

Normative Documentation in CIS region. Challenges for an EU Marketing Authorization Holder

Masterarbeit

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1. List of Terms and Abbreviations

AND	Analytical-Normative Document (local name of the ND in Kazakhstan and Belarus. Throughout the current master thesis the general abbreviation ND is used)
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
BY	Republic of Belarus, Belarussian language
CIS	Commonwealth of Independent States
CoA	Certificate of Analysis
CoC	Certificate of Conformity
CP	Centralized Procedure
CPP	Certificate of Pharmaceutical Product
DCP	De-Centralized Procedure
DRA	Drug Regulatory Affairs
EAEU	Eurasian Economic Union
EU	European Union
EEA	European Economic Area
GMP	Good Manufacturing Practice
GOST	GOvernmental STandard or (exact translation) State standard
HQ	Headquarters (of a MAH)
IMU	Instruction for Medical Use
KZ	Kazakhstan, Kazakh language
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
MQC	Methods of Quality Control (local name of the ND in Ukraine. Throughout the current master thesis the general abbreviation ND is used)
NCA	National Competent Authority
ND	Normative Document (the term is used in this master thesis for all variants of the

document – i.e. AND – in Belarus and in Kazakhstan, NTD – in Kyrgyzstan [10]; MQC – in Ukraine)

NTD	Normative-Technical Document (local name of the ND in Kyrgyzstan. Throughout the current master thesis the general abbreviation ND is used)
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
QP	Qualified Person
RU	Russian Federation, Russian language
SKU	Stock Keeping Unit
SmPC	Summary of Products Characteristics
SST	System Suitability Test
TJ	Tajikistan, Tajik language
TM	Turkmenistan, Turkmen language
TLC	Thin Layer Chromatography
UA	Ukraine, Ukrainian language
USP	United States Pharmacopeia
UZ	Uzbekistan, Uzbek language

2. Glossary

GOST	– set of regional standard documents defining technical requirements to the specific type of the product or equipment (not only medicinal) and applicable in the countries of the CIS. The name was not changed after the USSR disintegration and therefore still includes part “State” although it is used in several states.
IMU	– product information document in the CIS region consisting of the data from EU or reference SmPC and PIL and is used as a package insert
ND	– local document in the countries of CIS region containing short information on the medicinal product quality parameters, specification, analytical methods that is approved within MAA and is used in the local laboratories for the quality control testing of the product.

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5. Introduction (Issues under examination)

The Commonwealth of Independent States (CIS) region is located in Eastern Europe and Asia and is formed by previous country members of the Soviet Union. Although some of the countries officially left the CIS, the pre-existing historical similarities in the requirements to the medicines provision and Marketing Authorization (MA) of medicinal products in these countries as well as common language and similarities in the culture highlight the potential benefits of the centralized coordination of the regulatory activities in the countries of the region.

The market of the region is considered as emerging and some of the countries, namely Kazakhstan and Russian Federation were ranked in 2019 as high-growth pharmaceutical markets [22]. The Pharmaceutical Market Value in Russian Federation being 16,253 million Euro [22], which makes it the fifth market among evaluated European countries and is following Germany, France, Italy and United Kingdom [22]. The total population of the CIS countries on the 1st of January 2019 was 286 Million people [3] (for comparison – EU population is 446 million inhabitants [4]), 140 Million thereof are located in Russian Federation [29]. These aspects are surely drawing attention of the pharmaceutical companies and make the MAs in the region attractive, even taking into account some challenges caused by specific local requirements. Some Marketing Authorization Holders (MAH) create Centres of Regulatory Excellence or regulatory hubs in one of the countries to coordinate the activities in a group of countries or in a full region. This approach is also encouraged by the language used within the region – most of the countries still speak Russian language either as first or second national language or it is a commonly spread language of communication.

One of the national specific documents that is required for gaining a Marketing Authorization (MA) and for further regulatory life cycle as well as for the supply of the product in some countries of the CIS region is a Normative Documentation (ND) (also named Analytic Normative Documentation (AND), Normative-Technical Documentation (NTD) or Methods of Quality Control (MQC) depending on the country).

This master thesis is describing the role of the ND in the Marketing Authorization Application (MAA) as well as in regulatory life cycle in the countries of CIS region. The challenges for a MAH located in the EU are highlighted among others through comparison of the ND and the corresponding EU dossier modules. The influence of the ND on the combination of Stock Keeping Units (SKUs) is discussed also for the countries of the region that are not requiring the national ND for the MA at the current moment. The requirements for the document, its structure, as well as its impact on the documentation accompanying product's supply are included. The connection with the product's supply shows the interest to the ND also for the quality department of a MAH.

Another rather new development in the region is a formation of the Eurasian Economic Union (EAEU) – a cooperation of five countries from the CIS. It consists of four countries requiring the ND according to the national legislation (Russian Federation, Belarus, Kazakhstan and Kyrgyzstan) as well as one country – Armenia, for which the ND is currently not required. The influence of the EAEU on the ND requirements is also included to complete the thesis with the latest developments in the region.

Some specific conditions of ND preparation in single countries and in the region overall are described, including the role of a global MAH DRA as well as a local DRA on the strategy and coordination of the ND creation. Moreover the assurance of ND compliance in the countries of the region with the MAH's common dossier is described as well as particulars of current manufacturer's analytical quality control and therefore the ability to continuously release the product throughout its full life cycle ensuring uninterrupted supply.

6. Materials and methods

The thesis is based on a personal experience as well as (mostly Internet-) research and analysis of the currently available legislation and databases related to the requirements in the countries of the CIS region to cover the topic under evaluation. As I am a native speaker (Russian and Ukrainian) the overall translation of the documents not available in English has been done directly by own knowledge using for specific terms internet resources.

7. CIS region: general information

7.1. Countries, languages, formation of EAEU region

The history of the formation of the CIS falls back onto the 8th December 1991, when an agreement of formation of CIS between Republic Belarus, Russian Federation and Ukraine was signed. Two weeks afterwards in Almaty Kazakhstan, eleven countries signed a protocol according to this agreement confirming the formation of the CIS on equal footing. The eleven countries were: Azerbaijan, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, Tajikistan, Turkmenistan, Uzbekistan and Ukraine. Georgia entered the agreement in December 1993 [1]. The aim of the agreement was a development of international cooperation between countries in the political, economic, cultural and other fields.

Due to further conflicts between some countries of the region, Georgia announced leaving the membership in August 2008 [1] and Ukraine ceased to participate in the CIS sittings from 2014. Nevertheless the countries are still often included into the development strategy for the CIS region by pharmaceutical companies.

Figure 1: CIS region location



Figure 2: Emblem of CIS



Source: https://en.wikipedia.org/wiki/Commonwealth_of_Independent_States (08.11.2020)

Although all of the countries have a national language, most of the population can still speak or at least understand Russian language in a daily business and some of the countries use it

as an official language (see **Table 1**). This situation provides an opportunity for the companies, including pharmaceutical companies, to optimize the coordination of the local activities and to reduce the required resources at Headquarters (HQ) by grouping the responsibility for the region and delegating it to e.g. one representative office or one consultancy company depending on the MAH structure and strategy. This way the responsible persons at HQ will have only one or just a few contact points for the region instead of the separate contact points for every single country.

Table 1: National languages / languages spoken in the CIS region [39]:

Country	Official national language(s)	Comments / other widely spread languages
Azerbaijan	Azerbaijani	The most widely spoken minority languages are Russian and Armenian.
Armenia	Armenian	Russian is widely spoken as a first foreign language.
Belarus	Russian and Belarusian	Russian is still more popular within the population.
Georgia	Georgian	Russian language is still spoken in the country by emigrants and older Georgian generation. Currently English is supported by government as an important foreign language and it replaces Russian as the first foreign language among the younger population.
Kazakhstan	Russian and Kazakh	Multinational country
Kyrgyzstan	Russian and Kyrgyz	
Moldova	Romanian	Romanian and Moldovan refer to the same language. Russian is widely spoken as a language of communication.
Russian Federation	Russian	

Tajikistan	Tajik	Russian is the second most spoken language.
Turkmenistan	Turkmen	Russian is the second most spoken language.
Ukraine	Ukrainian	Russian is the second most spoken language.
Uzbekistan	Uzbek	Russian is the second most spoken language.

While CIS formation collected countries with similar history and local requirements, it did not have a significant impact on the regulatory activities for MA of medical products, comparing to the EU / EEA with DCP, MRP and CP Marketing Authorization procedures. However the current development of the Eurasian Economic Union (EAEU) [2] has a direct influence of the MA procedures in the region and foresees the MRP and DCP procedures as well. The EAEU member states must follow the EAEU MAA requirements starting from 01.01.2021 [44].

The EAEU was formed by five countries: Russian Federation, Kazakhstan, Belarus, Kyrgyzstan and Armenia, and acts starting 01.01.2016 based on the Customs Union Agreement from 2007 [9].

Figure 3: Countries of the EAEU



Source: <http://www.eaeunion.org/?lang=en#about-countries> (04.12.2020)

7.2. Description of the main regulatory requirements for medicinal product's MAA and regulatory life cycle in the region

The general requirements for the regulatory procedures in CIS countries vary depending on the country, based on the national legislation and capacities of the National Competent Authorities (NCA). Due to the different sizes of the countries in the CIS region, the size and staffing of NCAs also varies. Therefore, some (smaller) countries (e.g. Armenia, Georgia) tend to have a possibility of the recognition of the MA of country of origin if it is located in a country with developed regulatory framework, e.g. EU, USA. Countries with more capacities tend to have a comprehensive regulatory review of the full MA dossier (the structure of CTD and eCTD is however still not fully implemented in all of the countries of the region) and also add specific national requirements, e.g. results of local clinical studies in Russian Federation [28].

The important points to consider for MAA and regulatory life cycle planning for CIS countries include but are not limited to:

Local clinical trials

For drug product MAA and new formulation registration in Russian Federation local clinical studies are generally required [28, 29]. This should be considered during early stages of the product development in order to include Russian Federation in the international multicentre clinical trials that will potentially save time and resources in further steps of product registration.

Local GMP certification

A locally issued GMP certificate is required for submission of MAA in Russian Federation, Belarus and Kazakhstan. However if the local inspection of the same manufacturing site and the same production line has already been performed by the corresponding NCA, the previously issued local GMP may be accepted in Belarus and Kazakhstan. Meanwhile in Russian Federation a local GMP certificate is valid for three years only and will have to be renewed. Further information on the influence of the ND on the GMP inspection in Russian Federation is provided under section 11. At the same time in Ukraine only GMP clearance procedure should

be performed for the releasing site (in case of availability of the GMP certificate issued by PIC/S member countries, e.g. EU) since Ukraine is a member of PIC/S (see also section 7.4).

In EAEU a separate GMP certification for the region is foreseen. However at the current moment only Belarus can perform an EAEU GMP inspection with only 34 certificates issued as of 10.12.2020 [13]. Still the EAEU GMP certificates will be required for a MAA procedure in the countries of EAEU region starting from 01.01.2021. This means, that though purely national GMP certificates issued by the EAEU member countries before may still be valid, they cannot be used for the EAEU MAA procedures starting 2021.

Climatic zone and stability data

All the countries of the region are located in the Climatic zone II, therefore the stability data used for the EU would be acceptable. However, most of the countries of the region require full shelf life stability data for the MAA as well as during further regulatory life cycle, which needs to be considered during submission planning.

Reference to EU

As a part of ongoing EU integration Ukraine has adopted most of regulatory requirements of the EU, although their interpretation still differs from the EU to some extent. Generally, the EU requirements and documentation for any given procedure will suffice for the same procedure in Ukraine, considering a couple of local specifics – MQC, Instruction for Medical Use (IMU) as well as a Certificate for Pharmaceutical Product (CPP). For variation procedures in Ukraine an approval of the procedure from the EU or other reference registration is required.

Moldova, sharing the same language as Romania – an EU member state, and being its neighbouring country is also undergoing EU integration [41]. That influences the requirements to the medicinal product MA. A ND is not required as a part of the MA dossier in Moldova.

The countries accepting the requirements of Ph. Eur. are listed in the section 7.4.

Certificate of Pharmaceutical Product (CPP)

As for most of the countries outside of EU, USA, Japan and Canada, CIS countries require a CPP for MAA as well as for manufacturer site changes and some other regulatory procedures

(e.g. renewals, line extensions). Therefore the timelines of possible submission should take into consideration the necessity of approval of the change in EU or reference country at first and further period of preparation and issuing of the CPP by a Competent Authority in the reference country.

Local submission and fees

Submission of a regulatory dossier is done in paper and partly electronically (e.g. on a CD). The official electronic submission through a portal is under development in some countries as well as already partly functioning in others. The administrative documents are compiled in national language and the payment of fees should be made in national currency that makes availability of local representative unavoidable.

A search of an appropriate local representative is one of the initial activities to be performed during the planning phase before starting any regulatory activities. Not only it relates to the paper submission and payment of fees, but also to many specific requirements, which are not available in public access, but are known to experienced local partners. The changes in local requirements as well as its interpretation are also often communicated through local seminars only.

7.3. Regulatory differences concerning ND within the region

Although there was a historical period of cooperation between the CIS countries, which for some of the states also continues nowadays, the requirements to the medicinal product MAAs and regulatory life cycle may be quite different – from the requirement to perform a local clinical trial in Russian Federation to the shortened dossier and fast MAA procedure in case of the product previous registration in developed countries, e.g. EU – in Georgia.

The EAEU cooperation also defines the same requirements to the member states that unifies the MAA process in the five EAEU member states starting from 2021. A national procedure, mutual recognition procedure and decentralized procedure are foreseen according to the current EAEU regulatory framework. The requirements to the ND in EAEU are also defined in the regional legislation – “Guidelines for preparation of the normative document on the me-

dicinal product quality” [45]. No harmonization of the requirements to the local ND with other countries in CIS region is available. The table below summarizes the information on EAEU membership as well as on the availability of a local ND per country in CIS region.

Table 2: Availability of a requirements concerning local ND in CIS / EAEU countries

Country	EAEU member	Is local ND available?
Azerbaijan	No	No
Armenia	Yes	No – until end 2020, however it is expected that the ND will be introduced as part of the EAEU starting 2021.
Belarus	Yes	Yes , local name – Analytical Normative Documentation
Georgia	No	No
Kazakhstan	Yes	Yes , local name – Analytical Normative Documentation
Kyrgyzstan	Yes	Yes
Moldova	No	No
Russian Federation	Yes	Yes
Tajikistan	No	Yes
Turkmenistan	No	Yes
Uzbekistan	No	Yes
Ukraine	No	Yes , local name – Methods of Quality Control

Although the MA documentation in EAEU member states should be harmonized, the ND as well as IMU belong to the national documentation in Module 1 and will therefore maintain some local specifics. As it is seen from the table above, in Armenia a ND is currently not required according to the local legislation, however since the ND is a part of the EAEU MA dossier it will have to be implemented in Armenia as well for MA submissions starting from the 1st of January 2021.

7.4. International cooperation and participation in groups on quality related topics

The participation in international cooperation groups related to the medicines quality by the countries of CIS region may potentially impact the ND content, its implementation and use.

