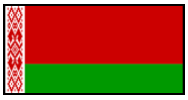
Update on Regulatory Approval Timelines and Local Requirements in Selected Countries of the Former "Eastern Block"

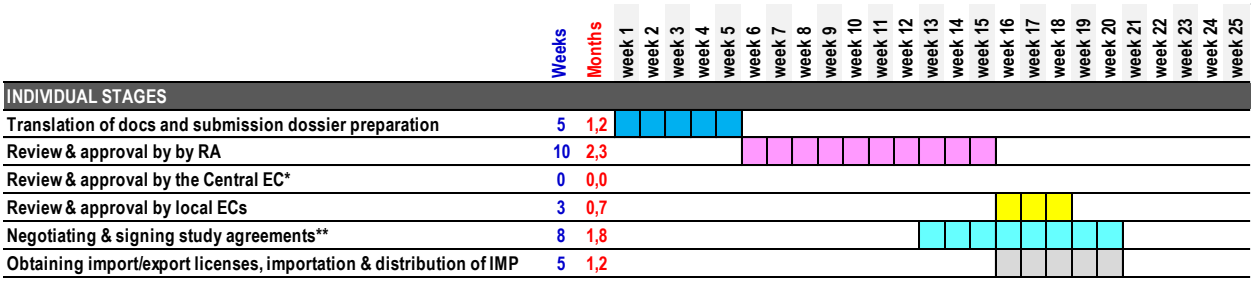
The complexity of regulatory approval pathways and time to "first site initiation" play a significant role in the decision as to which countries to include in an international clinical trial. As these parameters periodically change, this white paper is intended to give an update on both the timelines and the existing or emerging requirements that Cromos Pharma faces in its countries of operation.

BELARUS



Study Start-Up Timelines Chart

	Weeks	Months
INDIVIDUAL STAGES		
Translation of docs and submission dossier preparation	5	1,2
Review & approval by by RA	10	2,3
Review & approval by the Central EC*	0	0,0
Review & approval by local ECs	3	0,7
Negotiating & signing study agreements**	8	1,8
Obtaining import/export licenses, importation & distribution of IMP	5	1,2
SUMMARY		
From submission till study approval	13	3,0
From submission till first site initiation	15	3,5
From start of work till first site initiation	20	4,6



* no obligatory expertise of a Central Ethics Committee

** agreements with clinics only; no study contracts with PIs are allowed; study agreements need to be approved by the RA

Noteworthy Local Requirements

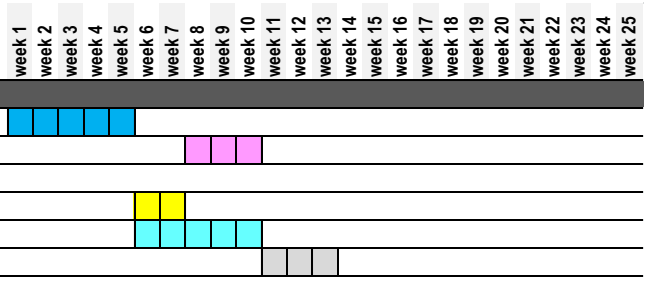
Belarus has favorable start up timelines, which could be further optimized if not for the required approval of site financial agreements by the Ministry of Healthcare, which takes around a month. While local legislation doesn't allow for direct agreements with the investigators, the sites' financial agreement can only be submitted for review by the Ministry of Healthcare after the study approval has already been issued.

In comparison to the review and approval procedure of financial agreements, reviews by the local ethics committees take less time, around 2-3 weeks on average. As the Central / National Ethics Committee doesn't exist, local ethics committees (LECs) are the only ethical safeguards for clinical trials in Belarus.

GEORGIA

Study Start-Up Timelines Chart

	Weeks	Months
INDIVIDUAL STAGES		
Translation of docs and submission dossier preparation	5	1,2
Review & approval by by RA	3	0,7
Review & approval by the Central EC*	0	0,0
Review & approval by local ECs	2	0,5
Negotiating & signing study agreements	5	1,2
Obtaining import/export licenses, importation & distribution of IMP**	3	0,7
SUMMARY		
From submission till study approval	5	1,2
From submission till first site initiation	8	1,8
From start of work till first site initiation	13	3,0



* not applicable in Georgia

** no importation license needed in Georgia

Noteworthy Local Requirements

When it comes to fast and seamless launch of a clinical trial, Georgia remains the champion among other former Soviet republics, and among former Eastern Bloc countries it can only be rivaled by Hungary.

