they already have existing systems for the verification of medicinal products and the identification of single packages, Belgium is currently planning to participate in the European system in 2019.

As Germany is so far the only country having developed its own national verification system, registration with the National Medicines Verification Organisation (securPharm e.V.) and upload into the national database is required in addition to the registration with the European Medicines Verification Organisation (EMVO) to access to the German market. In contrast to the German system, the blueprint systems used in other participating states do not require such an additional upload into a national database.

4 IMPLEMENTATION STRATEGY FOR ELEMENTAL IMPURITIES

On March 8, 2017, the EMA published a guideline on the implementation strategy of the ICH Q3D guideline (*Implementation strategy of ICH Q3D guideline*, EMA/CHMP/QWP/115498/2017), which should assist pharmaceutical entrepreneurs for the practical implementation of the requirements of the ICH Q3D guideline.

The new guideline addresses the following aspects:

4.1 Approaches to risk assessment

According to the ICH Q3D, the MAH should develop a control strategy for elemental impurities in his finished product on the basis of a risk assessment. The MAH has the option of carrying out this risk assessment as a product approach or as a component approach or as a mixture of both approaches.

The **drug product approach** is based on the finished product. Therefore, the manufacturer will analyse batches of the finished product for the presence of elemental impurities, perform a risk assessment and define a control strategy. If necessary, the control strategy will include specifications for individual impurities. Analytical data without a risk analysis are regarded as insufficient. If a risk assessment is not possible due to missing information from components or process procedures, all 24 elements in the finished product must be routinely tested. The risk assessment can reduce the scope of the test (number of batches tested).

The **component approach** is the method preferred by EMA. The risk of elemental impurities is examined for individual components, i.e. the active substance, excipients, manufacturing equipment and in packaging materials. The contribution of the respective elemental impurity in each component is summed up and compared in the risk assessment with the PDE value (Permitted Daily Exposure). In particular, excipients from natural "mined" origin should be examined carefully in the risk analysis.

If there is not sufficient information available on individual components and it is difficult to define a specification for elemental impurities in this component, specification limits can be set according to option 1 of ICH Q3D (see appendix 2, table A.2.2 of this guideline). The component can then be used in any proportion in the finished product within the scope of the selected route of administration.

If a Ph. Eur. monograph sets limits for elemental impurities for a specific substance, this substance should comply with this specification. Depending on the risk assessment, the acceptance limits may however also be tighter than the limits described in the monograph.

The test methods for determination of elemental impurities in individual components or in the finished product should be adequately validated for their intended purpose.

The summary of the risk assessment must be included in module 3 and discussed in the Quality Overall Summary in module 2.3.

4.2 Elements intentionally added

Frequently, metal catalysts are used in the synthesis of active substances. The risk for the presence of corresponding elemental impurities is higher the later the catalysts are introduced in the synthesis. The absence of a specification for elemental impurities in the actives substance and/or the finished product must be justified and supported by evidence that the elemental impurities in the finished product are consistently below the control threshold (30 % of the PDE). If limited data can not clearly demonstrate that the values are consistently below the control threshold, a specification limit in compliance with the PDE, as well as a skip testing may be acceptable.

4.3 ASMF and CEP

Although, according to ICH Q3D, the risk assessment is the responsibility of the manufacturer of finished products, EMA advises active substance manufacturers to include a summary of their risk assessment on possible sources of elemental impurities in the ASMF/CEP dossier. In principle, two possible scenarios are presented:

1. Submission of a risk assessment by the manufacturer of the active substance
2. If the manufacturer of the active substance does not submit his own risk assessment, detailed information on the synthesis of active substances, including the catalysts and reagents used, must be must be included in the active substance dossier.

5 MONITORING OF THE PRODUCT INFORMATION OF REFERENCE PRODUCTS

Pharmaceutical companies marketing a generic medicinal product are obliged to check the product information of the reference medicinal product regularly in order to monitor if any relevant changes have been made. If there have been safety-related text changes, e.g. addition of a new possible side effect, these must also be adopted by the marketing authorisation holders of the generic medicinal products in their product information.

In the case of centrally authorized medicines, the EMA sets a period of only 2 months for the submission of a corresponding variation (see question 4.2 of the Questions and Answers on "generic and hybrid applications", EMA homepage). For medicinal products authorized via other procedures, there is no clear guidance on the time frame, however, we would recommend to adapt the time frame for centrally authorized medicinal products as reference point.

Accordingly, the frequency of the review of the reference texts should warrant that this deadline can be met. A monthly review thus appears to be reasonable.

6 NEW RADIATION PROTECTION ACT ADOPTED

In April 2017, the new Radiation Protection Act was adopted. In the future, processing periods for the evaluation process by the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, BfS) will be implemented for clinical trials in Germany. This is an important step in making Germany more attractive again for clinical trials. Due to the unlimited time frame for the evaluation of "applications for the use of radioactive substances or ionizing radiation – including X-ray – in medical research subjected to approval" by the BfS, sometimes taking longer than one year, for many pharmaceutical companies, Germany has not been an attractive study location.

The new Radiation Protection Act, section 5 "medical research" now introduces processing periods. As before, the act distinguishes between the simplified procedure (notification) and the detailed approval procedure.

For the simplified procedure, used for accompanying diagnostic procedures during which the use of radioactive substances or ionizing radiation in itself is not the subject of the research project, the following applies:

The formal validation should be carried out by the authority within 14 days. If the documents are incomplete, the applicant may update them within 10 days. The authority then has another 12 days to review the updated documents.

The subsequent assessment of the content by the authority takes place within 28 days. If necessary, corrections may then be made by the applicant within 21 days, followed by an additional 21 days for the resumed assessment by the authority.

The use of radioactive substances or ionizing radiation within the clinical trial may be started if the time limit for the assessment by the authority has expired, or the time limit will not be fully exhausted as stated by the authority; if the receipt of the approval of an ethics committee has been confirmed and if the use has not been prohibited.

For the application for the detailed approval procedure, the authority's formal validation now is to take up to 21 days, the applicant may correct the notified defects within 21 days.

The authority's decision after assessment then should be made within 90 days. In difficult cases, the deadline may be extended for another 90 days by the authority. The application is deemed valid if the authority has not come to a decision within this time limit.

Process	Notification (simplified procedure)	Approval (detailed procedure)
Formal validation by the authority	**14 days**	**21 days**
Correction of documents by the applicant	10 days	21 days
Resumed validation by the authority	12 days	/
Assessment of content	**28 days**	**90 days (+ 90 days, if required)**
Correction by the applicant	21 days	/
Resumed assessment by the authority	21 days	/
Completion	**Positive response, expired processing period without negative response**	**Positive response, expired processing period without negative response**

The implementation of this new regulation is expected to come into force by the end of 2018.

7 PHARMACOVIGILANCE UPDATE

On May 22nd 2017 the European Medicines Agency (EMA) announced the full functionality of the EudraVigilance database.

This means that the system now fulfils all the functional requirements that have hitherto been subject to a transitional arrangement. For example, this also applies to the reporting of non-serious cases of adverse drug reactions (ADR).

The new EudraVigilance system will be unlocked on **November 22nd 2017**. From this date, the MAH is required to electronically submit all ADR cases (serious ones within 15 days, non-serious ones within 90 days) to the EudraVigilance database (the obligation to notify the national authorities, if still applicable, will cease from that date on). In addition, expanded functions in signal management and data analysis will be available (EudraVigilance Data Analysis System, EVDAS). For the registration, the EMA provides time slots for each company, which you can obtain on the EMA website.