The ICH quality guidelines [42] define many topics impacting the ND including:

- Q1A - Q1F Stability (influencing the approach to defining the shelf life and storage conditions of the product)
- Q2 Analytical Validation (description of analytical procedures is a major part of a ND)
- Q3A - Q3E Impurities
- Q4A - Q4B Pharmacopoeias
- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice

PIC/S “is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use” [43] aiming to harmonize the GMP standards and inspection procedures in the different countries around the World [43]. And as it will be described in the section 11 a ND may have an impact on the GMP inspection from CIS Authorities.

The relationship with the EDQM describes the acceptance of the Ph. Eur. by the respective country. In case Ph. Eur. requirements are not acceptable or not sufficient an additional testing may be required for single countries in order to comply with the local requirements.

The corresponding membership status per country is summarized in the table below.

Table 3: Overview of participation / membership in international cooperation groups related to quality

Country	ICH Observers [17]	PIC/S	EDQM Ph. Eur. members [19]	EDQM Ph. Eur. Observers [19]
Armenia	Yes, SCDMTE	No	No	Yes
Azerbaijan	No	No	No	Yes

Belarus	No	No	No	Yes
Georgia	No	No	No	Yes
Kazakhstan	Yes, National Center	No	No	Yes
Moldova	Yes, MMDA	No	Yes	No
Russian Federation	Yes, Roszdravnadzor	No	No	Yes
Ukraine	No	Yes, from January 2011 [18]	Yes	No
Uzbekistan	No	No	No	Yes

7.5. National Pharmacopoeias in the countries of CIS region

As it is seen in the section 7.4 most of the countries of the region accept the Ph. Eur. either completely (Ukraine and Moldova as EDQM members) or partly.

Additionally, some countries have previously developed national Pharmacopoeias with local specific requirements that are still valid and should be considered during preparation of the national dossier for submission for gaining MA and during the product's regulatory life cycle, especially for non-members of EDQM.

Following countries have national Pharmacopoeia [23]:

Table 4: Availability of national Pharmacopoeias in CIS / EAEU countries

Country	Name of the Pharmacopoeia	Language
Belarus	State Pharmacopoeia of the Republic of Belarus	Russian (RU)
Kazakhstan	The State Pharmacopoeia of the Republic of Kazakhstan	Kazakh (KZ), RU
Russian Federation [21]	State Pharmacopoeia of the Russian Federation	RU
Ukraine [21]	The State Pharmacopoeia of Ukraine	Ukrainian (UA), partly RU

A Pharmacopoeia of EAEU is currently under development and will have an important impact on the ND compiling and harmonization throughout the EAEU after its implementation, since three of the five EAEU member states currently have their own Pharmacopoeia to refer to in the ND.

8. Normative Document

8.1. Short excursus into the history and development of the ND, ND definition and legal framework

The development of the requirements to the drug product registration substantially reflects the history and development of each country in the CIS region and also their common history during the USSR time before 1991.

The primary role of the Normative Documents as a part of an MAA dossier is to summarize the requirements to the quality of each individual product and provide the instruction for the national laboratories for performing a local quality control of the product (either produced locally or imported), independently of the availability of the corresponding monography or method description in the national or international Pharmacopoeia. The national laboratories do not have the access to the full MAA dossier of the product and specifically its module 3 [45], however the approved ND is made available to the state laboratories after the successful completion of the MAA procedure (e.g. in Ukraine it is performed via national database). This function of the document shows the important difference in the requirements to the analytical documentation for product's MAA in CIS in a form of a ND and in EU in the corresponding CTD modules. Since in EU the reference to the Ph. Eur. is sufficient the level of detail is considerably lower that it may be necessary for a ND, since the ND should enable its use as a single separate document providing all the required data for the successful testing in the laboratory.

The ND may be seen as a "cooking recipe" that often requires more detailed information and therefore inclusion of the variables that may change at the manufacturing facility during the products life cycle. This situation consequently leads to the need to introduce variation procedure in order to bring the ND into compliance to the actual analytical procedure performed at the manufacturing site whenever a change occurs.

Another challenge rising from the level of detail in ND concerns the communication between the manufacturing site performing quality control and testing (in case it is a subcontractor

different from the MAH) and MAH. The MAH should ensure, that any changes in the manufacturing and quality control procedure of a product (e.g. change of the equipment to another validated equivalent one) are communicated by the manufacturing site to the MAH and then to the DRA department in a timely manner in order to be able to submit the change in the countries concerned. Currently, this challenge may be avoided by addition of a wording like “*or equivalent*” wherever some specific equipment is mentioned in the ND.

The knowledge of the requirements related to the compiling of a ND has been mostly concentrated at the local regulatory partners and colleagues, in the major extent due to the fact that the legislation is either available in national language only or cannot be accessed at all. Therefore it is very important to ensure cooperation of local partner with the MAH DRA during the development and revision of a ND for national regulatory procedures in the region.

Hereinafter the topic of the current section is described for several countries of the region as well as for the EAEU.

Russian Federation

In the national legislation of Russian Federation a Normative Documentation is a document containing a list of quality indicators and quality control methods for medicinal product determined by the results of relevant examinations and established by its manufacturer [20].

The awareness about the challenges related to the EU manufacturing sites implementing the ND were not that acute until the changes in the national legislation in Russian Federation requiring the national GMP certificate submission together with the regulatory procedures starting 2017.

In December 2014 new Federal Law No. 429 Φ3(FZ) [24], regulating MA and market access of pharmaceutical products was signed and published in Russian Federation. One of the major changes, impacting market access of the pharmaceutical products in Russian Federation is obligatory GMP inspections to be conducted by the Inspectorate of Russian Federation at foreign manufacturing sites, responsible for production of the bulk products, for packaging and for release of pharmaceuticals. This requirement came into force on 1st of January 2017.

The related wording of the Federal Law No. 429 ФЗ(FZ) has received the latest amendment in December 2019 and states the following:

“[...] In case the changes that are to be performed in the registration documentation [...] require quality expertise of the medicinal product [...] an Applicant additionally provides to the Federal Agency [...] a copy of the Manufacturing License issued by the Competent Authority of the Country of origin (legalized appropriately) and a copy of the conclusion on conformity of a manufacturing site to the GMP requirements issued by the responsible Federal Agency in case of production of the medicinal product is performed outside of Russian Federation.”

[translated from 24]

The first experiences with the national GMP inspections conducted by the Russian Authority have shown that the primary focus during the inspection was drawn to the compliance of the processes and procedures on the manufacturing site to the approved ND. This caused some dramatic failures (see the number of GMP refusals and further details in the section 11) to achieve the GMP certificate from Russian Authority with further complications for product’s regulatory life cycle activities. The local GMP certificate is also a necessary part of the renewal dossier – the procedure that cannot be postponed in case the product’s MAA is to be active, since the delay of renewal submission consequently causes a loss of MA.

Further experiences and discussions related to the local GMP inspection performed by the responsible authority of Russian Federation are provided within section 11.

As a major market among the CIS countries, Russian Federation in general has maintained the requirements developed during the USSR period and then continuously developed further national requirements.

Belarus

According to the local legislation of the Republic of Belarus [30] the quality of the medicinal product of the foreign manufacturer is defined by the requirements of the normative document of the manufacturer that contains quality control indicators and methods. Therefore,

medicinal products not complying with the requirements of the normative document are not considered to be of a proper quality.

Each batch of the medicinal product released by the foreign manufacturer is accompanied by the document confirming the compliance with the corresponding ND (i.e. CoA) [30]. In EU/EEA this approach corresponds to the requirements to the function of a Qualified Person (QP), who is personally responsible for the product's quality as well as for compliance with the MA of the importing country [56].

Ukraine

Ukraine, on the other hand, is making steps towards EU integration and is now a priority partner for the EU on the basis of the EU-Ukraine Association Agreement that came into full force on 1 September 2017 [8].

Shortly after the break-up of the USSR and already some time before it, Ukraine started to focus on the national healthcare system and develop further national institutions and requirements to ensure safety, efficacy and quality of the medicines produced in Ukraine and imported into the country. The decision on the harmonisation of the regulatory expertise procedure in Ukraine to the EU has been taken in 2000 – 2001 [14].

The requirements to the Normative Document developed during USSR time transitioned into national legislation of Ukraine, with later changing of the name of the document to Methods of Quality Control (MQC) in 2005 [15, 16]. Although the national MQC still exists and is still required to achieve the national MA in Ukraine as well as during the regulatory life cycle, the actual requirements to the content of the document and the analytical control of the product are generally complying to the common EU requirements (e.g. it is possible to supplement the specification part of the document with separate part for release and for shelf life specification that is not foreseen for a ND in other CIS countries).

EAEU

As was described in the previous sections five CIS countries have joined into the EAEU: Russian Federation, Belarus, Kazakhstan, Kyrgyzstan and Armenia. This has an impact on the processing of the ND during the MAA procedure due to the introduction of the EAEU DCP and MRP procedures. During the DCP and MRP procedures the EAEU Reference Member State approves the ND and the EAEU Concerned Member States should agree on it [44]. Since the procedures will be implemented starting the 1st of January 2021 there is currently a lack of experience as to the extent of the national changes allowed in the ND for the EAEU Concerned Member States. At the current moment the structure and national requirements to the ND in the four countries foreseeing the document as part of the MA dossier are slightly different.

The current national regulatory requirements in Armenia do not foresee a separate ND that will have to be changed after the coming the EAEU regulations into force in 2021.

The EAEU legislation defining the requirements to ND is separated for the chemically synthesized medicinal products and for the biologicals accordingly:

- Decision of Eurasian Economic Commission Board No 151 “On approval of the Guideline on compilation of the Normative Document on quality of medicinal preparation” from 07.09.2018 – for chemical medicinal products [45].
- Decision of the Council of the Eurasian Economic Commission No 89 “On approval of the Rules of studying of biological medicinal products of Eurasian Economic Union” (Section 6) from 03.11.2016 – for biological medicinal products [46].

The EAEU regulations broaden the definition of the ND in the following way [35, 45]:

“Normative Document on Quality is a document defining the requirements to the quality control of the medicinal product (containing specification and description of the analytical methods and tests or references to them, as well as corresponding acceptance criteria for the specified quality indicators etc.) based on the performed expertise of the medicinal product, and is approved by the Competent Authority during the registration on the territory of the Union

and is intended for quality control of the medicinal product in the post-authorization period on the territory of the Union”.

[translated from 35, 45]

The ND -definition of the EAEU provides more insights regarding the creation, compiling and use of the ND. As it is stated above, the document is developed **during** the registration procedure according to the outcomes of the expertise that therefore means, that the reference documentation alone (mainly 3.2.P.5) is not sufficient and the document submitted at the beginning of the MAA procedure is undergoing full evaluation and is likely to be changed in course of the MAA resulting in the potential differences with the company’s core dossier and possible incompliances that would likely need solving before product’s launch. This situation would not be new for an EU MAH, since the same may happen to the EU dossier during an EU MAA procedure as well as in other countries. However, it should be noted that the MAA in CIS is usually planned after the MAA in country of origin is finalized and many other non-EU countries often accept the EU core dossier without significant changes in quality documentation. This means that the faster and easier access to the market in CIS is being expected by the sales department of the MAH. Also some of the changes made during the procedure in CIS may become known only after the issuing of the approval documentation that may delay the implementation even more. Hence it is advisable to explicitly communicate this potential risk of delay of the launch to the relevant departments so that it is taken into consideration during planning of the product’s launch.

The second important information given in the EAEU ND definition is the clear purpose of the document – namely, *“quality control of the medicinal product in the post-authorization period on the territory of the Union”*. This means that the document approved in EAEU is not primarily intended for quality control at the manufacturing site located outside of the Union. However if this approach related to the GMP inspection requirements will be established by all the EAEU country members is not yet known, since as of now only Belarus NCA has established the procedure of EAEU GMP inspection. The current issues related to the purely na-

tional GMP inspections performed by the Russian NCA and influence of the ND on the inspection are further described in the section 11.

There is however not much experience with the interpretation of the EAEU regulation by the local authorities at the current time, since not all measures to transit from the single countries to the EAEU are finalized and the completion of the transition period is currently defined as 31.12.2025 [44]. The interpretation of the legislation may be a subject to different approaches of the member countries.

8.2. A place of the Normative Document in the registration dossier

The ND is a region specific document and is usually prepared in cooperation between a local partner and MAH HQ CMC department (or other depending on the MAH structure) in order to take into account the national requirements as well as correct details of current quality control methods performed at a manufacturing site while avoiding too much of a detail to prevent unnecessary variations in the future.

The ND is approved as a part of the MAA and must be reviewed and updated whenever any information mentioned in the document changes.

Since the local (at least partly) paper submission is unavoidable in the CIS countries at the current moment, the final compiling of a dossier package for submission according to the local rules lies under the responsibility of a local representative or a local partner.

From the content matter and considering the CTD structure the ND would belong to the Module 3 of the dossier. According to the current purely national Kazakh requirements the ND is included in the module 3.2.P.5. However, in the EAEU Dossier the ND would transition into the Module 1 being a region-specific document [44].

8.3. Normative Document Structure

The national definition of a ND in Kazakhstan defines it as *“a normative technical documentation on the quality control and safety of the medicinal product developed by the manufacturers for commercial batches of the medicinal product”*[32].

There are some specific national requirements to the compiling of the ND, also including quite technical and administrative requirements that must be followed in order to gain the approval for the ND during the MAA as well as during product's regulatory life cycle. The document should be compiled mostly in national (for Ukraine) or Russian (all other countries) language. Some of other administrative requirements to a ND include [36]:

- Requirements to the writing style, font type and font size as well as to the spaces between the lines, to the header / footer of the page etc.
- Abbreviations should generally be avoided unless they comply with the State Pharmacopoeia. After the EAEU Pharmacopoeia is finalized it should be used as reference for the EAEU member countries.
- Reagents, buffer solutions, indicators, titrating solutions used in the analytical methods should be chosen based on their availability in the State Pharmacopoeia (later EAEU Pharmacopoeia). However, if such approach is not possible, the characteristics, qualification and appropriate documentation defining the quality of the reagent, as well as describing the preparation of the reagents, buffer solutions, indicators and titrating solutions must be specified in the ND.
- If the requirements, methods and limits for the quality control of the medicinal product are defined in the State Pharmacopoeia or another acceptable State document no repetition of the description of the methodology might be necessary, but only the reference to the corresponding source document has to be added. Otherwise the full description of the methods and requirements is included in the ND.
- The listing of the symbols to be used in formula is strictly defined (see Annex 11 under the Section 16.11).

Since the requirements per country may slightly vary, the current master thesis is focusing on the general requirements described for ND for Russian Federation with comments on potentially significant differences in requirements for other countries where available. Some of the countries however either do not have own specific requirements to the ND (Tajikistan) or are

usually accepting the ND from another country of the region (as long as it is in Russian language) without significant national changes.

