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IMPURITIES IN NEW DRUG SUBSTANCES AND DRUG PRODUCTS AS A PART OF THEIR REGULATION PROCESS

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Astract: Any drug substance or drug product can exist in the market only after its registration process. During the registration, quality of the substance/product should be ensured. For that reason, there is the need for very clear understanding whether any impurities and/or degradation products can be raised during its manufacturing process and/or shelf life. In the case if they can occur, proper analytic procedures should be described and followed in order to understand which impact can have these compounds on the quality, safety and efficacy of the drug substance/product. This work extracts all parts of CTD where information about impurities should be provided align with ICH reference guidelines and main principles, which should be followed. Additionally, there were compared the main characteristics of the registration processes of drug substances and drug products.

Keywords: drug substance, registration process, degradation, safety and efficacy of the drug

Introduction

Control of the impurities in the drug substances and drug products is very important during their manufacturing process. That is why clear information regarding their existence and control should be provided in the dossiers during the registration process.

Clear and understandable sections ensures about the quality of the product. They should include information regarding the names of possible impurities, their acceptable limits and methods of control.

In the drug products it is possible to have degradation products as well, because sometimes ingredients are not stable and can be broken down during the shelf life of the drug product. That is why it is very to ensure the quality of the medicine during its shelf life as well, not only after the manufacturing process. Although sometimes the degradation products can be the result of keeping the drug under the temperature and humidity different that it is suggested. For example, in the general case the drug is suggested to be kept under the conditions 25°C ± 2°C/60% RH ± 5% RH, or 30°C ± 2°C/65% RH ± 5% RH for the countries of Climatic Zones III and IV. But because of some reasons, such as forgetting in the car, taking under the sunlight etc., the actual temperature and humidity are going to be changed, so the quality of the drug can be changed as well.

Degradation products can be raised during the stability studies as well. For example, during the accelerated studies in the general case, when the conditions are 40°C ± 2°C/75%, RH ± 5% RH, there may occur the degradation products. In this case, if the same is not covered during the long-term studies as well, it can be applicable. However, in the case if it is covered, risk and acceptable limits of the degradation product should be evaluated and discussed.

Methods and results

There has been done the research of main guidelines regarding the impurities in order to understand which documentation should be provided during the registration of drug substances and drug products regarding these compounds. For that reason, there were researched [1, 2].

Next step was the research the structure of CTD in order to understand where the information regarding impurities should be included. For that there was researched [3] found in [4].

According to [3], information regarding the impurities of new drug substance is included in M 3.2.S.3.2, which is the part of M 3.2.S.3, as well as in M 2.3.S as a tabulated summary with graphical representation. For new drug products, it should be included in M 3.2.P.5.5, which is a section of M 3.2.P.5, also in 2.3.P.5 as a summary.

Additional data should be provided in the stability sections, as the quality of the drug product and drug substance can be highly impacted during their shelf lives. From /3/ there were extracted the main sections regarding the stability of drug substances and drug products, which are the following:

For the drug substances:

3.2.S.7 section with its subsections as the part of Quality

2.3.S.7 section as the summary,

For the drug products:

3.2.S.8 section with its subsections as the part of Quality

2.3.S.8 section as the summary.

In order to understand which characteristics are common for both drug substances and drug products, these two lists of characteristics have been compared with each other. Results are provided in the table 1.

Table 1. Comparative characteristics of the lists of documentations needed for impurities during the registration processes of drug substances and drug products.

Document name	Relates to the drug substance Yes/No	Relates to the drugproduct Yes/No
Batch identity and size	Yes	Yes
Date of manufacture	Yes	Yes
Site of manufacture	Yes	Yes
Manufacturing process	Yes	Yes
Impurity content, individual and total	Yes	Yes
Use of batches	Yes	Yes
Reference to analytical procedure used	Yes	Yes
Immediate container closure	No	Yes
Batch number of the drug substance used in the new drug product	No	Yes
Storage conditions for stability studies	No	Yes

As it is clear from the table 1, all the documents, which are common for the drug substances, are common for the drug products as well. Moreover, there are additional documents, which are needed only for the registration of drug products, such as immediate container closure, Batch number of the drug substance used in the new drug product and Storage conditions for stability studies [1, 5].