Like in Belarus, there is no Central/National Ethics Committee and the study documents are subject to examination by ethics committees at the trial sites (LECs). However, in contrast to many other locales, the review and approval by the local ethics committees precedes the submission of study-related documents to the regulatory authorities (RA).

The total time to first site initiation is further shortened by the fact that neither special importation license for the IMP, nor the exportation license for biological samples is required and both importation and exportation are done on the basis of the study approval issued by the RA.

HUNGARY

Study Start-Up Timelines Chart

	Weeks	Months	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9	week 10	week 11	week 12	week 13	week 14	week 15	week 16	week 17	week 18	week 19	week 20	week 21	week 22	week 23	week 24	week 25
INDIVIDUAL STAGES																											
Translation of docs and submission dossier preparation	5	1,2																									
Review & approval by National Institute of Pharmacy (NIP)	6	1,4																									
Review & approval by the Central EC*	4	0,9																									
Review & approval by local ECs**	0	0,0																									
Obtaining import/export licenses, importation & distribution of IMP***	3	0,7																									
SUMMARY																											
From submission till study approval	6	1,4																									
From submission till first site initiation	9	2,1																									
From start of work till first site initiation	14	3,2																									

* Submission is performed to NIP only (forwarded by NIP to the Central EC); duration of review is irrelevant; done in parallel and within the timeframe of the RA review

** Local ECs are not involved into the study documents review and approval process

*** No importation license needed if imported from the EU

Noteworthy Local Requirements

Hungary keeps the record in the region for fast and smooth launch of clinical trials.

The studies are usually approved before expiration of the Directive-defined 60-day period; the Central EC review and approval run in parallel and take even less time, while LECs are only tasked with overseeing the trials at the appropriate sites and do not play any role in the study approval process.

As a result, it takes around 3 months to have a clinical trial up and running in Hungary, including the time for translation of essential documents and assembling the submission dossier.

LITHUANIA

Study Start-Up Timelines Chart

	Weeks	Months	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9	week 10	week 11	week 12	week 13	week 14	week 15	week 16	week 17	week 18	week 19	week 20	week 21	week 22	week 23	week 24	week 25
INDIVIDUAL STAGES																											
Translation of docs and submission dossier preparation	5	1,2																									
Review & approval by the RA	8	1,8																									
Review & approval by SDPI*	8	1,8																									
Review & approval by the Central EC	8	1,8																									
Review & approval by local ECs**	0	0,0																									
Negotiating & signing study agreements	12	2,8																									
Obtaining import/export licenses, importation & distribution of IMP***	4	0,9																									
SUMMARY																											
From submission till study approval	9	2,1																									
From submission till first site initiation	13	3,0																									
From start of work till first site initiation	18	4,1																									