As a rule the ND parts are consisting of the following [36]:

- Cover page
- Specification
- Composition
- Chemical name
- Structure formula
- Empiric formula
- Molecular weight
- Analytical methods. The section describes all analytical methods to be used for the product mentioned in the specification section of ND. As described above if the testing completely corresponds to the State Pharmacopoeia (for EAEU Countries – later EAEU Pharmacopoeia) a link to the respective monography may be sufficient in this section.
- Packaging
- Labelling
- Storage conditions
- Shelf life

The local versions as well as English translations of the ND templates per country are provided in the annexes as following:

- Annex 1: ND Template for Russian Federation in Russian language
- Annex 2: ND Template for Russian Federation, English translation
- Annex 3: AND Template for Kazakhstan in Russian language
- Annex 4: AND Template for Kazakhstan, English translation
- Annex 5: MQC Template for Ukraine in Ukrainian language
- Annex 6: MQC Template for Ukraine, English translation

- Annex 7: AND Template for Belarus in Russian language
- Annex 8: AND Template for Belarus, English translation

Further some main sections of the ND are discussed in more details.

8.3.1. Cover page

The cover page of the ND includes the general information about the product (name, MA number, dosage form, and strengths), MAH and/or applicant and drug product manufacturers. The required information slightly varies depending on the country.

Each ND receives a specific number in all the countries, however this number is referenced on the national MA certificate only in Russian Federation.

8.3.2. Composition

In all of the countries the ND includes brief information on product's composition, in a form of a table, including:

- Name and quantity of the active substance per dosage unit
- Reference to the document defining quality of the active substance (usually Ph. Eur. for the EU MAH)
- Name of excipients, including (except for Ukraine) quantity and reference document defining quality
- API Manufacturers (currently only in Russian Federation and Ukraine)

8.3.3. Specification

The specification part of the ND is similar in form and content to the common specification in the EU, however there are several important points to consider:

Release vs. shelf life specification

The finished product specification in the EU may be divided into the release specification and shelf life specification (ICH Q6) [50, 51] in order to display the tighter requirements to the product's quality at the release and tests that must be performed during release, but can be avoided during the product's shelf life [33].

Non-EU countries, including CIS, usually do not foresee two different specifications. One exception in CIS region is Ukraine which, moving towards the EU integration, actually allows dividing the columns in the specification part of the ND document into the release and the shelf life subsections. For all other countries the ND normally includes only one specification.

As an example to depict the potential issue with only one specification in CIS comparing with the two specifications in EU: in case a single specification with only the limits for release (which are normally tighter) is approved in ND it will not cause any concern during issuing the CoA and consequent release of the product on the market, since these limits are already established. However, if the same tight requirements must be complied with for the shelf life of the product as well, it might have an influence on the possible shelf life of the product, since full shelf life stability data under the conditions specified in ND is normally required for the MAA and further life cycle. Further influence of the ND on the CoA is described in the section 12.

The requirements to the ND compilation of EAEU [45] specify the approach in case of the availability of two specification limits for the release and shelf life, that is – the limit for the shelf life is mentioned in the ND.

Reference to the national Pharmacopoeia

As it is described in the section 7.5 there are several national Pharmacopoeias available as well as the regional EAEU Pharmacopoeia under development in the CIS region. The *Table 3: Overview of participation / membership in international cooperation groups related to quality* of the section 7.4 also highlights the acceptability of the Ph. Eur. in the different countries of a region. To sum up, most of the countries of the region are Ph. Eur. observers, while Moldova and Ukraine are members of the Ph. Eur. and therefore these two countries completely accept the requirements of the Ph. Eur. and consequently Ukraine does not require an additional confirmation of compliance and reference to the national Pharmacopoeia of Ukraine in the ND.

Other countries request addition of either a reference to the national Pharmacopoeia (in case a corresponding test exists) or to the separate national guideline and a full description of the method in case of an in-house method. Although most of the national Pharmacopoeias and analytical test requirements in the CIS region have been harmonised with the Ph. Eur. and EU guidelines, there are still some differences that require precise attention of the DRA and CMC or quality department (depending on the company's structure) during compilation of the national specification in order to avoid incompliance. As a general advice – a remark should be added in order to clarify e.g. that *the mentioned test is performed by the manufacturing site only according to the Ph. Eur.* (to avoid additional testing according to the national requirement), or that *other equivalent equipment may be used when appropriately validated* or any other clarification deemed necessary to avoid incompliance.

If the national authority requires the reference to the national Pharmacopoeia the optimal approach is to include the reference to the current version without actual mentioning the revision number or date of the document, since as with any other information in the MA dossier, such details would require additional variation procedures in the future as soon as the new revision of the Pharmacopoeia comes into force.

Influence on the Certificate of Analysis (CoA) for product supply

Each batch of a medicinal product marketed must comply with all the specifications defining its expected quality level [33].

The specification approved within the MAA procedure and within further renewal or variation procedures has its direct influence on the CoA for the product supply in the country. The parameters and their values tested for the product release to the market and reflected in the CoA must cover the requirements of the ND specification to allow smooth transition of the product through the local customs clearance procedure avoiding delay in product supply.

Some countries require a bilingual CoA with the national translation of the English version of the document. In these cases it is important to ensure transfer of the exact wording from ND

into the CoA also in national language, since even slight differences may cause complications during customs control. Further influence of the ND on the CoA is discussed in the section 12.

Specific national rules and additional parameters

Since the national regulatory know-how is concentrated at the local site by partner, he/she is responsible for compliance of the ND with the national specific rules and requirements and should communicate them to the HQ DRA / CMC department in order to gain the mutual understanding and required support during a ND compilation.

Analytical parameters to be tested for the product are dependent inter alia on the type as well as on the pharmaceutical form of the product. As an example, the corresponding lists of the minimum specification tests for the products depending on the pharmaceutical form in Kazakhstan are added in the Annex 10 section 16.10.

The level of details in the specification of a ND may be different comparing with the reference EU dossier: e.g. for the spectrophotometry analytical parameters the wavelength should already be included into the specification, not only to the analytical methods part of the ND; the wording for the limit of the parameter *Identification* “must be positive” or “complies to the reference solution” is considered insufficient, these test limits in ND are defined e.g. for TLC as “The main spot obtained in the chromatogram with the test solution corresponds in appearance and Rf-value to the main spot obtained from the chromatogram of the reference solution” and for HPLC as “On the chromatogram of test solution the retention time of the main peak should correspond to the retention time of *API* peak on the chromatogram of reference solution”.

Another specific point is that due to the national language of ND the changes cannot always be indicated in the national ND the same way as in the reference English EU dossier. There might be several purely linguistic particulars (e.g. for the description parameter – there are two different words meaning colour “blue” in both Russian and Ukrainian languages). The text should be consistent throughout the full ND, meaning – the parameter limits and de-

scription of tests in the specification section should fully correspond to the further description of the method in the analytical methods section.

Another difference of the ND specification comparing to the EU specification is the inclusion of additional parameters for the commercial product that also differ per country as summarized in the table below:

Table 5: Additional sections in the specification

Parameter included in the specification	BY	KZ	RU	UA	UZ
Packaging	No	Yes	Yes	No	Yes
Labelling	No	Yes	Yes	No	Yes
Transport	No	Yes	No	No	No
Storage conditions	No	Yes	Yes	No	Yes
Shelf life	Yes	Yes	Yes	Yes	Yes
Main pharmacological activity	No	Yes	No	No	No

8.3.4. Analytical methods

The analytical methods section of the ND is the major part of the document and although it is mostly based on the 3.2.P.5.2 analytical methods section of the CTD dossier, the details of this document alone are sometimes not sufficient for compilation a ND.

The overall linguistic difference of this section to the EU dossier is related to the sentence formulation. In this part of a ND the sentences are built not in the usual passive form as in the EU dossier, but in a form of an order – e. g. “take 2 ml of a solution [...]”, “mix [...]”, “fill with water [...]”.

The EU dossier does not require exact description of the preparation of the standard solutions and test solutions for testing. In the ND however (since the document, as described above, is used as a “cooking recipe”) these procedures are described with full details, including quantity of the reference standard and drug product taken as well as the volume of the solvent. In order to allow flexibility in the preparation procedure, here too a note should be added stating that the *provided amounts and volumes are exemplarily*.

Any other specifics of the solution preparation, including the type of the flask to be used (polypropylene instead of glass) should also be added under the note to the section.

The details on equipment are included into the method description as well, e.g. thickness of cuvette, name and manufacturer of the chromatograph and name and serial number of the column used, as well as chromatographic conditions. However in general if the same method is used for several tests (e.g. Identification and Assay) the exact details on the solution preparation and the conditions of the procedure can be described under one section and the reference to it is given in the other corresponding section(s).

Although the test limits are added into the specification section of the ND, they are repeated again in the analytical method description section for all tests.

As an outcome of the local requirement to include the reference to the national pharmacopoeia a corresponding section of the national Pharmacopoeia is referenced under this section additionally to the Ph.Eur. (or another Pharmacopoeia - e.g. USP, BP, used where relevant). It is advisable that the wording states, that the test is performed either according to the national Pharmacopoeia *or* according to the Ph.Eur.

For the national MA procedures in Belarus an inclusion of the exemplary chromatogram may be requested (see also a comparison of several of the same parameters' analytical test descriptions in the EU 3.2.P.5.2 and in the ND approved in Belarus and in Kazakhstan as an example in the Annex 9, section 16.9).

In the determination of impurities section a structural formula of each known impurity may be required.

As stated in the section 8.3, the symbols for the formula used for the determinations in the analytical methods are predetermined (see

Annex 11: Official listing of symbols to be used in the formula in the ND for medicinal product in form of a tablet in Russian Federation) and therefore will most probably differ from the symbols used in the reference EU dossier.

8.3.5. Other information

Following other information is included into the ND that is also mentioned in the specification part of the document additionally to the brief mentioning of these parameters in the specification (see also Table 5: Additional sections in the specification):

Packaging

The section describes the container and / or packaging type used for the finished product including pack size. This section corresponds to the EU SmPC section **6.5 Nature and contents of container**.

Shelf Life

The section corresponds to the EU SmPC section **6.3 Shelf life**. However the specific information on in-use stability mentioned in SmPC is not transferred into the ND.

Storage Conditions

The section corresponds to the EU SmPC section **6.4 Special precautions for storage** for the finished product excluding the information on the in-use storage conditions.

It should be taken into consideration during overall dossier preparation that another national specific document – Instruction for Medical Use (IMU), which serves as a national package leaflet, includes the information on packaging, shelf life and storage conditions as well. Therefore these parameters should correspond throughout the dossier modules as well as in both national documents – ND and IMU.

Labelling

Most of the countries of the region are requiring package mock-ups as part of the MA dossier, therefore the packaging mock-up are added as an attachment to the ND and are approved within the document. The listing of the information included on the national package is a part of the ND for Russian Federation. The labelling section of a ND is not structured in line with the EU labelling documentation in the CTD section 1.3, but includes listing of the information available on the primary packaging unit and separately on the secondary packaging unit (usually cardboard) where the parameters are separated by comma.

A single exemption is Ukraine where packaging mock-ups are not required as part of the regulatory procedure and not included into the MQC. The labelling section of the MQC in Ukraine includes a reference to the attached labelling texts that are prepared using the template identical to the template for the labelling texts used in the EU translated into Ukrainian.

Although these additional parts of an ND are not usually posing any challenge during compilation, it should however be considered, that any change of these parameters will lead to a variation not only in the CMC part of the dossier and national texts, but also in the ND.

8.3.6. Tabulated summary of national differences of ND

The overview below includes the information on the differences and main specific characteristics of the ND the countries with the most attractive markets for the foreign MAHs, as well as most influence in the CIS region – Russian Federation, Belarus, Kazakhstan and Ukraine.

Other countries of the region where ND is required (Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan) tend to accept the ND version already approved in one of the other countries as reference in order to reduce the local resources for the national review of the dossier.

Table 6: Summary of differences and specific requirements to the ND in different CIS / EAEU countries

Characteristic	Russian Federation	Belarus	Kazakhstan	Ukraine
Language	RU	RU	RU and KZ (only local trade name)	UA / UA and RU
Information on API included into a ND	Name (incl. chemical name, structural formula, empiric formula, molecular weight), quantity per dosage unit, manufacturing site(s)	Name (incl. chemical name, structural formula, empiric formula, molecular weight), quantity per dosage unit	Name, quantity per dosage unit	Name, quantity per dosage unit, manufacturing site(s)
Reference to national Pharmacopoeia required?	Yes	Yes	Yes	No
Compliance with Ph. Eur. / EU dossier	Local specific requirements additionally to Ph. Eur.	Local specific requirements additionally to Ph. Eur.	Local specific requirements additionally to Ph. Eur.	Full compliance possible
Labelling section of ND	Listing of the information added to the primary and secondary packaging	Reference to the separately approved mock-ups is added	Reference to the separately approved mock-ups is added	Reference to the separate national labelling part of the dossier
Other specifics	Other specifics for Russian Federation were described in the section above.	Exemplary chromatograms may be requested to be added into the corresponding ND section.	Information on main pharmacological activity and transport conditions (GOST 17768-90 [52]).	Reference to the analytical tests description of the corresponding test in MQC document is added in the specification.

9. Links between the information in the ND and CMC dossier, as well as product information

As seen from components of the ND described above, this document contains a mixture of the information from Module 3 of the CTD dossier, and some parts of the document correspond or refer to the information given in Module 1.3.