There was extracted the main structure of M 3.2.S.3 for the registration of drug substance, which is provided in the table 2.

Table 2. Main structure of M 3.2.S.3 according to [3]

Section number	**Section name**
3.2.S.3	Characterisation
3.2.S.3.1	Elucidation of Structure and Other Characteristics

3.2.S.3.2	Impurities

For the registration of drug products there was extracted the main structure of M 3.2.P.5, which is provided in the table 3.

Table 3. Main structure of M 3.2.P.5 according to [3]

Section number	Section name
3.2.P.5	Control of Drug Product
3.2.P.5.1	Specification(s)
3.2.P.5.2	Analytical Procedures
3.2.P.5.3	Validation of Analytical Procedures
3.2.P.5.4	Batch Analyses
3.2.P.5.5	Characterisation of Impurities
3.2.P.5.6	Justification of Specifications

For each section there is a need to provide ICH guidelines which should be provided as the reference guidelines, in order to understand where the main priciples can be found. ICH reference guidelines have been extracted from [6]. Results are provided in the table 4.

Table 4. Reference ICH Guidelines for impurities extracted from [6]

CTD section	Reference ICH Guidelines
M 3.2.S.3.2 Impurities	Q3A, Q3C, Q5C, Q6A and Q6B
M 3.2.P.5.5 Characterisation of Impurities	Q3B, Q5C, Q6A and Q6B

As it is clear from the table 4, ICH guidelines Q5C, Q6A and Q6B are common for providing both drug substance and drug product impurities sections.

According to the [6], information regarding impurities should be provided in Stability section as well. For that reason there were extracted stability sections from /3/ and reference ICH guidelines from [6]. Results are provided in the tables -8.

***Table 5. Main structure of the stability section of the new drug substance*.**

Section number	Section name
3.2.S.7	Stability
3.2.S.7.1	Stability Summary and Conclusions
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3	Stability Data

Table 6. Main structure of the stability section of the new drug product.

Section number	Section name
3.2.P.8	Stability
3.2.P.8.1	Stability Summary and Conclusions
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment
3.2.P.8.3	Stability Data

As it is clear from the tables 5 and 6, section names are same, so the main principles of the information provided should be same as well.

Table 7. Reference ICH Guidelines for stability of the drug substances.

CTD section	Reference ICH Guidelines
3.2.S.7.1 Stability Summary and Conclusions	Q1A, Q1B and Q5C
3.2.S.7.2 Post-approval Stability Protocol and Commitment	Q1A and Q5C
3.2.S.7.3 Stability Data	Q1A, Q1B, Q2A, Q2B and Q5C

Table 8. Reference ICH Guidelines for stability of the drug products.

CTD section	Reference ICH Guidelines
3.2.P.8.1 Stability Summary and Conclusions	Q1A, Q1B, Q3B, and Q5C, Q6A
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment	Q1A and Q5C
3.2.P.8.3 Stability Data	Q1A, Q1B, Q2A, Q2B and Q5C

In addition, there were extracted common ICH reference guidelines for the stability sections of drug substances and drug products. Results are provided in the table 9.

