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Some Specific Regulatory Aspects and Nuances of Drug Products Localization in the Russian Federation

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Abstract

Some important things you should know about drug products localization regulations in Russia. Brief overview of the main local regulations and factual law-enforcement practices that have an impact on your drug products localization projects. According to the Russian Government Decree, № 1289 dated by Nov. 30, 2015 "On limitations of drug products manufactured by foreign manufacturers as participants of Government Procurement" (so called rule "The third wheel"): if two applications at least for the Russian products are submitted, so any third application from some foreign manufacturer (not the Russian product) cannot be accepted. The Russian Federal Law 61 FZ "On drugs circulation" is the basic general legislation Act that regulates Drugs (DP & API) circulation (research & developing, clinical trials, manufacturing, expertise and registration, supply, sale, marketing etc.)

Keywords: Drug Product; Good manufacturing process; Russian drug product; Active pharma ingredient

Abbreviations: QND: Quality Normative Document; DP: Drug Product; LED: Life Essential Drugs; API: Active Pharma Ingredient; EEU: Eurasian Economic Union

Introduction

The state Russian pharmacopoeia

The Quality Normative Document (QND) is specific local quality manual for DP and API that is subject to be expertized by the Russian Regulatory Agency and approved by the Russian Ministry of Health (MoH). QND is Specification+Analytical methods+Shelf life+Storage condition+Packaging. In relation to foreign DP & API, QND Specification is the list of Quality parameters based on Release and Shelf life specifications of producers+some additional quality parameters based on local requirements; the quality parameters norms are on the basis of Shelf life specification. QND is to: any foreign manufacturer must release the registered DP (API) manufactured for Russia based on the approved QND; QND is the basis for local State analytical quality control of DP, from it entered to the Russian market to its expired date.

- Localization is full manufacturing transfer of some foreign registered in Russia Drug Product (=DP) to some Russian manufacturing site.
- The localized drug product (all manufacturing stages) has a status of the Russian Product.
- The Russian product is drug product developed and manufactured by the Russian manufacturer, drug product developed and manufactured by some EEU manufacturer (Russia, Armenia, Belarus, Kazakhstan, and Kyrgyzstan) and foreign localized product.
- Localization subjects are registered drug products+from the State Russian List of Life Essential Drugs (=LED)
- LED drug products only are subjects of Government Procurement.
- Factual law-Enforcement practices: factual requirements and actions of the Russian Regulator that may be in line with official published legislation but it may be not in line with official regulations; sometimes it covers/ compensates insufficiency and shortcoming of local regulatory framework.
- GMP Certificate issued by the Russian Ministry of Industry & Trade Registration dossier for application on DP localization project submission.
- Marketable API registration.

So, you decided to localize your registered in Russia drug product's manufacturing in the territory of the Russian Federation, you found your right strategic Russian manufacturing contract partner and signed all necessary agreements or maybe you already built your own production facility in Russia; analytical methods transfer is already completed successfully; DP test bathes are produced and their quality complies with specification requirements; DP 3 validation batches are produced, their quality complies with specification, and the Russian DP validation batches are under Stability Studies. Please find below some several important things you should know about Drug Product localization procedure, to be successful in this not an easy task.

Registration dossier for localized DP submission to the Russian MoH (Nuance) Administrative files (Module 1)

GMP Certificate issued by the Russian Ministry of Industry & Trade for each of foreign sites.

For each of foreign sites that is registered for DP according to the Russian Registration Certificate: GMP Certificate issued by the Russian MoIT is needed.

If several alternative sites are registered, you need to obtain GMP Certificate issued by the Russian MoIT not only for site-donor of technology transfer, but also for all alternative sites [1-10].

According to the draft of an Amendment to the Federal Law "On

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drug circulation", it will be possible to submit the dossier without GMP Certificate issued by the Russian MoIT but under condition if the MoIT Decision about GMP inspection date is agreed and available. The submitted application could be approved by the Russian MoH under condition if the GMP Certificates issued by the Russian MoIT for all the registered sites are available [10-15]. June 2018 is expected date of the mentioned Amendment implementation. For more information, please see the Table 1 brief overview of the main local normative acts that have an impact on DP localization projects.