* SDPI = State Data Protection Inspectorate

** irrelevant; done in parallel and within the timeframe of the RA review

*** No importation license needed if imported from the EU

Noteworthy Local Requirements

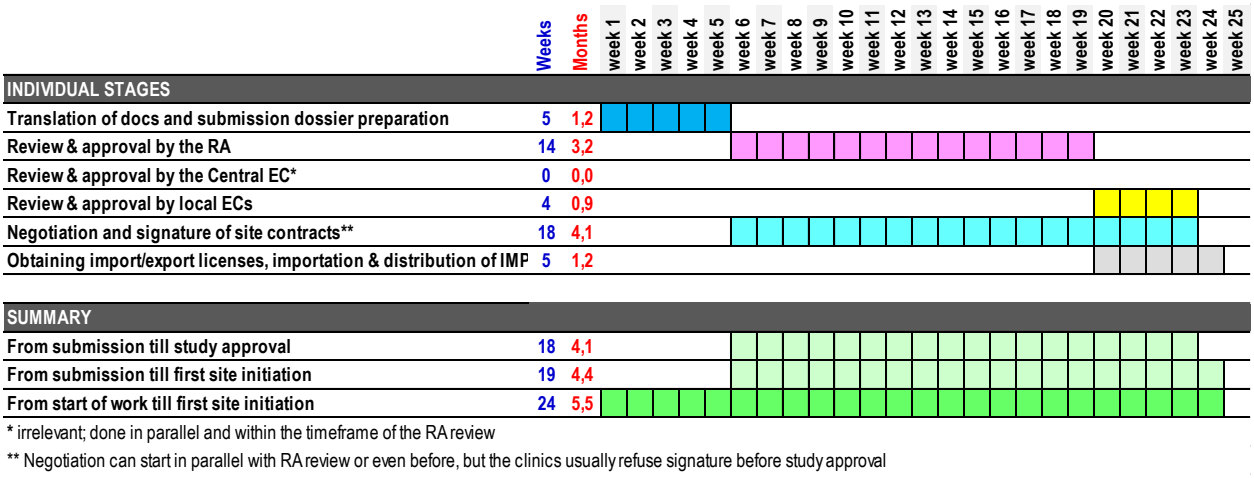
As in other EU countries, the national legislation has been harmonized with the EU Directive 2001/20/EC however, while theoretically the duration of study dossier review by the RA should not exceed 60 days, the real timelines in Lithuania are less favorable. The process is aggravated by the additional local bureaucratic burden – the so-called State Data Protection Inspectorate (SDPI), which is tasked with ensuring high level of data protection and privacy. The SDPI reviews study documents to make sure that not only health and well-being but also patients' data privacy are diligently safeguarded. In practice this translates into prolonging of the total study approval period.

The good news is that separate submissions to LECs are not needed and the Lithuanian Bioethics Committee forwards the application and all accompanying documentation to the appropriate LECs itself.

It should be noted than study approval and start-up times in the neighboring Latvia and Estonia are shorter that in Lithuania because the review by the SDPI is not required there. **Estonia is the regional leader with an average of around 45 days for RA review and approval.**

RUSSIA

Study Start-Up Timelines Chart



* irrelevant; done in parallel and within the timeframe of the RA review

** Negotiation can start in parallel with RA review or even before, but the clinics usually refuse signature before study approval

Noteworthy Local Requirements

In order to receive a marketing approval for a medicinal product in Russia such product must be tested locally as part of an international registration trial. In a situation where local patients didn't participate in a pivotal trial, the Ministry of Health requires that the late stage trial is repeated in Russia. The required local trial is usually smaller and less strenuous that a customary registration trial, but it does add both cost and time to the overall registration process.

The total duration of the study start-up period in Russia is determined by the length of the review of the submitted study documents by the RA. It should be noted that local ethics committees (whose approvals are not required by the federal law) in most cases refuse to provide a favorable opinion or even accept documents for review unless the clinical trial is approved by the RA.

As a rule, financial agreements with the sites cannot be finalized and signed without the study approval either.

Review by the Central EC does not exist as a separate process and is done in the framework of the RA review.

Recently adopted changes to the legislation have somewhat improved the regulatory environment by softening experience requirements for the investigators (from 5 down to 3 years of clinical trial experience), differentiating more clearly the processes of registration and of clinical trials of medicinal products and simplifying preparation of study application. The largest impact on start-up timelines can be expected in certain categories of medications, such as orphan drugs, first three generic drugs in class intended for registration in Russia and any drugs for children.

POLAND

Study Start-Up Timelines Chart

	Weeks	Months	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9	week 10	week 11	week 12	week 13	week 14	week 15	week 16	week 17	week 18	week 19	week 20	week 21	week 22	week 23	week 24	week 25
INDIVIDUAL STAGES																											
Translation of docs and submission dossier preparation	7	1,6																									
Review & approval by the RA	12	2,8																									
Review & approval by the Central EC*	11	2,5																									
Review & approval by local ECs**	3	0,7																									
Negotiating & signing National Coordinator's study agreements***	6	1,4																									
Negotiating & signing other study agreements****	17	3,9																									
Obtaining import/export licenses, importation & distribution of IMP*****	5	1,2																									
SUMMARY																											
From submission till study approval	14	3,2																									
From submission till first site initiation	18	4,1																									
From start of work till first site initiation	24	5,5																									

* the EC of the National Study Coordinator is considered to be the Central EC

** the local ECs are responsible for giving within 14 days an opinion to the Central EC on the investigator and the site facilities

*** it is a must to finalize at least National Coordinator's contracts (with PI & Institution) to be able to make a submission;

**** Agreements with other sites can be submitted as substantial amendment after study approval (but not during review by the RA)

***** No importation license needed if imported from the EU

Noteworthy Local Requirements

As in the case of Lithuania, in theory the RA review timelines do not differ from the ones described in Directive 2001/20/EC, however the review of the submitted dossier begins only after the RA has checked the study dossier for completeness and accepted it. Hence, the total actual time from submission to approval in Poland ends up to be more protracted than in the neighboring CEE countries.