The EAEU legislation states that a ND contains information from the following modules of the CTD dossier [45]:

- 3.2.P.1 Drug Product Description and Composition
- 3.2.P.5.1 Drug Product Specification
- 3.2.P.5.2 Drug Product Analytical Control Methods
- 3.2.P.7 Container Closure System
- 3.2.P.8.1. Stability Summary and Conclusions

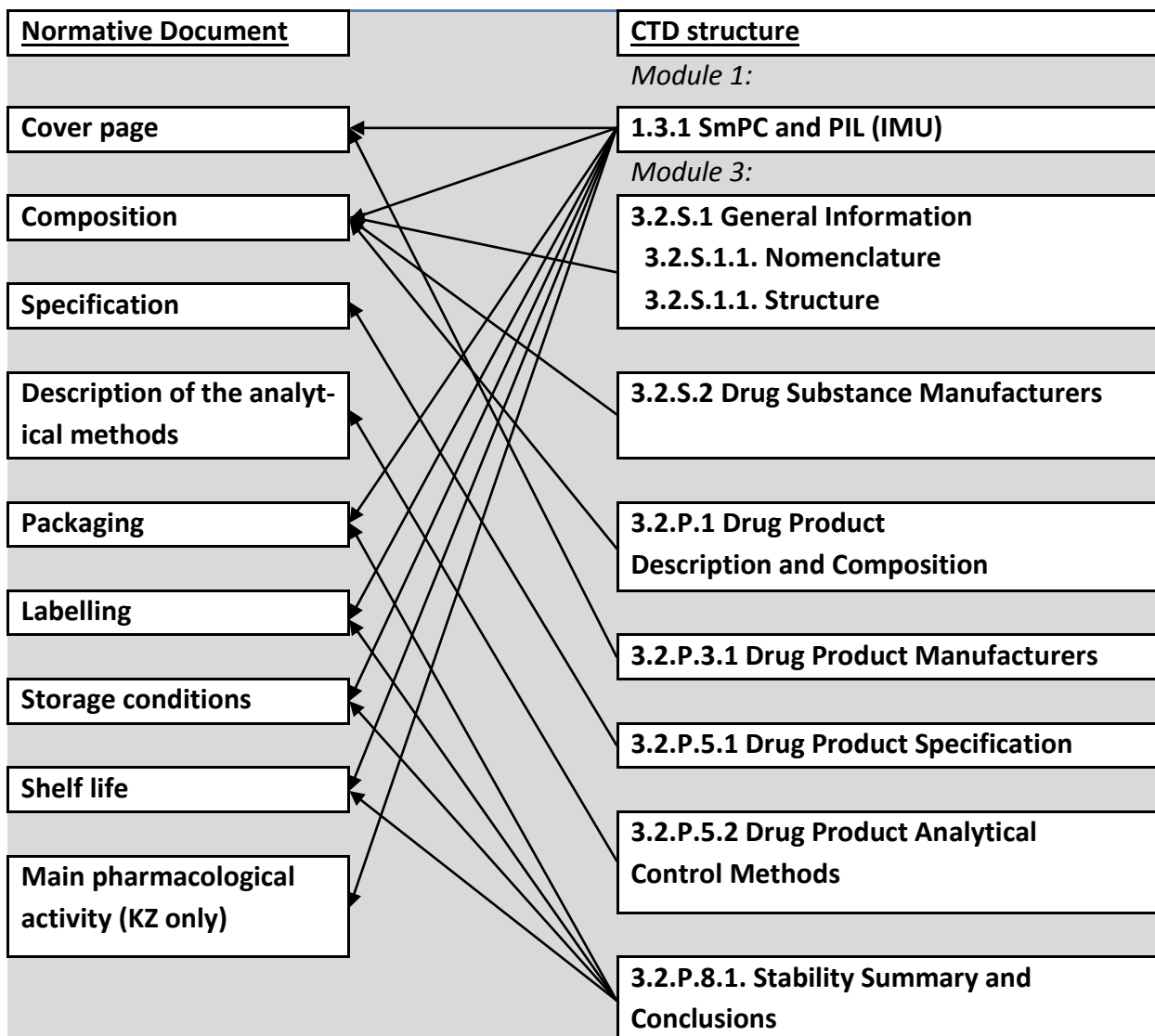
Nevertheless, some additional details are required to compile the document that can be extracted from the following CTD modules:

- 3.2.S.1.1 Nomenclature (for Russian Federation and Belarus)
- 3.2.S.1.2 Structure (for Russian Federation and Belarus)
- 3.2.S.2 Drug Substance Manufacturers (for Russian Federation and Ukraine)
- 3.2.P.3.1 Drug Product Manufacturers (for all countries)
- Module 5 or 1.3.1 for the information on the main pharmacological activity (for Kazakhstan)

In particular cases when information in the dossier does not contain all the details required to be added to a ND (e.g. examples of equipment and its manufacturer) the modules 3.2.P.5.3 Validation of Analytical Procedures and 3.2.P.5.4 Batch Analyses or a manufacturer's SOP on manufacturing process and analytical control may be used as a reference to obtain the missing data. Nevertheless, special care should be given to such information in order to ensure its continuous compliance with the current manufacturing process by adding the explanation that the *provided information is exemplary*.

The schematic table below shows the links between the ND sections and the modules of a CTD dossier for the common case. It includes the requirements of all countries and therefore gives a broad overview of all connections possible.

Table 7: Links between a ND sections and the CTD modules



The Annex 9 (section 16.9) shows the differences in the level of details between the actual AND approved in Belarus and in Kazakhstan comparing to the EU CTD for the same parameters of the same product. As it is seen the amount of information and details may be higher in the ND, but in some cases the description is also more detailed in the EU dossier while the ND only provides the reference to the corresponding monograph.

10. Compilation of a ND

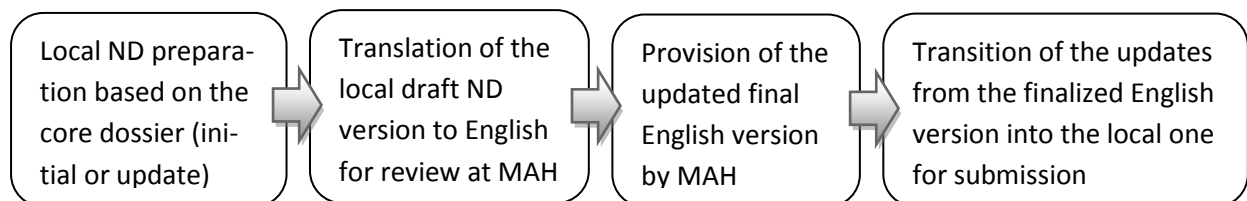
10.1. Role and involvement of the local partner in the ND compilation

Local regulatory partners play a major role as a liaison between the MAH and the local NCA. Since the national websites often either do not have an official version in English or this version is incomplete, the local partner's role also includes regulatory intelligence by timely informing the MAH about the latest requirements of the national legislation. Some changes in the legislation and clarifications on the interpretation thereof are also provided via local seminars performed only in national language, which confirms the need to rely on a local partner for obtaining of the important information on the updates of the local requirements.

The level of involvement of the local partner in the decision-making processes on the MAH overall strategy in the particular country depends on the company's size and structure (in large Companies the local partner is often an official legal representative and therefore is a completely independent functioning unit of a company with full responsibilities), conditions of the regulatory agreement between MAH and the partner, as well as established SOPs and internal MAH procedures. Depending on a settled relationship with the partner compiling of a ND and its compliance may be either completely delegated to the local partner or be shared between the partner and the MAH DRA (CMC) department.

The ND is a purely national document that is submitted in local or Russian language. Hence, in case of the ND compilation in collaboration between the local partner and the EU MAH an English translation of the draft of the document would normally be required for discussion. This document will then have to be translated back into the local language for submission after finalization of the draft at both sides.

For this approach the process steps may be schematically depicted as following:

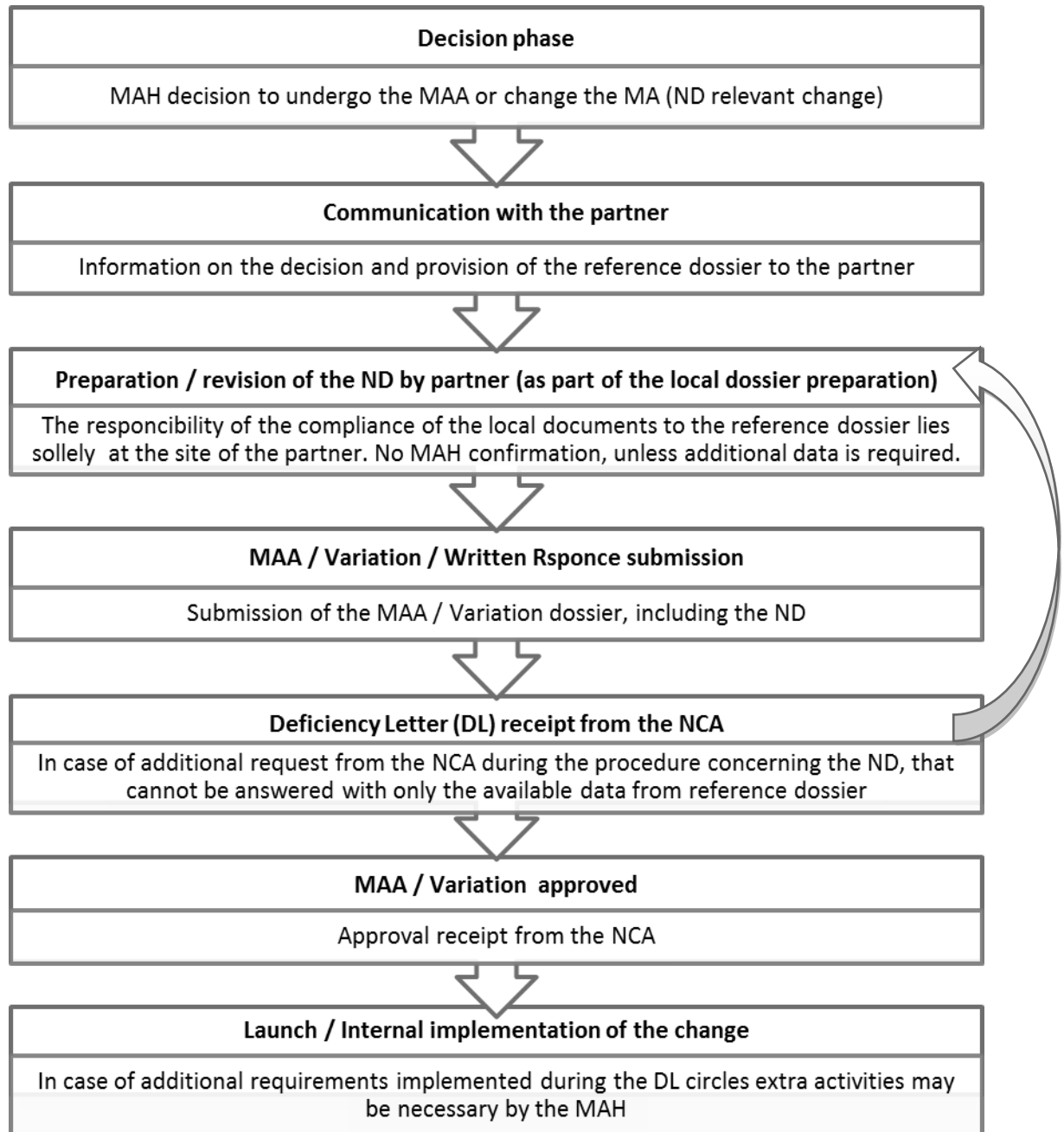


The described translation steps highlight another potential challenge, namely the possibility of a translation error (both into English and back to the national language for submission). It also brings up the necessity of a good CMC knowledge by the local partner or availability of a separate local CMC or quality responsible person in the corresponding CIS country in order to correctly implement the core dossier requirements into the national ND.

Another complication arising from the necessity of translation is the potential difference in interpretation of the same words in English and in local language in CIS. As an example from recent experience: the description of the limit of impurities with the wording “*any other unidentified impurity [...]*” when translated into Russian can be misinterpreted with the meaning “*some unidentified impurity [...]*”, as though not all of unidentified impurities must comply with the given limit, but only *some* of them. This specific case may be settled through changing the wording to “**each** unidentified impurity” that provides the required meaning both in Russian and in English. Without knowing this linguistic specific and correspondingly without proper communication the obvious question arises on why the original wording from the core dossier has not been used in the English version of the ND that can lead to unnecessary confusion and delay in ND confirmation from the MAH side.

The compilation of a ND as a part of the preparation of the local dossier for submission of a regulatory procedure (regardless of the type of procedure) begins after the provision of necessary modules of a reference dossier to the partner (see section 9). In case the document is prepared in cooperation between the partner and MAH, the draft ND is provided for the review and confirmation to the MAH DRA (CMC) department before submission. Otherwise the document is prepared by the partner under his own responsibility and only requests for the information or documentation missing to finalize the ND are communicated to the MAH DRA (CMC). The finalized ND draft is then submitted to the NCA for the review with further usual steps of a regulatory procedure. If a deficiency letter is received from the NCA during the procedure and its contents are related to the ND a respective communication and collaboration with the MAH DRA (CMC) may be required depending on the question(s) raised.

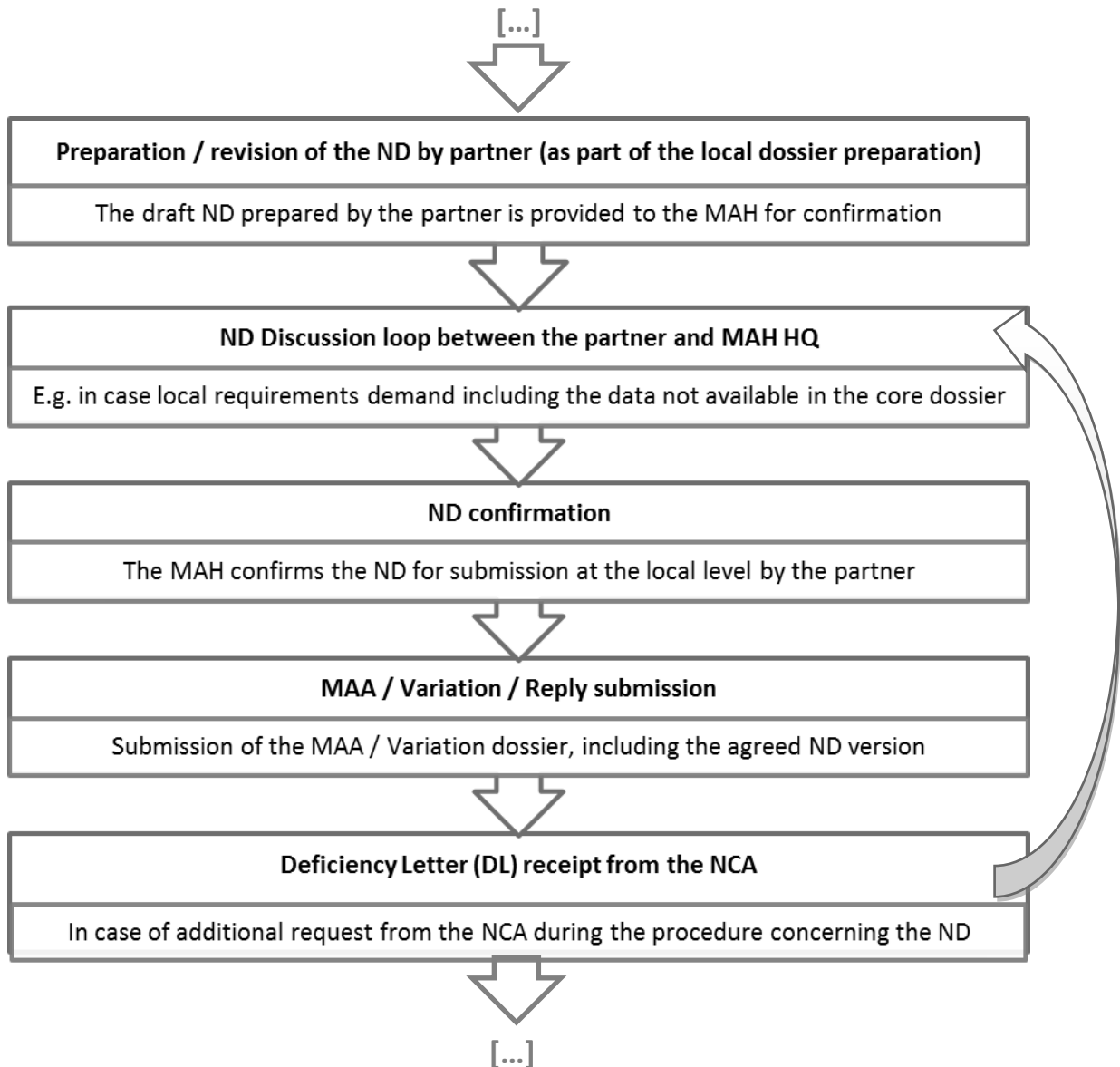
Following scheme summarizes the workflow of the regulatory procedure involving a ND – an independent compilation by the local partner scenario:



It has to be highlighted, that in the approach described above, the compliance function is also delegated to the local partner. Therefore any deviations from the core reference dossier

required due to local legislation or due to the NCA request must also be explicitly communicated to the MAH DRA in order to ensure the compliance at the manufacturing facility.