Registration dossier for localized DP submission to the Russian MoH The list of technical regulatory documents (Module 3, 32P part, 32S part)

The general list of recommended documents and brief overview of the main local normative acts that have an impact on DP localization projects (Tables 1 and 2) for more information regarding the local requirements to stability study for localized DP (the point 10).

Timeline

- 90 workdays (about 5 months) without stop clock.
- Stop clock: the time needed for DP sample and standards substance for local laboratory expertise ordering, delivering and submitting & the time needed for RUS HA' deficiency letters answering.
- Average factual timeline: 9 months +/- 2 months (it depends).

API registration is a necessary condition for the registered Russian drug product production and sale

It is very important to submit an application on API registration as soon as possible, because factual timeline for API registration is much longer than localized DP registration.

In accordance with the Federal Law FZ-61 "On drug circulation":

- The Russian registered DP (including the foreign localized DP) can be produced from the «registered» API extremely. "Registered API" is =API that is included into the Russian Register (GRLS) as a separate registry record.
- Foreign API included into the Russian Register (GRLS) only can be imported to the Russian Federation for the purpose of the registered localized DP production.
- Marketable API is subject to be registered.
- Marketable API should be included into the GRLS on the basis of producer's application and based on the submitted dossier examination expertise & based on pharmaceutical (laboratory) expertise of API quality. As the result of the submitted application approval: the approved Quality Normative Documents for API.

No	Act of Law	Law Content/ Requirements	Factual law-enforcement practices	Notes
1	FZ-61 "On drug circulation" 09.2010/ Addendum FZ-429 12.2014, come into force 01.01.2016	New regulation: CTD format (Modules 1,3, 4,5)	Only general list of docs is available for each of Modules	Sources of our understanding what are RUS HA requirements to the dossier building: • MoH Expertise Centre guidance (semi-official status) • Professional associations (AIPM, SPFO) • RUS Ph. (General monographs) • Factual low-enforcement practices • ICH guidelines • Eurasian Economic Union developing guidelines NB! FZ-61/Addendum FZ-429 (come into force 01.01.2016) provides the option of MoH Scientific Advice. But this option doesn't work. What is the reason why the RUS MoH don't elaborate on FZ-61 (there are not any legal instruments of the 2nd and 3rd levels): • The RUS HA have to develop legal instruments of the 2nd and 3rd levels for local legislation (FZ-61) and new EEU legislation in parallel • EEU legislation is supranational legislation • EEU legislation is the higher level than local regulations • Local regulations are subject to be in line with EEU legislation in the future (except regulations which remain at national level) • The RUS HA doesn't have any resources to elaborate on local FZ-61 and EEU regulations in parallel
			There are not any requirements to CTD format	
	CTD format		There not any guidelines to building of CTD format dossier	
2	The Order # 725n of the MoH (21.09.2016): "Administrative Regulations for drug circulation"	=The extract from the FZ 61 "On drug circulation"/ Addendum FZ-429 (come into force 01.01.2016)	Only general list of docs is available for each of Modules	
			There are not any requirements to CTD format.	
	The list of docs, state due, time line, stop clocks		There are not any guidelines to building of CTD format dossier	
3	FZ-61 "On drug circulation" 2010/ Addendum FZ-429 12.2014, the articles 30 and 31, come into force 01.07.2015	Variation Procedure-description 2 general types: declarative variation (not subject to be expertized, 30 work days) and variations are subject to be expertized (90 work days)	There is not any information about variations classifications, types, and the list of docs (modules 3,4,5).	
	Variation procedure		The electron application on GRLS for Variations corresponds to the electron application for DP Registration. The Applicant should determine the scope of the involved documents and data independently.	
4	The Order # 959n of the MoH (13.12.2016) "On Variations Classification"	The list of Variations that are subject to be expertized (42 positions)	There is not any information about variations detailed classifications, types and the list of docs (modules 3, 4, 5).	
		The list of Variations that are not subject to be expertized (11 positions)		
	Variation procedure	For each of 53 positions: what Module (s) of 1, 3, 4, 5 Modules should be presented by the Variation dossier		
5	The Order # 429n of the MoH (12.07.2017):	=The extract from the FZ 61 "On drug circulation"/ Addendum FZ-429 (come into force 01.01.2016)	Only general list of docs is available for each of Modules	
			There are not any requirements to CTD format.	
	The list of docs needed for drug products and API registration, renewal, variations within CTD format		There are not any guidelines to building of CTD format dossier	