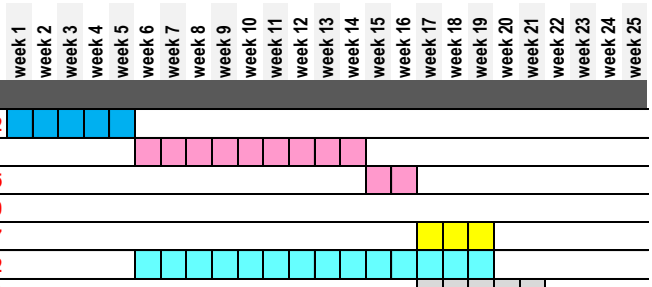
Another factor that contributes to longer start-up times is the requirement for inclusion into the submission dossier of fully executed financial agreements with sites and investigators. It means that these documents need to be negotiated and signed before submission (not during RA review or after study approval as in most other CEE countries). In practice this is somewhat mitigated by standard approach applied by pharma companies and CROs that submit the financial agreements with both PI's and institutions *only for the leading site of the National Study Coordinator*, while agreements with other sites are signed and submitted as amendments after the study has been approved by the RA. Another interesting detail is that during the review period of the submission dossier by the RA no additional documents can be submitted unless directly requested by the RA, so that this time can and should be used for negotiation and signing of the rest of the site agreements, which can be submitted after the official study approval.

The role of the Central Ethics Committee is allocated to the LEC at the site of the National Study Coordinator. The Central EC reaches out to the LECs to get their opinion on the appropriate investigators and site facilities, which have to provide such opinion within a rather short time frame making it essentially a formality. Thus, the review by the local ECs does not have any impact on the study approval timelines.

UKRAINE

Study Start-Up Timelines Chart

	Weeks	Months
INDIVIDUAL STAGES		
Translation of docs and submission dossier preparation	5	1,2
Review & approval by the RA (SEC*)	9	2,1
Issue of the approval by MoH	2	0,5
Review & approval by the Central EC**	0	0,0
Review & approval by the local ECs	3	0,7
Negotiating & signing study agreements***	14	3,2
Obtaining import/export licenses, importation & distribution of IMP	5	1,2
SUMMARY		
From submission till study approval	11	2,5
From submission till first site initiation	16	3,7
From start of work till first site initiation	21	4,8



* SEC - State Expert Center of MoH of Ukraine

** not applicable

*** Negotiation can start in parallel with RA review or even before, but the clinics usually refuse signature before study approval

Noteworthy Local Requirements

As it stands today, the duration of the review of study documentation by the State Expert Center (SEC) can vary significantly. It is further prolonged by the additional 2-3 weeks that it takes to issue an official study approval (based on the opinion of the SEC) by the Ministry of Healthcare. Once such approval is issued, the local ethics committees start their reviews, which usually take 3-4 weeks. Another milestone in the study start-up is the need to obtain not only study drug importation license, but also importation permit for each study drug shipment crossing the Ukrainian boarder. It remains to be seen if the strategic objective of harmonization of standards and potential future integration into the EU would entail simplification and shortening of clinical trials approval timelines.

It has been recently reported that the MoH is going to amend the importation procedure of unregistered medicinal products for purposes of clinical trials obviating the need to obtain a special import license and making the study approval the only legal ground for importation of the investigational drug. If this happens it would significantly simplify and accelerate the process of importation of unregistered medicinal products into the country, thus shortening the total start-up timelines.

CONCLUSIONS

As we have noted earlier, study initiation timelines play an important role in the selection of participating countries. These are quite favorable in the former “Eastern Block” countries and the decision as to which countries to select should be based on its specific capabilities, patient populations and level of investigators’ expertise. With this being said, if the study rescue is being contemplated, countries with very short start up times, such as Georgia, Hungary and Estonia may be of special interest.

We hope that you found this report of interest and would be happy to answer any additional questions that you might have.