In case the responsibility for the ND compiling is shared between the local partner and the MAH DRA (CMC) some additional steps added in the process. The additional steps are described in the scheme below.



Regardless of the approach chosen by the MAH, it is important to ensure timely a provision of the appropriate training to the local partner in order to gain a mutual understanding of the processes and mutual expectations.

10.2. The influence of the type of medicinal product and its pharmaceutical form on a ND

The classification of the medicinal products based on their structure often divides between chemically synthesized medicinal products and biologically driven medicinal products due to the considerable difference in the particularities of the product's risks, manufacturing process and approaches to quality control. For the biological medicinal products the manufacturing process plays a major role in the product quality and defines the product, therefore more attention is given to the in-process control during manufacturing.

Biologics

The legislation of EAEU provides a separate guideline for the specification and analytical methods requirements for the biological medicinal products as a part of a ND for these products [46]. This guideline is almost fully harmonized with the ICH Q6B Guideline [50]. Therefore, in case the ICH requirements (also adopted in EU) are met by the MAH (which is normally the case, otherwise either the MA in EU would not be possible or the sound justification for deviation from the guideline exists) the corresponding analytical documentation should be sufficient for the MAA in EAEU as well. However, some differences in the interpretation of the requirements in EAEU still exists: e.g. related to the concept of the *Specification release limits vs. shelf-life limits* (point 2.5 in the ICH Q6B) – in the EAEU guideline it is stated that the release limits (that may be tighter than the shelf life limits) can **replace** the shelf life limits (instead of the word *vs. (versus)* in ICH interpretation). According to the experience this particular situation can be an issue during the MAA e.g. in Kazakhstan. The situation was related to the request of the NCA to use the specification limit for release specification for both release and shelf life time points. This has shortened the final approved shelf life of the product (according to the available stability data) and therefore complicates the product's supply.

ATMP

The Advanced Therapeutic Medicinal Products (ATMP) are innovative medicines based on genes or cells. These therapies provide new opportunities for the patients with diseases untreatable with other products [47]. Together with great advantages these types of products bring also some very specific risks and correspondingly require particular safety measures also related to the product's quality. Although no separate EAEU guideline on the requirements to the quality of the ATMP is available, the specifics of the GMP related to this type of the product are included into the EAEU GMP rules [49]. It should be considered, that there are separate requirements to the labelling of the ATMP, especially for the autologous ATMPs for which the unique patient identifier and the corresponding note [49] should be added that consequently should be reflected in the labelling section of a ND.

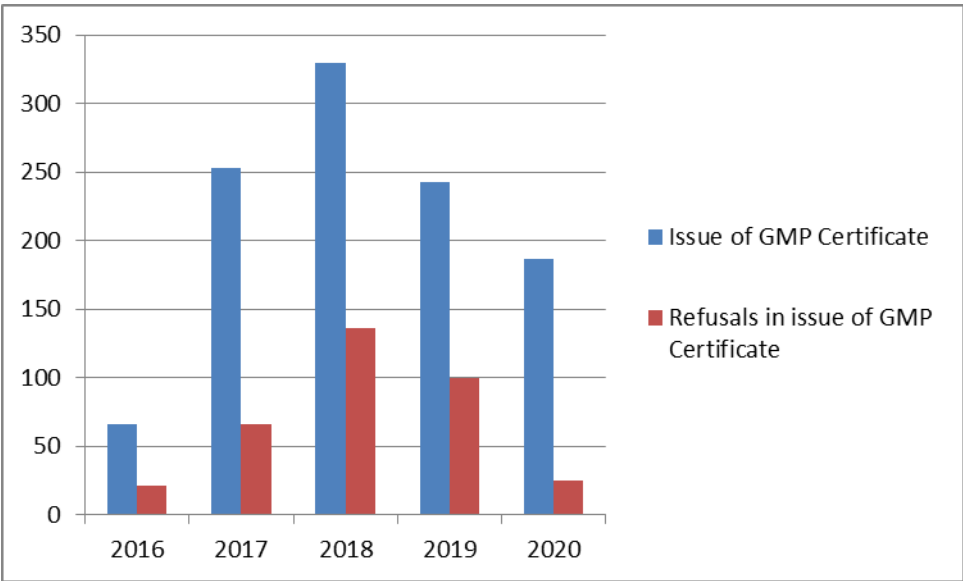
As already stated before, the pharmaceutical form of a product impacts the parameters required to be tested to confirm the product's quality and that are consequently included into a ND. The exact required tests depending on the pharmaceutical form for Kazakhstan are listed in Annex 10, section 16.10.

11. Impact of the ND on the national GMP inspection by Competent Authority of Russian Federation

The changes in legislation of Russian Federation, which came into force starting from 1st of January 2017, posed a significant challenge for the MAHs not only during planning of the authorization of the medicinal products in Russian Federation, but also for already authorized medicinal products. The challenge was caused by the new requirement to undergo a GMP inspection performed by Russian NCA and include the corresponding GMP certificate into the submission dossier for any regulatory procedure, incl. variations and renewals. The first GMP inspections showed that not only the compliance with the global GMP requirements were examined during the inspection procedure, but that the actual focus of the inspection is ensuring the compliance of the quality control procedures at the manufacturing facility with the national ND, while some manufacturing facilities did not have the information on the existence of this specific document.

Overall refusal rate to issue the GMP certificate of Russian Federation for foreign manufacturers was 39 refusals in 2016, 111 – in 2017, 241 – in 2018, 196 – in 2019 and as of 17.10.2020 there were 49 refusals issued for 2020. Overall 636 refusals were issued for foreign manufacturers starting 2016, of which 345 were issued for the manufacturers located in the EEA [38]. The number of successful GMP inspections in the countries outside the Russian Federation as of 17.10.2020 is 1693, out of which 1083 GMP certificates were issued to the EEA manufacturing facilities [38]. The total refusal rate from 2016 is 27 % for all countries outside Russian Federation and 24 % for the manufacturers from EEA countries. In 2020 only manufacturers from EEA were inspected so far and the refusal rate dropped to 12 %.

Figure 4: Graphic analysis of issuing of the GMP certificate vs. refusal in issuing the GMP certificate from Russian Federation to the manufacturers located in EEA [based on data from 38]



The improvement of positive GMP inspection rates may be caused by both more effective preparations at the manufacturing sites due to gained own experience and experience shared in the field during the years after new legislation implementation, as well as advances in clarity of the national interpretation of the requirements at the NCA related to the ND.

A failure to obtain a GMP certificate from Russian NCA however does not necessarily mean the refusal in approval of the related regulatory procedure or impossibility of further product supply, since only some critical findings may cause such effect.

12. Influence of the ND on the supply documentation (CoA, CoC) in CIS countries.

As described in the section 8.3.3 the specification part of a ND has a direct influence on the documentation accompanying product's supply. The CoA must fully reflect the parameters and limits from the approved national ND. Even the tighter limits comparing to the approved ones are not acceptable in the CoA for Russian Federation during the customs clearance of the goods during product's supply.

In Ukraine the requirements to the CoA for a medicinal product fully comply with the Internationally Harmonised Requirements for batch certification [53, 54] however the translation into local language is required. Other countries also require local translation of the documentation accompanying the product batch [55]. It is therefore important that the translation of the analytical part of the CoA should comply also in wording with the national ND document approved in local language. This point highlights the importance of the cooperation of the DRA department, both on the local level as well as at the HQ, with the quality department and QP to timely share ND for transfer of the relevant data into the CoA template for supply to the countries of the CIS region where the document is approved separately.

The influence of the correctness of the documentation accompanying the supply is researched on the basis of the current legislation in Ukraine [57].

One of the critical points during the product supply is time. Some products have a rather short shelf life and each month may be decisive for the acceptance of the product for the local distributor and customer.

In order to ensure the appropriate product quality for the imported medicines a state quality control step is performed after the customs clearance of the goods. The duration and the extent of the quality control depend on the several characteristics of the product:

- the medicinal products imported to Ukraine for the first time must undergo a laboratory quality control step;

- the further imports of the same product to Ukraine normally require only the provision of the documentation confirming compliance of the quality of the batch to the GMP requirements and to the requirements of the local MA for the product.

The MA documentation, which the batch must comply with, include not only the registration certificate, IMU and labelling texts, but also the nationally approved MQC. In case the CoA accompanying the product batch do not exactly (including wording) correspond with the approved MQC, the batch of the product might be a subject for the laboratory testing and therefore will stay in quarantine until the laboratory control is finalized and until the quality compliance of the product is confirmed.

The additional laboratory control step has not only a direct financial impact due to the extraction of the samples of the product from the batch for control and due to the other related costs, but also the impact on the timing of the availability of the product for the customer.

The table below provides the information on the duration of the steps of the state quality control procedure in Ukraine depending on the necessity of the laboratory control testing step for the imported product batch [57]:

Table 8: Duration of the different steps of the state quality control during product supply to Ukraine

Step description	Duration	Comments
Submission of the application for obtaining a decision on the quality of the medicinal products after successful completion of customs clearance	5 working days	
Visual control of the batch	3 working days	After the successful completion of this step the batch can be taken out of the quarantine.
Completion of the procedure of the state quality control	8 working days	If no reasons for laboratory control testing has been discovered.

If quality control testing is required, additional steps include:

Sampling process	3 working days	
Laboratory control testing	14 working days	Unless the testing procedures described in the approved MQC define different duration.
Issue of conclusion from the state quality control Authority	1 day	
Overall calculated duration of the procedure in case the laboratory control testing is required	26 working days	In calendar days – approximately five weeks.

The table shows that the duration of the state quality control in Ukraine without the laboratory testing is approximately 1,5 weeks, while in case a laboratory testing is required the overall duration prolongs to more than a month. This time difference of the product availability on the local market may play an important role during product supply especially during the period of drug shortages and for products with short shelf life as well as in other cases depending on the local agreements with distributors and product-specific characteristics.

12.1. Challenges and approaches for a shared SKU

As mentioned earlier Russian is the common language still spoken in the countries of the region. Some countries also accept the Russian language on the package labelling of the medicinal products that allows combining the requirements for several countries into one SKU of the company. Such approach allows sharing the production batch of the product within the countries and allows supply into the countries with lower forecast rates, which are not allowing a separate SKU from an economical perspective.

The approach is commonly used by the pharmaceutical companies where the SKU is based on one of the countries with higher potential or confirmed demands for the product and with own distinctive requirements to the product information on the packaging materials – usually Russian Federation, Kazakhstan or Ukraine. In Kazakhstan two languages are used on the

packages – Russian and Kazakh. In Ukraine the product information must be provided in Ukrainian, however, adding another language, as long as the information provided fully corresponds to the Ukrainian text, is allowed. Therefore, Russian may be added as an additional language on the package labelling that will allow using the same packaging materials in some other countries of the CIS region.

The influence of the ND on the shared SKU is related to the connection of the details of specification part of the ND with the CoA. Since the same CoA will be used for the other countries where the SKU is marketed, the specification parameters and limits must comply within the countries of shared SKU even if ND is not available in some of them. This has an impact on the planning of the regulatory activities in these countries in the following way: the submission of the regulatory procedure including ND should be done in the country that serves as basis to the shared SKU at first, and the further countries receive the variation documentation of the same change based on the approval of this first country. Any other changes in the documentation during further regulatory procedures should be avoided; otherwise repeated submission in the first country may be necessary. As another option to be considered is the issuing of the several CoAs for the same batch of the product prepared according to the national requirements of the different countries.

13. Summary

The current master thesis researches the legislative and historical background of and summarizes the requirements for the Normative Documentation (ND) within the countries of CIS region. It also includes the description of the differences thereof between the countries concerned.

The ND is a specific document defining the quality of the medicinal product and it is required in some of the countries in the CIS region for gaining the MA as well as during the life cycle of a medicinal product. Although most of the requirements to the documentation necessary for the MA of the medicines in the CIS countries are comparable with the requirements in the EU, the ND still stays a national specific document and it is reviewed during the MA expertise together with the dossier and is approved by the NCA.

An EU QP of a pharmaceutical company is responsible for overall product's quality and confirms the compliance of the product to the applicable legal requirements in the country of origin as well as its compliance to the product's marketing authorization [56]. Therefore the compliance of the product's batch with the approved ND must be ensured for releasing the product for the countries where the document is a part of the MA.

The structure of the ND as well as the corresponding links between a ND and the CTD dossier modules in the EU are analysed. As it is seen from the annexed ND templates (Annexes 1 to 8), the structure of the document as well as the information included in it is quite similar in the different countries of the region. However, several specifics exist, some of which are also described in the current thesis.

The position of a ND in the registration dossier is provided as well as the specifics and challenges of the cooperation with the local partner during the compiling of the document. The stepwise approach is illustrated showing the dossier preparation stage at which a ND is compiled as well as the level of HQ involvement depending on the company's structure and agreed extent of the responsibility of a local partner.

A major role in preventing incompliances related to the ND is given to the local partner and his/her bilateral function of communicator between the NCA – ensuring compliance with current local legislation, and the MAH – ensuring compliance with the company’s dossier.

The latest legislative developments in the region related to the activation of the EAEU requirements for medicinal product MAAs and to the ND as a part of the EAEU MAA dossier are indicated as well. The ND stays an important part of the dossier in the EAEU member states and will also have to be implemented in Armenia, where this document has not been required before.

The impact of the ND on the GMP inspections by the EAEU NCAs cannot be evaluated at the current moment due to lack of EAEU GMP inspections performed and since only one member state can perform these inspections until now.

The latest part of this thesis provides the details of the influence of the ND on the quality supply chain documentation accompanying the batches of the product after the release on the market and the impact on the customs clearance of goods in the countries of the CIS region.

13.1. Summary of challenges

As the second part of the thesis title is related to the challenges linked to the ND in the CIS region that the EU MAH can face during the preparation of the MAA and further life cycle of a product, the summarized listing of the described challenges is provided as following:

- **Local requirements and legislation.** The local requirements are usually not available in English and therefore a full delegation of the regulatory intelligence function to the local partner is often necessary. Other options for solving this issue would be either regulatory intelligence in MAH HQ by a bilingual responsible, who will be able to find and understand the national requirements in CIS, as well as interpret it for the other colleagues; or delegating the regulatory intelligence function to a qualified third party company either in the EU or in the CIS.