<table>
<tr><td rowspan="5">6.1</td><td rowspan="6">FZ-61 “On drug circulation” 2010/ Addendum FZ-429 (12.2014), come into force 01.01.2016

RUS GMP for DP</td><td rowspan="5">GMP Certificate issued by the Russian MoIT for each foreign site that is involved in DP production is needed to apply: DP registration, renewal, any variation (except declarative variation)</td><td>Decision No. 57 of the Government of the Russian Federation of 03 Dec. 2015 “About GMP compliance for drugs manufacturers”</td><td rowspan="5">The following Addendum to FZ-61 (No: 327290-7) on GMP (regulatory procedures improvement) was approved by RF Parliament on May, 17-2018; according to the procedure, the Addendum can be expected to come into force on June 2018 :
The following Applications for a submission only need the RUS GMP Certificate or the copy of the Russian MoIT Decision about the agreed Inspection date:
NDA, ANDA, Renewal, CMC Variation (manufacturing site replacement, manufacturing site addition, Specifications change, Analytical methods change).
Manufacturing site replacement or manufacturing site addition (including localization):
For a submission: GMP Certificate for each of old (to replaced)/current (to be added) and new (applied) manufacturing sites issued by the Russian MoIT or the copy of the Russian MoIT Decision about the agreed Inspection date of old (to replaced)/current (to be added) and new (applied) manufacturing sites
The submitted Variation could be approved under condition if the RUS GMP certificates for each of old (to replaced)/current (to be added) and new (applied) manufacturing sites issued by the Russian MoIT are available by the expected approval date + 180 workdays
NDA, ANDA, Renewal, Specification (s) changes, Analytical methods changes:
For a submission: GMP Certificate for each of foreign manufacturing sites issued by the Russian MoIT or the copy of the Russian MoIT Decision about the agreed Inspection date of each of foreign manufacturing sites
The submitted NDA, ANDA, Specification (s) changes, Analytical methods changes: could be approved under condition if the RUS GMP certificates for each of foreign manufacturing sites issued by the Russian MoIT are available by the expected approval date + 180 workdays
All other CMC, Labeling, Declarative Variations do not require GMP Certificate for foreign manufacturing sites issued by the Russian MoIT for a submission & approval</td></tr>
<tr><td>The MoIT Order # 916 (GMP) with addendum come into force 18.12.2015</td></tr>
<tr><td>The MoIT Order # 9 “On state due for manufacturing sited inspection” come into force 11.01.2016</td></tr>
<tr><td>The MoIT Order # 261 “On Application Form for foreign manufacturers in order to apply GMP inspection” come into force 04.02.2016.</td></tr>
