

Minutes from the CMDh TC with industry associations (AESGP, EFPIA, EUCOPE and Medicines for Europe) on Brexit readiness- 1 October 2018

The objective of the TC 1 October was to present the outcome of the industry survey on the BREXIT readiness and to raise some outstanding issues related to MPR/DCP products.

Laura Oliveira, the chair of the CMDh opened the call and welcomed all participants.

On behalf of all industry associations present at the call, Beata Stepniewska from Medicines for Europe thanked the CMDh for organizing this teleconference outside the regular CMDh meetings. In view of the “ticking clock” the regular exchange between the CMDh and industry is very important.

Summary of the discussion at the TC:

Presentation of the results of industry survey:

Transfer of the RMS:

From the industry perspective, progress has been made in transferring procedures to new RMS.

- Based on the internal Medicines for Europe surveys performed in May 2018 and September 2018, 60% of procedures have already been transferred by September in comparison with 32% in May 2018,
- Based on industry aggregated data for September 2018 (Medicines for Europe, EFPIA and AESGP), 56% of procedures have already been transferred

However, despite all parties’ efforts; around 40% percent of the procedures still have to be transferred from the UK RMS to EU 27, including around 24% which are blocked by on-going regulatory procedures. The risk is that “easy to transfer” procedures have already been transferred; more difficult one still need to be done. An additional risk factor is that the capacity of available RMSs may be reduced.

A suggestion was made by the industry that an exception should be agreed that the RMS transfer can start even if another regulatory procedure is pending. CMDh did not support this proposal.

Based on the CMDh general survey, only 30% of procedures have already been transferred. The industry statistics were “over optimistic” for the CMDh. The industry commented that better results from members being a member of trade associations might be related to the intense process of informing/ raising awareness by the trade associations. Not all companies in the EU are members of trade organisations.

CMDh asked if industry also included an agreement with future RMS as a transfer in its statistics? No, the industry counted the procedures already transferred, not “intending to be transferred”, to agreed new RMS.

Issues other than on-going regulatory procedures identified by the industry

Capacity

Based on the outcome of the survey, several companies experienced refusal (with or without justification). The most frequent reason was capacity. Industry asked if, based on the HMA/ CMDh assessment, there is enough capacity to take over the role of the RMS from the UK. Although the assessment of network capacity due to Brexit is the responsibility of the HMA/EMA Task Force, the CMDh confirmed that there is enough capacity in the network.

CMDh suggested trying some new countries instead of choosing the most experienced/ most often used MSs. Industry explained the limited choice due to availability of all strengths.

Industry suggested a clear and transparent communication from individual MSs on available capacities at the next F2F meeting.

Examples of countries refusing to accept the role of new RMS were provided to the CMDh. Despite these, there is also a lot of positive experience with the transfer, proven by the successful transfer of 60% of procedures based on the industry survey.

Industry highlighted a long waiting time to receive a response from proposed new RMS whether they can accept the procedure.

Additional requirements

Additionally, some MSs are requesting more data than the “transfer package” identifies in the CMDh guideline. Detailed examples were provided to the CMDh in advance.

PT, ES and IT gave some feedback on additional national requirements.

- Assessment report from previous RMS depended on use of different repository (ES, PT). PT declared a change to its position. ES and IT will reflect on this. It will be re-discussed at the next F2F meeting (November 2018).
- Italy - the request for a consolidated eCTD dossier depends on Agency’s internal system. Other requirements reported by industry can be discussed further.

Reason for not transferring the procedures yet

CMDh asked the reason why those 20% of procedures have not yet been transferred.

Possible reasons identified by the industry:

- This could still be an issue of choosing the RMS (complexity of strengths)
- Revision of the portfolio with a risk that some products from this “20% basket” might be withdrawn and MAs might be cancelled
- Refusals of RMS by countries approached by MAH and the search for a new one still on-going
- Additional national requirements to be fulfilled

Communication on the intention to transfer

All companies have used the CMDh template to communicate their intention to transfer the procedure to new RMS and they have found it very useful.

For procedures not transferred yet, CMDh insists on an urgent declaration of “intention to transfer” to the new RMS, even if the transfer itself cannot be done yet due to some barriers (i.e. on-going regulatory procedures). The contact person for a procedure should be well indicated. CMDh asked for this information to be transmitted to companies.

If a MAH cannot find a new RMS, it should be reported to the CMDh to find a solution.