- **Language barrier.** This point plays a major role in the topic above and also during the communication with the partner explicitly concerning the ND. Although it may not be an issue during communication on the general regulatory topics, a ND discussion requires profound knowledge of the quality requirements and terminology for the partner in both native language as well as in English.
- **Differences in the interpretation of the requirements and the wording.** Even if the correct translation of a ND to English is available, there is still room for misinterpretation after the translation into local language in CIS. The same is also valid for the interpretation of legislation – even the native Russian speaker cannot know the interpretation of the legislation foreseen by the national NCA in CIS, unless the person possess some experience as well as attend to the local workshops held by the NCA.
- **Necessity of provision of additional data and maintenance of this information.** As described in the thesis, one of the main differences of a ND to the EU core dossier is the level of details required (see also Annex 9, section 16.9 for some real life examples of the analytical test description comparison). Consequently the MAH must request additional data from the manufacturing facility, which may require additional time and costs especially in case of contract manufacturing. And in case if the note e.g. *“or other equipment”* is neglected in some testing description, the continuous control of the compliance at the manufacturing facility will be required or a variation procedure to add the note must be submitted. Either way, additional resources will be needed to deal with the issue.
- **Communication.** The language barrier is not the only potential obstacle during interactions between the local partner and the MAH HQ. The regional cultural specifics as well as differences of experience and knowledge play an important role in communication in general. As an example, the role of a QP has been introduced in Russia only recently and therefore the function and the level of responsibility of a QP during product’s release could have been unclear to the local partner in this country before. The EU QP, on the other hand, has an established **personal** responsibility for the me-

dicinal product's quality and its compliance to the national MAA of the target country [56]. In Germany specifically the violation of the QP responsibilities foresee not only the financial penalties, but may as well lead to the imprisonment of a QP [58]. These aspects highlight the particular attention to the correctness of the MA data provided to the MAH and its influence on the product release by the QP.

At the same time, the necessity to maintain a good professional relationship with the NCA in CIS region plays much more important role comparing to EU.

- **Influence on the GMP inspections.** Whether ND will further pose a challenge during the GMP inspection remains an open question, since the GMP inspections from the Russian NCA should be performed under EAEU requirements starting from 2021. Until then the national GMP inspections from Russian Federation foresee not only the check of compliance with the GMP rules and requirements, but also the compliance of the quality control at the manufacturing facility to the requirements of the local ND.
- **Influence on the shared SKU in CIS.** In order to enable sharing the SKUs among several CIS countries where the similar labelling requirements exist, the availability of a ND in at least one of these countries should be taken into consideration. The ND has a direct impact on the specification that correspondingly transfers into the CoAs that should comply with the approved specification for all the countries sharing the SKU or otherwise, the separate CoAs should be prepared for the same SKU according to the local specification approved in the importing country.

14. Conclusion

The ND is a specific document required for the MAA and for the regulatory life cycle in some countries of the CIS region. There are specific challenges related to this document and its maintenance for the MAHs outside of the CIS.

The productive approach to ensure the compliance of the ND with the company's reference core dossier requires the knowledge of the specifics as well as close cooperation with the local partner and good communication skills on the both local and MAH HQ sides. The approaches to deal with the situation depend on the company, its size, structure and internal procedures. It may vary from delegating the full responsibility for ND compliance to the local partner, establishing the local quality compliance function or establishing the region-specific function at the MAH HQ DRA department, who will be responsible for establishing the fruitful communication and act as liason between the local partner and the responsible departments at the MAH HQ.

The impact of the ND highlights also the significance of the communication between the different departments of the MAH at the HQ, since not all data and details of the quality control performed at the manufacturing site are available at the DRA department. In order to achieve the continuous and uninterrupted supply of the product to the patients the ND compliance with the company's standards, as well as implementation of the national specific requirements for ND are necessary.

Therefore the preparation of a ND and ensuring its compliance might not be the simplest task, but it is definitely a feasible one.

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Приказ Министра здравоохранения Республики Казахстан №754 «Об утверждении Правил составления, согласования и экспертизы нормативно-технического документа по контролю за качеством и безопасностью лекарственных средств», от 19 ноября 2009 г.

33. EMA Guideline on Specifications and Control Tests on the Finished Product:

https://www.ema.europa.eu/en/documents/scientific-guideline/specifications-control-tests-finished-product_en.pdf (23.05.2020)

34. ICH Topic Q 6A “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances”:

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-6-test-procedures-acceptance-criteria-new-drug-substances-new-drug-products-chemical_en.pdf (23.05.2020)

35. Decision of the Eurasian Economic Commission No 78 from 03.11.2016 (red. 30.01.2020) “About the Rules of registration and Expertise of medicinal products for medicinal products”.

Name in original language (RU):

Решение Совета Евразийской экономической комиссии от 03.11.2016 N 78 (ред. от 30.01.2020) «О Правилах регистрации и экспертизы лекарственных средств для медицинского применения»:

https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78 (24.10.2020)

36. Manual on medicinal product expertise, volume II, - M.: Grif & K, 2014. (edition 2019)
– 280 p., ISBN 978-5-8125-1865-3.

Name in original language (Russian):

*Руководство по экспертизе лекарственных средств. Том II. — М.: Гриф и К, 2014.
(издание 2019 г.) – 280 с., ISBN 978-5-8125-1865-3*

37. WHO Quality Assurance of Medicines Terminology Database - List of Terms and related guideline:

https://www.who.int/medicines/services/expertcommittees/pharmprep/20171109ReportQASTerminology_database.pdf?ua=1 (02.07.2020)

38. State register of the conclusions on the GMP compliance (Russian Federation). Status date 16.10.2020

Name in original language (Russian):

Государственный реестр заключений GMP на 16.10.2020:

https://minpromtorg.gov.ru/docs/#!reestr_zaklyucheniy_gmp (17.10.2020)

39. <https://www.worldatlas.com> (24.10.2020):

- Languages spoken in Azerbaijan:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-azerbaijan.html>
(24.10.2020)

- Languages spoken in Armenia:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-armenia.html>
(24.10.2020)

- Languages spoken in Belarus:

<https://www.worldatlas.com/articles/languages-spoken-in-belarus.html> (24.10.2020)

- Languages spoken in Georgia:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-georgia.html>

(24.10.2020)

- Languages spoken in Kazakhstan:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-kazakhstan.html>

(24.10.2020)

- Languages spoken in Kyrgyzstan:

<https://www.worldatlas.com/articles/languages-spoken-in-kyrgyzstan.html> (24.10.2020)

- Languages spoken in Moldova:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-moldova.html>

(24.10.2020)

- Languages spoken in Russia:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-russia.html>

(24.10.2020)

- Languages spoken in Tajikistan:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-tajikistan.html>

(24.10.2020)

- Languages spoken in Turkmenistan:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-turkmenistan.html>

(24.10.2020)

- Languages spoken in Ukraine:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-ukraine.html>

(24.10.2020)

- Languages spoken in Uzbekistan:

<https://www.worldatlas.com/articles/what-languages-are-spoken-in-uzbekistan.html>

(24.10.2020)

40. The law No. 1456 of Republic of Moldova “On pharmaceutical activity” from 25.05.1993

Name in national language (Romanian):

LEGE Nr. 1456 “Cu privire la activitatea farmaceutică”

Name in Russian language:

ЗАКОН Nr. 1456 “О фармацевтической деятельности”

<http://lex.justice.md/viewdoc.php?action=view&view=doc&id=313276&lang=2> (05.10.2020)

41. Ministry of foreign Affairs and European Integration of the Republic of Moldova. Moldova-EU relations:

<https://mfa.gov.md/en/content/moldova-eu-rela->

[rela-](#)

[tions#:~:text=European%20integration%20is%20not%20only%20a%20fundamental%20basis,important%20results%20have%20been%20achieved%20in%20this%20field.">tions#:~:text=European%20integration%20is%20not%20only%20a%20fundamental%20basis,important%20results%20have%20been%20achieved%20in%20this%20field.](#) (05.10.2020)

42. ICH Quality Guidelines:

<https://www.ich.org/page/quality-guidelines> (06.10.2020)

43. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) official Website. Introduction:

<https://picscheme.org/en/about> (06.10.2020)

44. Pharma Forum Webcast International “Regulatory Affairs in EAEU”, 22.09.2020.

45. Decision of Eurasian Economic Commission Board No 151 “On approval of the Guidelines for preparation of the normative document on the medicinal product quality”.

https://docs.eaeunion.org/docs/en-us/01226892/clcd_12092018 (17.10.2020)

Document in Russian language:

Решение Коллегии Евразийской Экономической Комиссии № 151 «Об утверждении Руководства по составлению нормативного документа по качеству лекарственного препарата» от 07 сентября 2018 г.

https://docs.eaeunion.org/docs/en-us/01418849/clcd_12092018_151 (08.10.2020)

46. Decision of the Council of the Eurasian Economic Commission No 89 “On approval of the Rules of studying of biological medicinal products of Eurasian Economic Union” (Section 6) from 03.11.2016 (only Russian version available).

Name in original language (Russian):

Решение Коллегии Евразийской Экономической Комиссии № 89 «Об утверждении правил проведения исследований биологических лекарственных средств Евразийского экономического союза» от 03 ноября 2016:

https://docs.eaeunion.org/docs/ru-ru/01411954/cncd_21112016_89 (08.10.2020)

47. EMA News 24.11.2017: New guidelines on good manufacturing practices for advanced therapies:

<https://www.ema.europa.eu/en/news/new-guidelines-good-manufacturing-practices-advanced-therapies#:~:text=The%20European%20Commission%20has%20published%20a%20set%20of,opportunities%20for%20the%20treatment%20of%20diseases%20and%20injuries.> (08.10.2020)

48. EudraLex Volume 4, Good Manufacturing Practice “Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products”:

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf (08.10.2020)

49. Decision of the Council of the Eurasian Economic Commission No 77 “On approval of the Rules of Good Manufacturing Practice of Eurasian Economic Union” from 03.11.2016

Name in original language (Russian):

Решение Коллегии Евразийской Экономической Комиссии № 89 «Об утверждении правил надлежащей производственной практики Евразийского экономического союза» от 03 ноября 2016:

https://docs.eaeunion.org/docs/en-us/01411922/cncd_21112016_77 (08.10.2020)

50. ICH harmonised tripartite guideline specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B:

<https://database.ich.org/sites/default/files/Q6B%20Guideline.pdf> (12.10.2020)

51. ICH harmonised tripartite guideline specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A:

<https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf> (12.10.2020)

52. GOST 17768-90 „Medicinal products. Packaging, labeling, transporting and storage“.

Name in Russian language:

ГОСТ 17768-90 “Средства лекарственные. Упаковка, маркировка, транспортирование и хранение“:

https://standartgost.ru/g/%D0%93%D0%9E%D0%A1%D0%A2_17768-90 (17.10.2020)

53. Ukrainian pharmaceutical institute of quality „Requirements to contents of the quality certificate for the batch of a medicinal product“.

Name in original language (Ukrainian):

Український фармацевтичний інститут якості «Вимоги до змісту сертифіката якості серії лікарського засобу»:

<http://gmpcenter.org.ua/news/vimogi-do-zmistu-sertifikata-jakosti-seriji-likarskogo-zasobu>

(24.10.2020)

54. EMA “Internationally harmonised requirements for batch certification”
EMA/INS/MRA/387218/2011 Rev 5 from 1 June 2011:

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/mra_batch-certificate_05-2011.pdf (24.10.2020)

55. Federal Customs Service. Medicinal products. Transition of the medicinal products including those containing narcotic and psychotropic substances.

Name in Russian language:

Федеральная таможенная служба. Лекарственные средства. Перемещение лекарственных средств, в том числе содержащих наркотические и психотропные вещества:

<https://customs.gov.ru/fiz/pravila-peremeshheniya-tovarov/lekarstvennye-sredstva>

(24.10.2020)

56. DIRECTIVE 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use:

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf (24.10.2020)

57. RESOLUTION OF THE CABINET OF MINISTERS OF UKRAINE No 902 "On approval of the Procedure of state quality control of medicinal products imported in Ukraine", from 14.09.2005 (with changes).

Name in national language (Ukrainian):

ПОСТАНОВА КАБІНЕТ МІНІСТРІВ УКРАЇНИ № 902 «Про затвердження Порядку здійснення державного контролю якості лікарських засобів, що ввозяться в Україну» від 14.09.2005 р. (зі змінами):

<https://zakon.rada.gov.ua/laws/show/902-2005-%D0%BF#Text> (31.10.2020)

58. Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), zuletzt geändert durch Art. 16a Abs. 3 G v. 28.4.2020 I 960:

http://www.gesetze-im-internet.de/amg_1976/AMG.pdf (09.12.2020)

16. Annexes

16.1. Annex 1: ND Template for Russian Federation in national language

НД _____ С. 1

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

Регистрационное удостоверение №

Дата регистрации

(наименование юридического лица, на имя которого выдано регистрационное удостоверение,
адрес)

НОРМАТИВНАЯ ДОКУМЕНТАЦИЯ

торговое наименование лекарственного препарата

международное непатентованное или группировочное наименование

лекарственная форма, дозировка

ПРОИЗВОДИТЕЛЬ ГЛФ

ФАСОВЩИК (ПЕРВИЧНАЯ УПАКОВКА)

УПАКОВЩИК (ВТОРИЧНАЯ (ПОТРЕБИТЕЛЬСКАЯ) УПАКОВКА)

ВЫПУСКАЮЩИЙ КОНТРОЛЬ КАЧЕСТВА

СПЕЦИФИКАЦИЯ

Показатель	Метод	Норма

НОРМАТИВНАЯ ДОКУМЕНТАЦИЯ

Состав на 1 мл:

Компонент	Количество, мг	Стандарт
<u>Действующее вещество:</u>		
<u>Вспомогательные вещества:</u>		

Характеристика активного вещества

МНН:

Химическое название:

Структурная формула:

Эмпирическая формула:

Молекулярная масса:

УПАКОВКА

МАРКИРОВКА

ХРАНЕНИЕ

СРОК ГОДНОСТИ

Примечание. Производитель гарантирует безвозмездную поставку стандартных образцов, необходимых для контроля качества препарата в РФ.

Представитель фирмы

16.2. Annex 2: ND Template for Russian Federation English translation

THE MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

Marketing authorization No.

Date of registration " ____ " _____ 20__.

(name and address of marketing authorization holder)

NORMATIVE DOCUMENT

_____ (number)

drug product trade name

international nonproprietary name

pharmaceutical form, dosage

MANUFACTURER

PRIMARY PACKAGING SITE

SECONDARY PACKAGING SITE (CONSUMER PACK)

RELEASE QUALITY CONTROL

SPECIFICATION

Test parameter	Methods	Limit

Normative document

Product composition per 1 *dosage unit*:

Active substance:

Manufacturer:

Excipients:

Active ingredient characteristics

Chemical name

Structural formula

Empiric formula

Molecular weight

Full description of the methodology for analytical product control

Packaging

Labelling

The details of the information presented on the product primary and secondary packaging is described.

Storage

Shelf life

Note. The manufacturer guarantees free supply of reference standards used for product quality control in the RF.

16.3. Annex 3: AND Template for Kazakhstan in national language

УТВЕРЖДЕН

наименование организации-производителя

_____ подпись Ф.И.О должность

« ____ » _____ 200 __ г.

М.П.

ЭКСПЕРТИЗА ПРОВЕДЕНА

ПРИКАЗ

наименование экспертной организации

наименование государственного органа

подпись Ф.И.О. должность

от « ____ » _____ 200 __ г.

№ _____

подпись Ф.И.О. должность

М.П.

« ____ » _____ 200 __ г.

М.П.

АНАЛИТИЧЕСКИЙ НОРМАТИВНЫЙ ДОКУМЕНТ

Наименование лекарственного препарата лекарственная форма, дозировка, концентрация

на государственном языке

на русском языке

МНН (при наличии) _____

наименование и страна организации-производителя _____

наименование и страна владельца регистрационного удостоверения _____

наименование и страна организации-упаковщика _____

АНД РК 42 –

Срок введения установлен с

«__» _____ 20__ г.