<tr><td>6.1.1.</td><td>GMP Certificate issued by the Russian MoIT for each foreign site that is involved in DP production is needed to apply: any variation (except declarative variation)</td><td>NB! In order to apply any variation: RUS GMP certificates are needed for each registered foreign sites (any stages except quality control stage) that are involved in introduction of DP registered in Russia.</td><td>NB! It is impossible to apply any Variation for registered DP if the RUS GMP certificate is available but DP is not presented by the Attachment “The list of DP” to the GMP Certificate (if any)</td></tr>
<tr><td rowspan="6">6.2</td><td>The MoIT Order # 3667 dated by 20.10.2017 (The Changes to the Order MoIT № 1714 dated by 26.05.2016); come into force 11.2017</td><td>The availability and quality parameters of GMP Inspection State Services are defined clearer</td><td rowspan="2">Since 11.2017:
CAPA plan is not meant as the additional documents that could be taken into account by the MoIT in order to reach a decision to issue or refusal to issue the GMP Certificate</td><td rowspan="6">As CAPA is not accepted by the MoIT since 11.2017 in order to reach a decision to issue or refusal to issue the GMP Certificate, so any foreign manufacturer needs to make every possible effort to close the identified observations fully or partially and/or to minimize the identified observations grade during the inspection and during 21 calendar days after the inspection, in order to avoid negative decision of the MoIT (GMP Certificate refusal)
It is unclear to the current moment what will be the factual law – enforcement practices:
Will be it possible to require the MoIT to confirm the agreed Inspection date only after that the Addendum to FZ-61 (№ 327290-7) (see the point 6.1) comes into force or this opportunity will be available regarding any applications on GMP inspections submitted before</td></tr>
<tr><td>Explanation of the MoIT regarding actions taken by foreign manufacturers based on the results of the GMP inspection of manufacturing sites, dated by February 18, 2018</td><td rowspan="3">Foreign manufacturer can submit any additional materials and data, justifications and explanations to the State Institute of the good practices during 21 calendar days, based on the draft results of the GMP inspection that were voiced by the Inspectorate during the inspection.</td></tr>
<tr><td>Explanation of the MoIT regarding actions taken by foreign manufacturers based on the MoIT refusal to issue the GMP certificate, dated by February 08, 2018</td><td>CAPA plan should be submitted to the MoIT under condition if the foreign manufacturer was refused in GMP Certificate issue.</td></tr>
<tr><td>The draft of the Addendum to the Order MoIT № 1714 for the purpose of realization of the MoIT Order # 3667 (expected implementation date is June 2018)</td><td rowspan="2">The point No 491 of the Order MoIT No 1714 will be added:
The MoIT provides the applicant with the copy of the Decision to hold an GMP Inspection of the foreign manufacturing site</td></tr>
<tr><td>RUS GMP for DP</td></tr>
</table>