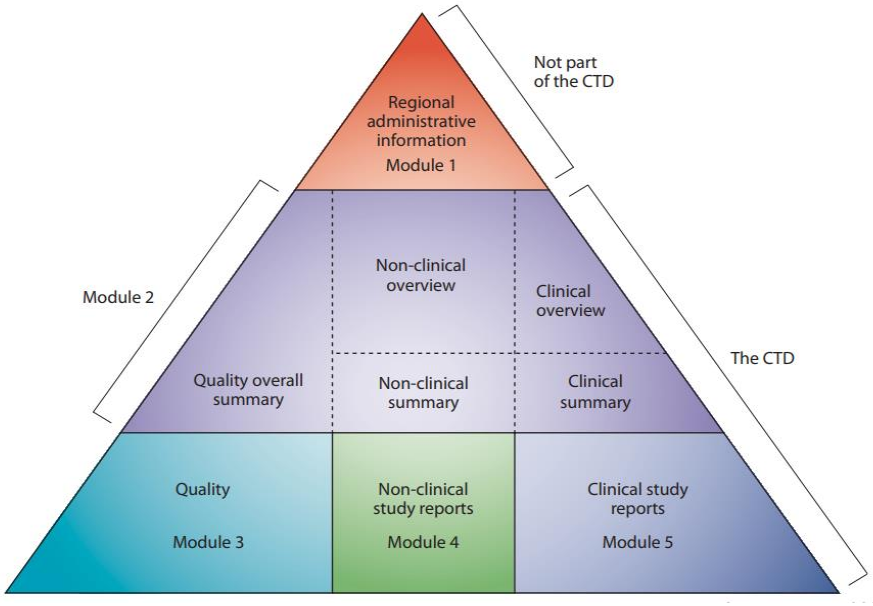
As it is clear from the tables 8 and 9, there are reference guidelines which are common for the same sections of both drug substances and drug products, as well as there are reference guidelines which are specific only for the drug substance/product. Common ICH reference guidelines for the stability sections of drug substances and drug products are provided in the table 9.

Table 9. Common ICH reference guidelines for the stability sections of drug substances and drug products.

Section name	Common ICH reference guidelines
Stability Summary and Conclusions	Q1A, Q1B and Q5C
Post-approval Stability Protocol and Stability Commitment	Q1A and Q5C
Stability Data	Q1A, Q1B, Q2A, Q2B and Q5C

As it is clear from the table 9, ICH reference guidelines for Post-approval Stability Protocol, as well as for Stability Commitment and Stability Data are the same during the registration processes of new drug substances and new drug products. For the section Stability Summary and Conclusions, there are additional Q3B and Q6A reference guidelines for new drug products, which are absent for new drug substances stability.

Overall it is clear from the tables 2-8 that the information regarding the impurities is included in the Module 3, summary about them is included in the Module 2 of CTD (see picture 1).



Picture 1. Structure of CTD.

From [6] there was also extracted that release and stability limits of impurities can differ from each other. For example, release limits can be ≤ 0.04%, end of shelf life limits: ≤ 0.08%.

From this there was tried to provide typical acceptable stability results for impurities for the drug, which shelf life is two years.

In order to understand which data should be provided and which will be acceptable, /7/ was researched. As an example there was chosen a drug which shelf life is two years and which should be kept in the room temperature (general case). According to /7/, three stability results should be provided: long time, intermediate and accelerated. The storage conditions and minimum time period covered by data at submission are provided in the table 10.

Table 10. The storage conditions and minimum time period covered by data at submission for the general case of stability studies.

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	Accelerated	6 months

From [7] there were extracted the time points for each type of stability study (long term, intermediate, accelerated) during which quality checking should be done.

As it was decided to choose the drug which shelf life is two years and as in table 11 twelve months are provided as the minimal time, there was decided to provide stability data of 24 months. 18 and 24 months have been chosen as the next time points according to the /7/, where is provided that for the first year stability data as a time point there will be provided for each third month, for the second year: for each sixth month, for the next years: for each twelfth month. For intermediate

and accelerated stability, there was not any additional data, so it was decided to keep time points as is. Results are provided in the table 11.

Table 11. Time points for each type of stability study during which quality checking should be done.

Type of the stability study	Time points (month)
Long-term	0, 3, 6, 9, 12, 18, 24
Intermediate	0, 3, 6
Accelerated	0, 3, 6

First time point is 0 time, which means immediately after the manufacturing process. As it should be align with release data, for the acceptable amount of impurities there is provided ≤ 0.04%. Starting from the next time points it seems to be as stability time data, so as an acceptable limits were provided ≤ 0.08%.