Вводится впервые

или

Срок действия до

взамен (категория и номер)

«__» _____ 20__ г.

Спецификация качества

Показатели Качества	Нормы отклонений	Методы испытаний

Состав на один флакон препарата, в миллиграммах

Активного вещества

Вспомогательные вещества

Описание методов испытания

Упаковка.

Маркировка.

Транспортирование.

Хранение.

Срок хранения

(the form for the last page of AND)

с. ____ АНД РК - (колонтитул четной страницы - слева)

или для нечетной страницы

АНД РК - с. ____

(34 знака для номера - справа)

Организация-производитель _____

наименование организации, страна

Заявитель _____

должность подпись Ф.И.О.

« ____ » _____ 200 __ г.

М.П.

16.4. Annex 4: AND Template for Kazakhstan English translation

APPROVED

Name of the Manufacturing Organization

signature Name Position

« ____ » _____ 200 __.

Stamp here

EXPERTISE PERFORMED

ORDER

Name of the Expert Organization

Signature Name Position

Name of the Authorized Institution
from « ____ » _____ 200 __.
No _____
Stamp here

« ____ » _____ 200 __.

Stamp here

ANALYTICAL NORMATIVE DOCUMENT

Name of the medicinal product, dosage form, dosing, concentration

In national language

In Russian language

INN (if available) _____

Name and Country of the Manufacturing Organisation

Name and Country of the Marketing Authorizazion Holder _____

Name and Country of the Packaging Organization _____

AND PK 42 –

Effective date

First introduced

« ___ » _____ 20 __.

or

replaces (category and number)

Valid till

« ___ » _____ 20 __.

Quality specification

Quality Indicators	Acceptance criteria	Test methods

Composition for one vial of the medicine, milligram

Active substance

Excipients

Description of the test methods

Packaging.

Labeling.

Transportation.

Storage.

Shelf life

(the form for the last page of AND)

p. ____ AND PK - (even page footer - left)

or for an odd page

AND PK - p. ____

(34 symbols for the number - right)

Manufacturing Organization _____

name of the organization, country

Applicant _____

Position signature name

« ____ » _____ 200 ____.

Stamp here

16.5. Annex 5: MQC Template for Ukraine in national language

ЗАТВЕРДЖЕНО

Наказ Міністерства охорони

здоров'я України

DD.MM.YYYY № XXXX

Реєстраційне посвідчення

№ *UA/00000/00/00*

Заявник, країна:

Виробник, країна:

МЕТОДИ КОНТРОЛЮ ЯКОСТІ

ЛІКАРСЬКОГО ЗАСОБУ

PRODUCT NAME

Dosage form, strengths and packaging

Склад

1 *dosage form unit* містить:

Найменування інгредієнту

Кількість на *one dosage form unit*

Діючі речовини:

Виробник діючої речовини

Допоміжні речовини:

СПЕЦИФІКАЦІЯ

Product name

№	Назва показника	Допустимі межі	Методи контролю
1.			<i>Includes the reference to the MQC section describing the specific analytical method. May also include the reference to Ph. Eur. monography</i>

МЕТОДИ КОНТРОЛЮ ЯКОСТІ

Product name

УПАКОВКА

МАРКУВАННЯ

ТЕРМІН ПРИДАТНОСТІ

УМОВИ ЗБЕРІГАННЯ

16.6. Annex 6: MQC Template for Ukraine English translation

APPROVED

Order of Ministry of Health of Ukraine

DD.MM.YYYY No. XXXX

Marketing Authorization

No. *UA/00000/00/00*

Applicant, country:

Manufacturer, country:

DRUG QUALITY CONTROL METHODS

PRODUCT NAME

Dosage form, strengths and packaging

COMPOSITION

1 *dosage form unit* contains:

Active substances:

Quantity per 1 *dosage form unit*

Manufacturer of the active substance:

Exipients:

Quantity per 1 *dosage form unit*

SPECIFICATION

Product name

No.	Test	Acceptable criteria	Control methods
1.			<i>Includes the reference to the MQC section describing the specific analytical method. May also include the reference to Ph. Eur. monography</i>



QUALITY CONTROL METHODS

Product name

PACKAGING

LABELLING

SHELF LIFE

STORAGE CONDITIONS

16.7. Annex 7: AND Template for Republic Belarus in national language

ТОРГОВОЕ НАЗВАНИЕ ПРЕПАРАТА

ЛЕКАРСТВЕННАЯ ФОРМА

МЕЖДУНАРОДНОЕ НЕПАТЕНТОВАННОЕ НАЗВАНИЕ ИЛИ
ГРУППИРОВОЧНОЕ НАЗВАНИЕ

ЗАЯВИТЕЛЬ РЕГИСТРАЦИИ

ПРОИЗВОДИТЕЛЬ ГЛФ

ФАСОВЩИК (ПЕРВИЧНАЯ УПАКОВКА)

УПАКОВЩИК (ВТОРИЧНАЯ/ТРЕТИЧНАЯ УПАКОВКА)

ВЫПУСКАЮЩИЙ КОНТРОЛЬ КАЧЕСТВА

НОРМАТИВНАЯ ДОКУМЕНТАЦИЯ

Характеристика активного вещества

Международное непатентованное название:

Химическое название:

Эмпирическая формула:

Молекулярная масса:

СОСТАВ
лекарственного средства

В одном *dosage form unit* содержится:

Наименование ингредиентов	Количество	Предназначение ингредиента	Ссылка на нормативный документ по контролю качества

СПЕЦИФИКАЦИЯ

Показатели	Методы	Нормы
1	2	3

Методы анализа

УПАКОВКА

МАРКИРОВКА

УСЛОВИЯ ХРАНЕНИЯ

СРОК ГОДНОСТИ

16.8. Annex 8: AND Template for Republic Belarus English translation

Trade name

Pharmaceutical form

INN

Applicant

Manufacturer of the finished product

Primary packer

Final packer

Release control

Normative documentation

Characteristics of active substance

INN:

Chemical name:

Empirical formula:

Molecular weight:

**Composition
of drug product**

One *dosage unit* contains:

Name of ingredients	Amount	The purpose of the ingredient	Link to the Normative document on quality control

Specification

Parameters	Methods	Limits

Methods of analysis

PACKAGING

LABELLING

STORAGE CONDITIONS

Shelf life

16.9. Annex 9: Comparison of the single methods description from the approved ND in Belarus with the corresponding section in 3.2.P.5.2 of the EU dossier

Residual solvents test:

EU reference dossier section 3.2.P.5.2	AND approved in Belarus (BY)*	ND approved in Kazakhstan (KZ)*
<p>Residual solvents, 2-propanol:</p> <p>The test for the residual solvent isopropanol (2-propanol) is performed according to the latest PhEur by gas chromatography head space. The content of 2-propanol in the test substance must be ≤ 0.2 per cent (m/V).</p>	<p>RESIDUAL ORGANIC SOLVENTS</p> <p><u>Limits:</u> isopropanol – not more than 0,2 %.</p> <p>The test is performed according to RB St.PH. II and Ph.Eur, method 2.4.24 «Identification and assay of residual solvents», 5.4.4 «Limits of residual solvents content».</p> <p>Determination is performed by method of headspace gas chromatography (2.2.28) on chromatograph Agilent, 6890 (or analogue), with flame-ionisation detector and fused-silica capillary column Optima 1701 size 30 м x 0,25 mm (stationary phase: 88 % dimethylpolysiloxane, 7 % diphenylpolysiloxane, 5% cyanopropylpolysiloxane with particle sizes 1 μm, cat M&N 726965.30).</p> <p>Allowed to use a column of another manufacturer with equivalent characteristics and correct conditions of determination according to requirements of system suitability. Sam-</p>	<p>Residual quantities of organic solvents.</p> <p>Perform the test by gas chromatography method (St. Ph. of RK I, Vol. 1, 2.2.28).</p> <p>Transfer 0.200 g of the product to a 10 ml autosampler vial, add 2.0 ml of <i>dimethylformamide R</i>, dissolve, seal tightly (<i>test solution</i>).</p> <p>The solution should be freshly prepared.</p> <p>Chromatograph 1 ml of phase of the test solution, reference solution and blank solution (<i>dimethylformamide R</i>) on a gas chromatograph with plasma ionization detector with Head Space receiving not less than 6 chromatograms for the reference solution and 2 chromatograms for the test so-</p>

	<p>pling and injection into the column is performed using an automatic headspace sampler Agilent, model 7694 (or equivalent).</p> <p><i>Reagents and materials:</i></p> <ul style="list-style-type: none"> Isopropanol (CP) 1,4-dioxane (CP) Dimethylsulfoxide (AR) Helium Hydrogen Nitrogen Technical air <p><u>Preparation of solutions</u></p> <p><u>In-house standard solution</u></p> <p>10 ml of dimethylsulfoxide transfer to 100 ml volumetric flask, add 40 mg (accurately weighted) 1,4-dioxane, then adjust to the volume with dimethylsulfoxide and shake.</p> <p><u>Calibrating solution</u></p> <p>10 ml of dimethylsulfoxide transfer to 100 ml volumetric flask, add 40 mg (accurately weighted) 1,4-dioxane and 40 mg (accurately weighted) of isopropanol, adjust to the volume with dimethylsulfoxide and shake.</p>	<p>lution under the following conditions:</p> <ul style="list-style-type: none"> - 30 x 0.32 mm column filled with SGE sorbent (6 % cyanopropylphenyl, 94 % dimethylpolysiloxane), size of particles – 1.8 µm, or equivalent; - carrier gas – nitrogen; - carrier gas rate – 1.0 ml/min; - column temperature: initial – 40 °C, delay time – 8 minutes; increase at 40 °C/min, final – 220 °C, delay time – 8 minutes; - equilibrium time – 0.5 min; - injector temperature – 180 °C; - detector temperature – 260 °C; - flow split – 1 : 25. <p>Head Space conditions:</p> <ul style="list-style-type: none"> - syringe – 2.5 ml; - incubation temperature – 80 °C; - incubation time – 25 min; - mixing rate – 250 rev/min; - start mixing time – 5 s;
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Preparing vials for sampling of calibrating solution

0.5 ml of calibrating solution transferred via pipette to 20 ml HS vial, seal with stopper with crimp cap.

Preparing vials for sampling of sample solution

200 mg (accurately weighted) of the product transferred to 20 ml HS vial, dissolve in 0,5 ml of in house standard solution, seal with stopper with crimp cap.

Preparing vials for sampling of blank test

0,5 ml of dimethylsulfoxide transfer to 20 ml HS vial, seal with stopper with crimp cap.

Automatic headspace sampler properties

Matrix: Dimethylsulfoxide, boiling temperature 189°C.

Temperature of thermostate sample oven: 120°C.

Time of samples thermostating: 90 min.

Temperature of sample loop: 200°C.

Volume of sample loop: 1 ml.

Transfer line temperature: 210°C.

Time of vial pressurisation: 1,50 min.

Shaking agitation: low

Time of sampling: 0,40 min.

- end mixing time – 2 s;
- syringe temperature – 95 °C;
- fill rate – 1 ml/s;
- voltage increase delay – 1 s;
- delay before injection – 500 ms;
- delay after injection – 500 ms;
- syringe flushing – 3 minutes;
- run time – 30 min.

Calculate in percent the 2-propanol (X) in the product according to the following formula:

$$X = \frac{(S_1 - S_2) \times m_0 \times 10 \times P \times 2 \times 100}{(S_0 - S_2) \times m_1 \times 100 \times 100 \times 100} =$$

$$= \frac{(S_1 - S_2) \times m_0 \times P}{(S_0 - S_2) \times m_1 \times 500},$$

where:

S_1 – mean value of 2-propanol peak areas calculated from chromatograms of the test solution;

	<p><i>Time of loop equilibration:</i> 0,05 min. <i>Time of sample injection:</i> 1,00 min. <i>Time of oven stabilization:</i> 1,00 min. <i>Extractions:</i> 1. <i>Puncture mode:</i> 1.</p> <p><u>Conditions</u></p> <p><u>Injector</u></p> <ul style="list-style-type: none"> - Injection technique: split - Split ratio: 10 : 1 - Split flow: 12,2 ml/min - temperature: 250°C <p>Carrier gas conditions on enter the column:</p> <ul style="list-style-type: none"> - type of carrier-gas: helium - option: constant column flow - pressure on enter the column: 102,7 kPa - Flow rate: 1,2 ml/min - Stop: 12 min <p>Thermostate temperature option:</p> <ul style="list-style-type: none"> - start temperature: 60°C 	<p>S_0 – mean value of 2-propanol peak areas calculated from chromatograms of the reference solution; S_2 – mean value of other peak areas with 2-propanol retention time calculated from chromatograms of the blank solution; m_0 – weighed 2-propanol RS, in grams; m_1 – weight of the product, in grams; P – content of 2-propanol in 2-propanol RS, in percentage;</p> <p>The content of 2-propanol in the product should be not more than 0.2 %.</p> <p>The results of analysis are considered valid, if the requirements of the “System suitability test” are met.</p> <p>Notes. Preparation of reference solution. Place 0.500 g of <i>2-propanol R</i> in a 100 ml volumetric flask containing 50 ml of <i>dimethylfor-</i></p>
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	<ul style="list-style-type: none"> - start temperature holding: 1 min - temperature gradient: 10°C/min - final temperature: 170°C - final temperature holding: 1 min <p>Detector:</p> <ul style="list-style-type: none"> - temperature: 260°C - H2-flow: 40 ml/min - Air-flow: 450 ml/min - type of make-up-Gas: nitrogen - make-up-Gas-Flow: 25 ml/min <p><u>Chromatography</u></p> <p>Inject in chromatograph «blank» solution twice, than calibrating solution three times, than twice sample solution, and calibrating solution once.</p> <p>Approximate retention times</p> <ul style="list-style-type: none"> - isopropanol – about 2,8 min - 1,4-<u>dioxane</u> – about 5,1 min - dimethylsulfoxide – about 9,6 min. <p><u>Evaluation of system suitability</u></p> <p>The system is considered suitable if:</p>	<p><i>mamide R</i>, fill to volume with the same solvent and mix (stock solution).</p> <p>Place 10.0 ml of the stock solution in a 100 ml volumetric flask, fill to volume with <i>dimethylformamide R</i> and mix.</p> <p>Place 2.0 ml of the obtained solution in a 10 ml autosampler vial and seal tightly.</p> <p>System suitability test. The chromatographic system is considered suitable if the following conditions are met:</p> <ul style="list-style-type: none"> - relative standard deviation calculated from the peak areas of 2-propanol in the chromatograms of the reference solution should be not more than 10.0 %.
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- peak area of isopropanol on the chromatogram of blank solution is lower than determination level;
- relative standard deviation of peak area of isopropanol on the chromatogram of calibrating solution should not exceed 10 %;
- resolution factor of isopropanol peak on chromatograms of calibrating solution and any peak existing also of the chromatograms of blank solution, not less than 1,3.