6.3	FZ-61 “On drug circulation” 2010/ Addendum FZ-429 912.2014), come into force 01.01.2016 RUS GMP for DS	GMP Certificate issued by the Russian MoIT for foreign site of DS is needed to apply: DS registration, renewal, any variation (except declarative variation)		The following Addendum to FZ-61 (№ 327290-7) on GMP (regulatory procedures improvement) was approved by RF Parliament on May, 17-2018; according to the procedure, the Addendum can be expected to come into force on June 2018 : It is possible to apply API registration if the MoIT Decision about GMP inspection date is agreed and available. API registration application could be approved under condition if the RUS GMP certificates for all the involved sites are available. The point 6.2 (see above) is valid for DS as well
7	FZ-61 “On drug circulation” Articles 18, 19, 23, 27, 33: DP registration	The Module 3 of CTD consists of 3S part and 3P part. 3S and 3P parts are subject to be expertized. API and DP are subjects to be expertized in laboratory (pharmaceutical laboratory expertise) The following information about API should be included in the State Register (GRLS) for the registered DP: API name (INN or trade), API producers(s) and its address, the reference to quality standard (pharmacopoeia monograph or RUS ND or foreign producer’s ND), Shelf life, storage condition	The part 3S is not subject to be expertized. API samples and standards for API are not required; pharmaceutical laboratory expertise is not performed for API. MoH FGBU Expert Report for DP regarding API (3S part) presents the following information: it is not a subject to be examined	The State Register (GRLS) Record for the registered DP presents the following information about API: API name, API producer and its address, the reference to API quality standard (for example, foreign producers ND = producer’s specifications & test procedures), shelf life, storage condition. 3S part of DP Module 3 is not subject to be expertized. ND for API as the part of DP dossier (3S part) is not subject to be expertized. API samples quality is not examined. DP Expert Report issued by the MoH FGBU does not provide any information about 3S part and API quality. For foreign DP: 3S part of the producer’s DP dossier is accepted by the RUS HA/=API is approved within the DP registration. For domestic DP (including the localized in Russia DP): 3S part of the DP Module 3 is not examined. The Russian producers provide CoA for API from its manufacturer and incoming control CoA for API from the Russian site only. API is subject to be registered in accordance with separate procedure. The Russian registered DP (including the localized DP) can be produced from the registered API extremely. Domestic DP or localized DP can be registered without previous API registration.
8	FZ-61 “On drug circulation” Articles 33,34,45,47: Marketable DS “registration” (=API included in the State Register)	The Russian registered DP can be produced from API included into the Russian Register (GRLS) extremely. DP and API included into the Russian Register (GRLS) only can be imported to the Russian Federation. API cab be included into the GRLS based on producer’s application and based on the pharmaceutical expertise of API quality. The following information about API should be included in the State Register (GRLS) as the separate API Register Record: API name (INN or trade), API producers(s) and its address, the reference to quality standard (pharmacopoeia monograph or ND), Shelf life, storage condition, the date of the including the approved ND into the Register	API is subject to be “registered” (to be included into the State Register): For any domestic DP: registered domestic DP can be produced from the registered API extremely. For any localized DP: registered localized DP can be produced from the registered API extremely. Only registered foreign API can be imported to the Russian Federation. Unregistered API can be imported to the Russian Federation for API registration, domestic DP registration, localized DP registration on the basis of MoH Import License Based on the RUS GMP rules: DP quality that is produced by the overseas producers for the Russian Federation should correspond to the dossier approved by the RUS HA. If API is registered in Russia (=RUS ND for API is included into the RUS state Register), so Global DP should be produced from API that is released in accordance with the RUS ND for API	NB! API included into the Russian Register (GRLS) for the purpose of the registered localized DP production, impact on Global DP as well. Based on the RUS GMP rules: DP quality that is produced by the overseas producers for the Russian Federation market should correspond to the dossier approved by the RUS HA. So, Global marketed DP should be produced from API that is released in accordance with the RUS approved ND for API.
	FZ-61 “On drug circulation” DP registration (3S Part) DS registration	The list of Module 3 docs needed for DP registration (3S Part) and for DS registration is the same		