Acceptable stability results are provided in the tables 12-14.

Table 12. Typical acceptable results of long time stability data for impurities for the drug product, which shelf life is two years.

Characteristic time / months/	0	3	6	9	12	18	24
Impurities	≤ 0.04%	≤ 0.08%	≤ 0.08%	≤ 0.08%	≤ 0.08%	≤ 0.08%	≤ 0.08%

Table 13. Typical acceptable results of intermediate stability data for impurities for the drug product, which shelf life is two years.

Characteristic time / months/	0	3	6	9	12
Impurities	≤ 0.04%	≤ 0.08%	≤ 0.08%	≤ 0.08%	≤ 0.08%

Table 14. Typical acceptable results of accelerated stability data for impurities for the drug product, which shelf life is two years.

Characteristic time	0	3 months	6 months
Impurities	≤ 0.04%	≤ 0.08%	≤ 0.08%

Literature

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Abbreviations

ԸՏՓ – Ընդհանուր Տեխնիկական Փաստաթուղթ
ОТД – Общий Технический Документ
CTD- Common Technical Document
ICH – International Council of Harmonisation
M - Module

Ղազոյան Վ.Մ., Քենավի Էլ Թ.Խ.Մ. - ԿՈՂՄՆԱԿԻ ԽԱՌՆՈՒՐԴՆԵՐԻ ՀՍԿՈՒՄԸ ՆՈՐ ԴԵՂԱՆՅՈՒԹԵՐԻ և ԴԵՂԵՐԻ ԲԱՂԱԴՐՈՒԹՅԱՆ ՄԵՋ ԴՐԱՆՑ ԳՐԱՆՑՄԱՆ ԳՈՐԾԸՆԹԱՑՈՒՄ. Ցանկացած դեղանյութ կարող է ներմուծվել շուկա միայն գրանցումից հետո, որի ընթացքում պետք է ստուգվի նրա որակը: Անհրաժեշտ է պարզել, թե արդյո՞ք դրանց պահպանման ժամկետի ընթացքում կարող են առաջանալ որևէ կողմնակի խառնուրդներ և/կամ քայքայման արգասիքներ: Եթե կարող են առաջանալ, պետք է պարզվի, թե ինչ ազդեցություն կունենան այդ միացությունները դեղանյութի/դեղի որակի, անվտանգության և արդյունավետության վրա:

Աշխատանքում տրված են ԸՏՓ-ի բոլոր այն մասերը, որտեղ պետք է տրամադրվի կողմնակի խառնուրդների մասին տեղեկությունը՝ համահունչ ICH-ի ուղեցույցներին և հիմնական սկզբունքներին: Բացի այդ, համեմատվել են դեղանյութերի և դեղերի գրանցման գործընթացների հիմնական բնութագրերը:

Газоян В.М., Кенави Эль Т.Х.М. - КОНТРОЛЬ ПРИМЕСЕЙ В НОВЫХ СУБСТАНЦИЯХ И ЛЕКАРСТВЕННЫХ ПРЕПАРАТАХ В ПРОЦЕССЕ ИХ РЕГИСТРАЦИИ. Любой препарат может быть выведен на рынок только после регистрации, в ходе которой необходимо проверить его качество. Необходимо определить, могут ли в течение срока годности образовываться какие-либо побочные продукты и/или продукты разложения. Если да, то следует определить, какое влияние эти соединения окажут на качество, безопасность и эффективность лекарственного средства/препарата.

В работе представлены все части ОТК, в которых информация о побочных продуктах должна быть предоставлена в соответствии с рекомендациями и основными принципами ICH. Кроме того, были сопоставлены ключевые характеристики лекарственных субстанций и процессы регистрации лекарственных средств.

Ключевые слова: лекарственный препарат, регистрация, качество