Calculate the content of isopropanol in preparation (X), %, by formula:

$$X = \frac{S_{spl} \cdot W_{std} \cdot P}{S_{std} \cdot W_{spl} \cdot 100}$$

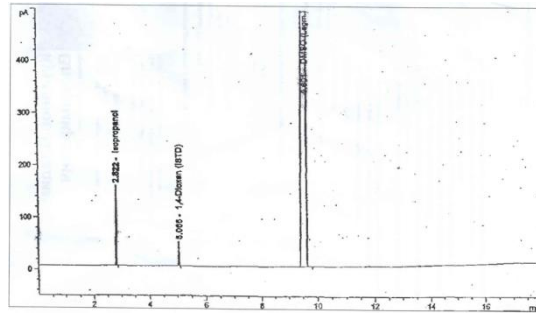
where: S_{spl} = relation of peak area of isopropanol to peak area of in-house standard on chromatogram of sample solution;

S_{std} = relation of peak area of isopropanol to peak area of in-house standard on chromatogram of standard solution;

W_{std} = weight of isopropanol standard, mg;
 W_{spl} = weight of sample, mg;
 P = purity of isopropanol standard, %.

Limit of determination of isopropanol (test-sensitivity) is about 0,05 %. Disregard the lower values.

Exemplary chromatogram is provided below:



Sterility testing:

EU reference dossier section 3.2.P.5.2	AND approved in BY*	AND approved in KZ*
<p>Sterility:</p> <p>The test for sterility is carried out under aseptic conditions using, for example, a class A laminar-air-flow cabinet located within a class B clean-room, or an isolator. The precautions taken to avoid contamination are such that they do not affect any micro-organisms which</p>	<p>STERILITY</p> <p>The test is performed according to RB St.PH. II and Ph.Eur, methods 2.6.1 (membrane filtration).</p>	<p>Sterility.</p> <p>The product should be sterile. Perform the tests in accordance with the requirements of St. Ph. I of RK, Vol.</p>

<p>should be revealed in the test. The working conditions in which the tests are performed are monitored regularly by appropriate sampling of the working area and by carrying out appropriate controls such as those indicated in the appropriate European Community Directives and associated Notes for guidance on GMP.</p> <p>The sterility test is performed using the technique of membrane filtration according to the latest PhEur.</p> <p>The number of samples tested corresponds to the minimum number of items recommended for parenteralia to be tested according to PhEur.</p> <p>Does the batch consist of not more than 100 vials, 10 % of the batch or 4 containers have to be tested (whichever is the greater).</p> <p>Between 100 and 500 vials of one batch 10 containers have to be tested. Does the batch consist of more than 500 vials 2 % or 20 containers (whichever is the less) have to be tested.</p> <p>The results of the test must be according to the demands, no microbial growth must be detected.</p>	<p>The product doesn't have antimicrobial activity.</p> <p>Limits: the product should be sterile.</p>	<p>2, 2.6.1.</p>
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* please note, that the information provided is extracted from the current approved version of the document irrespective of the potential ongoing variations in the AND, since for the variation the NCA opinion is not yet issued.

16.10. Annex 10: English translation of the extract from the Order of the Minister of Health of the Republic of Kazakhstan as of November 19, 2009 № 754 – Lists of main AND sections depending on the medicinal product type / dosage form

1. Drug substance

Item №	Section title
1.	Description
2.	Dissolution
3.	Identification
4.	Melting point *
5.	Boiling point or distillation range *
6.	Freezing point *
7.	Relative density *
8.	Specific optical rotation (optical rotation)*
9.	Specific absorbance *
10.	Refractive index *
11.	Viscosity *
12.	Quality parameters of a solution: clarity colour * acidity (alkalinity) or pH*
13.	Particulate matter *
14.	Related impurities: identified impurities unidentified impurities total impurities
15.	Residue solvents *
16.	Easily flammable substances *
17.	Microbial limits or sterility
18.	Inorganic anions (chlorides, sulfates, nitrates, etc.), cations (iron, etc.)*
19.	Loss on drying or Water content *
20.	Bacterial endotoxins and / or pyrogens *
21.	Arsenic *
22.	Heavy metals *
23.	Total ash or sulfated ash *
24.	Assay
25.	Activity *
26.	Packaging
27.	Labelling
28.	Transportation

29.	Storage conditions
30.	Shelf life
31.	Main pharmacological activity
32.	Precautions*

Note. Sections marked with an «*» are included depending on the nature of medicinal substance. Introduction of additional sections is allowed.

2. Liquid dosage forms for parenteral use

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives, stabilizers)
3.	Clarity
4.	Colour*
5.	pH
6.	Stability (for suspension)
7.	Particle size (for suspension)*
8.	Syringeability (suspension)
9.	Particulate matter (visible particles, if necessary, subvisible particles)
10.	Relative density *
11.	Osmolality (osmolarity)**
12.	Viscosity **
13.	Related impurities: identified impurities unidentified impurities Total impurities
14.	Extractable volume
15.	Bacterial endotoxins or pyrogens *
16.	Abnormal toxicity *
17.	Content of the histamine-like agents *
18.	Sterility
19.	Uniformity of content (for suspension)
20.	Antimicrobial preservative content
21.	Assay
22.	Packaging
23.	Labelling
24.	Transportation
25.	Storage conditions
26.	Shelf life
27.	Main pharmacological activity
28.	Precautions*

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Section marked with «**», is included for infusions.

Introduction of additional sections is allowed.

3. Dry dosage forms for parenteral use

Item №	Section title
1.	Description
2.	Identification
3.	Uniformity of mass * (except freeze-dried)
4.	Dissolution
5.	Solution quality indicators: clarity colour* acidity (alkalinity) or pH
6.	Particulate matter
7.	Related impurities: identified impurities unidentified impurities Total impurities
8.	Mass loss on drying or water content
9.	Bacterial endotoxins and / or pyrogens
10.	Abnormal toxicity *
11.	Content of the histamine-like agents *
12.	Sterility
13.	Uniformity of content * (except freeze-dried)
14.	Assay
15.	Activity *
16.	Packaging
17.	Labelling
18.	Transportation
19.	Storage conditions
20.	Shelf life
21.	Main pharmacological activity
22.	Precautions*

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

4. Eye drops

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives, stabilizers)
3.	Clarity (for solutions)
4.	Colour (for solutions)
5.	Acidity or alkalinity, or pH
6.	Particulate matter
7.	Viscosity *
8.	Osmolarity (osmolality)*

9.	Particle size (for eye drops in a suspension form)*
10.	Related impurities: identified impurities unidentified impurities total impurities
11.	The volume of the contents of the container (for multi-dose containers) Fill volume (for single-dose containers)
12.	Sterility
13.	Antimicrobial preservative content
14.	Uniformity of content (for single-dose containers)
15.	Assay
16.	Packaging
17.	Labelling
18.	Transportation
19.	Storage conditions
20.	Shelf life (including after opening of the package)
21.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

5. Liquid dosage forms for internal and external use

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives, stabilizers, colorants)
3.	The acidity (alkalinity) or pH *
4.	Clarity (ear drops)
5.	Colour (ear drops)
6.	Stability (for suspensions)
7.	Particle size (for suspensions)
8.	Relative density *
9.	Viscosity *
10.	Related impurities: identified impurities unidentified impurities Total impurities
11.	The volume of contents of the container (for multi-dose containers). Dose and uniformity of dosage drops for oral administration. Uniformity of mass of the medicinal product in one dose of a multi-dose container (for suspensions and emulsions).
12.	Microbiological purity or sterility
13.	Ethanol *
14.	Antimicrobial preservative content (ear drops)
15.	Assay
16.	Packaging

17.	Labelling
18.	Transportation
19.	Storage conditions
20.	Shelf life (including after the opening of the primary packaging)
21.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

6. Aerosols

Item №	Section title
1.	Description
2.	Identification
3.	Pressure
4.	Air-tightness of the container
5.	Test of valve device
6.	Average dose weight *
7.	Maximum number of doses per container *
8.	Container contents output
9.	Aerosol particles size (suspension) *
10.	Water content *
11.	Related impurities: identified impurities unidentified impurities Total impurities
12.	Microbial limits
13.	Uniformity of content in a dose (for emulsions and suspensions)*
14.	Assay
15.	Packaging
16.	Labelling
17.	Transportation
18.	Storage conditions
19.	Shelf life
20.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

7. Tablets

Item №	Section title
1.	Description
2.	Identification (including colorants, preservatives)
3.	Average mass and uniformity of mass
4.	Mass loss on drying or water content *

5.	Talc, aerosil *
6.	Disintegration *
7.	Dissolution
8.	Related impurities: identified impurities unidentified impurities Total impurities
9.	Friability *
10.	Hardness*
11.	The degree of dispersion *
12.	Microbial limits
13.	Residual solvents *
14.	Uniformity of content (in dosage form unit)*
15.	Assay
16.	Packaging
17.	Labelling
18.	Transportation
19.	Storage conditions
20.	Shelf life
21.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

8. Powders (dry dosage forms for external and internal use)

Item №	Section title
1.	Description
2.	Fineness or dispersity* (for external use)*
3.	Identification (including colorants and preservatives)**
4.	Mass contents of the container (for powders in multi-dose containers)
5.	Loss in weight on drying (or water content)*
6.	Related impurities: ** identified impurities unidentified impurities total impurities
7.	Microbial limits or sterility
8.	Uniformity of mass or uniformity of content (for powders in single-dose container)
9.	Assay
10.	Packaging
11.	Labelling
12.	Transportation
13.	Storage conditions
14.	Shelf life
15.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Sections marked with “**” are included for powders intended for internal use.

Introduction of additional sections is allowed.

9. Capsules

Item №	Section title
1.	Description (including capsule shell and contents)
2.	Identification (including colorants and antimicrobial preservatives)
3.	Uniformity of mass
4.	Disintegration*
5.	Dissolution
6.	Loss in weight on drying (or water content)*
7.	Related impurities: ** identified impurities unidentified impurities total impurities
8.	Microbial limits or sterility
9.	Acid and peroxide index (for soft capsules containing oils)*
10.	Uniformity of content *
11.	Assay
12.	Packaging
13.	Labelling
14.	Transportation
15.	Storage conditions
16.	Shelf life
17.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

10. Suppositories (pessaries)

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives)
3.	Average mass and uniformity of mass
4.	Melting point or time of full deformation
5.	Disintegration
6.	Particle size *
7.	Related impurities: ** identified impurities unidentified impurities total impurities

8.	Dissolution *
9.	Microbial limits
10.	Uniformity of content *
11.	Assay
12.	Packaging
13.	Labelling
14.	Transportation
15.	Storage conditions
16.	Shelf life
17.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

11. Soft medicinal forms

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives)
3.	Mass contents of the package or removable mass for single-dose containers
4.	Air-tightness of the container *
5.	Uniformity of consistency *
6.	pH*
7.	Particle size (for the dispersed particles)*
8.	Related impurities: ** identified impurities unidentified impurities total impurities
9.	Microbial limits or sterility Acid and peroxide index *
10.	Antimicrobial preservative content
11.	Assay
12.	Packaging
13.	Labelling
14.	Transportation
15.	Storage conditions
16.	Shelf life
17.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

12. Tinctures

Item №	Section title
1.	Description

2.	Identification
3.	Content of ethanol or relative density
4.	Methanol and 2-propanol
5.	Dry residues
6.	Heavy metals
7.	The volume of the contents of the container
8.	Microbial limits
9.	Assay
10.	Packaging
11.	Labelling
12.	Transportation
13.	Storage conditions
14.	Shelf life
15.	Main pharmacological activity

13. Extracts

Item №	Section title
1.	Description
2.	Identification (including antimicrobial preservatives)
3.	Relative density or the content of ethanol (liquid extracts)
4.	Methanol and 2-propanol (liquid extracts)*
5.	Dry residue (liquid and thick extracts)
6.	Loss in weight on drying (water content) (dry extracts)
7.	Residual solvents *
8.	Heavy metals
9.	The volume of the contents of the container (liquid extracts)
10.	Uniformity of mass (dosed extracts) *
11.	Granulometric composition (dry extracts) *
12.	Microbial limits
13.	Assay
14.	Packaging
15.	Labelling
16.	Transportation
17.	Storage conditions
18.	Shelf life
19.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal substance and dosage form peculiarities.

Introduction of additional sections is allowed.

14. Herbal medicinal material, preparations, packed products (bricks, bags, filter bags)

Item №	Section title
1.	Definition

2.	Identification: a. Macroscopy; b. Microscopy; c. Qualitative and / or histochemical reactions; d. Chromatographic tests (TLC, GC, HPLC and other)
3.	Impurities (parts of plants not to be collected, the particles of raw materials that lost natural colour, crushed, the presence of mold, rot, sustainable foreign smell that does not disappear after ventilation; droppings of rodents and birds, pests, organic and mineral impurities, and other harmful impurities) *
4.	Mass loss on drying (water content)
5.	Disintegration (briquettes and cut-pressed products) *
6.	Uniformity of mass (briquettes and cut-pressed products) * Mass contents of container for the packed raw material
7.	Total ash
8.	Ash insoluble in hydrochloric acid *
9.	Extractives *
10.	Swelling rate *
11.	Bitterness indicator *
12.	Microbial limits
13.	Assay *
14.	Radionuclides (for solid materials)
15.	Packaging
16.	Labelling
17.	Storage conditions
18.	Shelf life
19.	Transportation
20.	Main pharmacological activity

Note. Sections marked with an «*» are included depending on the nature of medicinal herbal material and dosage form peculiarities.

16.11. Annex 11: Official listing of symbols to be used in the formula in the ND for medicinal product in form of a tablet in Russian Federation

Note: the legend symbols are extracted and translated from the Manual on medicinal product expertise, volume II, - M.: Grif & K, 2014. (edition 2019) – 280 p., ISBN 978-5-8125-1865-3 (Name in original language (Russian): *Руководство по экспертизе лекарственных средств. Том II. — М.: Гриф и К, 2014. (издание 2019 г.) – 280 с., ISBN 978-5-8125-1865-3*) [38].

a – weight of test sample

a_0 – weight of standard sample / reference standard

m – mass

G – average tablet mass

n – number of the tablets

L – declared value of the API assay in the tablet

C – concentration of the substance in the solution

V – volume

W – water content

N – dilution factor

P – Assay of the main substance in the standard sample / reference standard in per cent or as decimal

t – substance retention time

t_0 – retention time of the non-sorbent substance

$t_R = t - t_0$ – declared retention time

$k' = (t - t_0) / t_0$ – capacity factor

$R_r = (t_1 - t_2)$ – relative retention time

$r = (t_2 - t_0) / (t_1 - t_0)$ – relative retention

W – peak width at base

$W_{0,5}$ – peak width at half height

p/v – factor – impurity peak height to the height of the lowest point on the curve dividing the impurity peak and main substance peak related to the extrapolated baseline ratio

T – peak asymmetry factor

f – distance between the

S – peak area of the chromatogram of the test solution

S_0 – peak area of the chromatogram of the reference / standard solution

B – ratio of the peak area of the spiked sample to the peak area of the internal standard on the chromatogram of the test solution

B_0 – ratio of the peak area of the spiked sample to the peak area of the internal standard on the chromatogram of the reference / standard solution

For TLC:

R_f – retention factor

$R_s = R_{f1} / R_{f2}$ – relative retention factor

Spectrophotometric methods:

A – absorbance

$A_{1\text{CM}}^{1\%}$ – specific absorbance

b – optical path length

Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Hamburg,

Unterschrift