	FZ-61 "On drug circulation" Articles 33, 34, 45, 47: Marketable DS "registration" (= API included in the State Register) NB! Expected draft of Addendum to the FZ-61 that is initiated by the Russian producers and senators	The suggestions are the following: - Not to "register" API separately - To register API within DP registration - To import API for the registered DP production based on the DP Register Record/ Information about API	Draft of Addendum to the FZ-61 is in line with FZ-61 harmonization procedure with new EEU regulations EEU regulations don't provide any separate API registration EEU provides for 3S Part of the Module 3 expertise within DP registration. EEU regulations do not provide for EEU GMP inspection of API sites. It seems, it relates to NDA or GDA only, not to Variations procedure	It seems there is not any impact on ongoing localization projects because: - The registered DP, that are subject to be localized, were registered in Russia without any API (3S Part) examination expertise - The registered API is API that is approved by the RUS HA on the basis of 3S Part expertise, ND for API expertize and approval, API sample quality laboratory examination
9	The Russian Pharmacopoeia XIII Ed., come into force 01.01.2016 The Order # 771 of the MoH (29.10.2015) "On Ratification of Ph. General monographs and special monographs " The Order # 1037 of the MoH (21.12.2017) "On Changes to the Order # 771 "	Normative Documents for DP and API registered or submitted before 2016, need to be updated in accordance with RUS Ph. XIII requirements: General monographs: before 01.2018 Special monographs: before 01.2019 General monographs: before 01.2019		For example, the following general methods of RUS Ph. XIII are harmonized with EP methods: Clarity, Color, Visible particles, Invisible particulate matters, Mibio tests, Extractable volume (volumetry), Endotoxins, Disintegration, Dissolution, Uniformity of dosage units etc. Nevertheless, there are a lot of some special local requirements to DP/ API quality
10.1	DP Localized Projects Stability Study (= SS): Registration Long-Term SS and Follow-Up (On-going) SS, Storage Condition	At the Storage Condition registered in Russia		The registered Storage Condition for DP in Russia may be different from those approved in the country origin due to different requirements and approaches to the Stability Study and the Labeling accordingly. For example, the Storage Condition for DP in the country origin (ICH Region) for Climatic Zones I-IV is "No special storage condition is required". The registered storage condition in Russia (Climatic Zone II) "Not higher than at 30 ^{0}C" because the temperature storage condition should be limited in accordance with the RUS Ph. requirements. NB! So, in such case you need to search/ confirm the localized DP long-term stability at 30^{0}C/65% (CZ IVa) but not at 25^{0}C/60% (CZ II)
10.2	DP Localized Projects Stability Study: The Russian Pharmacopoeia XIII (General Monograph 1.1.0009.15 "DP and DS Shelf life, stability testing") Stability Program, Long-term registration stability study, Sampling time points	Long-term registration stability study in accordance with RUS Ph. XIII: Time points: 0, 3, 6, 9, 12, 18, 24, 30, 36, 48, 60	The additional 30-months' time point for long-term stability study is restricted to the Russian manufacturing. This RUS Ph. requirement applies to the products produced by the Russian sites including transfer Russian products. This requirement does not apply to Global products (=overseas product).	The additional 30-months' time point for long-term stability study in accordance with RUS Ph. XIII does not apply to Global products (= overseas product). There is the National Standard "Stability Testing of new DS and DP, general provisions", come into force 10.2016; made by the Russian Federal Agency for technical regulations and Metrology. This Standard is identical to ICH Q1A:2003. The scope is: for international reg. dossier building within the framework of the Russian original DS and DP application on registration to the HA of the ICH region countries. At the current moment, the RUS Ph. is higher than this Standard for the Russian market. In the future, when we guide by the EEU guidelines, which are adequately harmonized with ICH guidelines, we will be able to remove the 30 months-point from the long-term stability study program for any localization DP.
10.3	DP Localized Projects Registration Stability Study Program: The list of testing quality parameters and their testing frequency		The Stability Program for Global DP (based on ICH guidance) is accepted by the Russian HA	
10.4	DP Localized Projects Registration Stability Study Program: Accelerated & Long-Term (& Interim if any) stability data that is needed at the submission date		The Stability data based on ICH guidance is accepted by the Russian HA for the localized DP	In general case, Solid dosage forms (stable API): 3 months Accelerated + 3 months Long-Term Injection dosage forms (stable API): 6 months Accelerated + 6 months Long-Term
10.5	DP Localized Projects Stability Study Follow-Up (On-going) Stability (GMP stability) Program The MoIT Order # 916 (GMP rules)	1 batch per year Follow-Up stability should identify any trends to DP quality changes.	Follow-Up stability Time points: 0, 12, 24, 36, 48, 60 Quality parameters testing: All quality parameters in accordance with Shelf Life specification, for each of time points	There are not any several (reduced) testing programs for Follow-Up (GMP) stability study. All DP (API) quality parameters should be controlled in accordance with Shelf Life specification, for each of time points. This requirement covers and local (localized) DP both Global DP produced for Russia.

11	FZ-61/ Addendum FZ-425 dated by 28.12.2017 Track & Trace (Serialization & Aggregation)	Obligatory identification marking DP consumer packaging, will come into force staring from 01.2020	NB! DP–members of the State Life Essential Drugs (LED) List could be involved in obligatory track & trace marking before 01.2020	Usually, all localized DP are members of the LED list
12	The localized DP Feasibility of DP Validation batches releasing to the Russian market	There are not any local regulations that regulate this issue. There are not any local regulations that prohibit to sell the validation batches	It is actually possible to release DP validation batches to the Russian market	DP validation batches release to the market reduces launch time It is DP MAH responsibility. No authorized RUS HA's permit for DP issue to the market is required. The open question: Is it possible or not to issue DP validation batches to the market if API is not registered yet?
13	The localized DP The use of the registered API for the localized DP production		The Russian manufacturers can use mix of APIs of some different Lots for one batch DP production, based on their internal SOP that are based on their internal quality risks assessment This practice is neither authorized nor prohibited by the Russian MoIT & Roszdravnadzor	The foreign MAH needs to take into account the fact described in the column № 3 of the point 13. If the described approach is not in line with your Company Quality System, you need to provide for the relevant provisions of the Quality Agreement with your Russian manufacturing partner.

Table 1: Brief overview of the main local normative acts that have an impact on Drug products localization projects.

CTD 3.2.P Part				
CTD code	**CTD Title**	**Global TRD**	**RU TRD Site-Donor**	**Local guidelines/ Comments Site-Recipient**
P	DRUG PRODUCT	-	-	-
P.1	Description and Composition of the Drug Product	-	-	-
	Description of DP Exact Composition of DP	-	-	-
P.2	Pharmaceutical Development	-	-	-
P.2.4	Container Closure System	-	-	-
P.3	Manufacture	-	-	Guarantee Commitment about unchanged manufacturing process. Information about any differences between manufacturing processes of the donor and recipient sites should be specified and explained/ justified
P.3.1	Manufacturer (s)	-	-	All manufacturers including the Russian site (s) should be presented.
P.3.2	Batch Formula	-	-	Any differences should be specified and explained/justified =guarantee of the unchanged quality of DP
P.3.3	Description of Manufacturing Process and Process Controls	-	-	Any differences should be specified and explained/ justified = guarantee of the unchanged quality of DP
P.3.4	Controls of Critical Steps and Intermediates	-	-	Any differences should be specified and explained/ justified =guarantee of the unchanged quality of DP
P.3.5	Process Validation and/or Evaluation	-	-	Any differences should be specified and explained/ justified =guarantee of the unchanged quality of DP
P.4	Control of Excipients	-	-	-
P.4.1	Specification	-	-	CoA from manufacturer/supplier and CoA incoming control from the Russian site
P.4.2	Analytical Procedures	-	-	-
P.4.5	Excipients of Human or Animal Origin	If any	-	-
P.4.6	Novel Excipients	If any	-	-
P.5	Control of Drug Product	-	-	-
P.5.1	Specification(s) Release and Shelf life	-	-	Normative Document
P.5.2	Analytical Procedures	-	-	Normative Document
P.5.3	Validation of Analytical Procedures	-	-	Transfer of analytical methods (Protocol, results, conclusion) in accordance with release and shelf life specif. methods (if differ) Verification of pharmacopoeia methods
P.5.4	Batch Analyses	-	-	CoA for 3 validation batches produced by the Russian site

	Proof of Product Equivalence after change of production site	-	-	-
	Comparative batch analysis data	-	-	For all dosage forms
P.5.4.12	Comparative dissolution test	-	-	For oral dosage forms additionally
P.5.6	Justification of Specifications	-	-	-
P.6	Reference Standards or Materials	-	-	It should be specified what RS is used: working or/and pharmacopoeia (EP, USP etc.) CoA for all RS
P.7	Container Closure System	-	-	Any differences (if any) should be specified and explained/ justified = guarantee of the unchanged quality of DP
	Primary packaging materials Functional secondary packaging materials (if any) Description, Specifications, test procedures	-	-	CoA from manufacturer/supplier and CoA incoming control from primary packaging materials from the Russian site
P.8	Stability	-	-	-
P.8.1	Stability Summary and Conclusion	-	-	-
P.8.1.01	Stability Summary and Conclusion	-	At the Submission date, in general case Solid dosage forms: 3 months Accelerated + 3 months Long-Term Injection dosage forms: 6 months Accelerated + 6 months Long-Term	It should be made the conclusion about the stability testing results (accelerated stability data and long-term stability data for the purpose of submission) for new DP (produced by the site-recipient) are comparable with the same results for old DP (produced by the site-donor)
P.8.1.02	Shelf life	-	-	-
P.8.2	Post-Approval Stability Protocol and Stability Commitment	-	-	-
P.8.3	Stability Data	-	-	-
P.8.3	On-going (Follow-Up/ GMP) Stability Data	-	-	At the registered storage condition in Russia
CTD 3.2.S Part				
S	Drug Substance	-	-	-
S.1	General information	-	-	-
S.1.1	Nomenclature	-	-	One of sections of the Normative Document
S.1.2	Structure	-	-	One of sections of the Normative Document
S.2	Manufacture(s)	-	-	-
S.2.1	Manufacturer(s)	-	-	One of sections of the Normative Document
S.4	Control of Drug Substance	-	-	-
S.4.1	Specification	-	-	CoA from manufacturer/supplier and CoA incoming control from the Russian site
S.4.2	Analytical procedures	-	-	-
S.7	Stability	-	-	-
S.7.1	Stability Summary and Conclusion	-	-	-

Table 2: The general list of recommended technical regulatory documents for DP LOCALIZATION procedure/CMC VARIATION/FULL MANUFACTURING TRANSFER to the Russian site.

- The dossier for API registration should include GMP Certificate issued by the Russian MoIT for API foreign manufacturing site.
- According to the draft of an Amendment to the Federal Law "On drug circulation", it will be possible to submit the dossier without GMP Certificate issued by the Russian MoIT but under condition if the MoIT Decision about GMP inspection date is agreed and available. The submitted application could be approved by the Russian MoH under condition if the GMP Certificates issued by the Russian MoIT for API registered sites are available. June 2018 is expected date of the mentioned Amendment implementation.
- The following information about API should be included in the State Register (GRLS) as the separate API Register Record: API name (INN or trade), API producers(s) and its address, the reference to quality standard (pharmacopoeia monograph or QND number), Shelf life, storage condition, the date of the QND including into the Register (GRLS).

Based on the factual law-Enforcement practices:

- Domestic DP or localized DP can be registered without previous API registration
- API is subject to be registered in accordance with separate procedure
- API included into the Russian Register (GRLS) for the purpose of the registered localized DP production, impact on Global DP as well (if any)!. Based on the RUS GMP rules, DP quality that is produced by the overseas producers for the Russian Federation market should correspond to the dossier approved by the RUS HA. Therefore, Global marketed in Russia DP should be produced from API that is released in accordance with the RUS approved QND for API.

Disputable question (blank spot on the local regulations)

What is a "marketable" Drug Substance (DS) that is subject to be

registered? Is it for sale to any interested legal body only? Or/ and, is it for own purposes as well?

For more information, please see the (Table 1) "Brief overview of the main local normative acts that have an impact on DP localization projects" (the points 7, 8).

Timeline:

- 60 workdays (about 3 months) without stop clock.
- Stop clock: the time needed for API sample and reference standards for local laboratory expertise ordering, delivering and submitting & the time needed for RUS HA' deficiency letters answering.
- Average factual timeline: from 9 months to 24 months (it depends).

Conclusion

In this content we have mentioned the different types of specific regulatory aspects and nuances of drug products localization in the Russian Federation. The Quality Normative Document (QND) is specific local quality manual for DP and API that is subject to be expertized by the Russian Regulatory Agency and approved by the Russian Ministry of Health (MoH). Drug product production and sale mainly depends on registration of API. Technical regulatory documents and the timeline required for the registration are essential elements for the localization of drug products in Russian Federation.

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