Earlier engagement of new agreed RMS

At the last meeting at the EMA, industry learned about new rapporteurs in the CP already taking over some responsibilities from IV Q 2018 (i.e. processing new variations). In view of pending variations still blocking the transfer, the industry would welcome the same solution for the DCP products where new agreed RMS can already start some activities earlier - before the old/ pending procedures are finalized by MHRA. As some variations related to Brexit/ FMD implementation still need to be submitted before March 2019, new variations being taken by the new agreed RMS would avoid a congestion of the system.

CMDh understands the position but indicates that the context for MRP/DCP compared to CP is different. The approach proposed by the industry will not work as NCAs cannot work with two parallel RMS.

No transfer to the new RMS before March 2019

Despite an effort from both sides, it may happen that some transfers will not be done before March 2019. Industry understanding is that if the RMS transfer is not done before March 2019, the MAs remain valid in EU 27 and the new RMS still can be agreed after March 2019. Obviously, no regulatory processes can be initiated as long as the transfer has not been done.

Industry asked CMDh to confirm this interpretation.

CMDh could not confirm this interpretation. The CMDh position is that such a situation should be avoided.

The MHRA has established a Brexit Task Force to ensure any pending Renewals/Variations are finalized and any RMS transfers are not blocked. Industry was asking if there is a contact point for any procedures that are not progressing. UK response (Keith MacDonald from MRHA): all pending renewals have now been completed and companies should contact the respective unit manager regarding any pending variations.

Medicines at risk of supply disruption

There are several countries asking for information on potential supply disruption. Industry questioned what those MSs will do with this collected information. Do the countries raising these questions intend to provide transparency, such as provide a list of products with a high shortage risk? Is there any plan for specific measures needed in case of emergency/ public health?

CMDh encouraged industry to contact MS in question in case there is a risk of shortage. The CMDh has received very little industry input until now, just two cases. There will be no European action from the CMDh perspective to address shortage of supply.

Some authorities have indicated their position. In Germany, the Paul Ehrlich Institute has a good overview of products at risk; the assumption is that BfArM does the same.

Industry asked if in exceptional cases of tech transfer of analytical methods, art. 51 of the Directive could be used to avoid shortages. CMDh cannot give a general exemption response. Companies should inform MS affected regarding any potential shortages for essential products- specific cases will be reviewed by EC and CMDh.

Specific questions:

Topic	Question	Comment
Inspections (GMP Inspections)	<p>Please advise what measures are being taken to plan for additional inspection resources to compensate for MHRA’s departure from the inspection collaboration programme?</p> <p>http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf</p> <p><i>Q21: “It is expected that findings of inspections, in particular to determine compliance with good manufacturing practice, good clinical practice and pharmacovigilance obligations, conducted by the UK competent authority before 30 March 2019 are implemented by the inspected entities in accordance with the applicable legislation, in particular Directive 2003/94/EC, Commission Delegated Regulation (EU) No 1252/2014 and Directive 91/412/EEC with regard to good manufacturing practice, Directive 2001/20/EC and Commission Directive 2005/28/EC with regard to good clinical practice and Regulation (EC) No 726/2004, Directive</i></p>	<p>FYI- Industry raised this also with the EMA at the meeting on 24 September.</p> <p>The initial feedback received was that UK-issued GMP certificates can be used as supportive documents after 30 March 2019 and any need for an inspection by an EU27</p>

	<p><i>2001/83/EC and Commission Implementing Regulation (EU) 520/2012 with regard to pharmacovigilance obligations”.</i></p> <p>Industry understands that the inspected entities should implement the recommendations of MHRA inspection. Nothing is written regarding the validity of GMP certificates issued by MHRA. Can EMA confirm that MHRA GMP certificates will remain valid in EU also after 29.3.2019?</p> <p>In addition, industry has identified the issue of GMP certificates about to expire (issued by the MHRA) with no intention to perform inspection by the MHRA to extend the validity.</p> <p>The CMDh answer: The CMDh cannot deviate from the position of the network already provided. Keith McDonald stated that he is not aware that MHRA would be unwilling to inspect. This is not in line with the UK government objectives to reach agreement with EU for activities post March 19. If companies experience such a case it should be communicated to Keith McDonald MHRA and Brendan Cuddy EMA.</p>	<p>inspectorate will be taken on a risk-based approach.</p>
<p>Procedural Change Management Variations</p> <p>Brexit related type IA (“do and tell”) variations</p>	<p>According to the current EU legal framework, any Type IA notification (submission to the Competent Authorities), however, has to be submitted within a period of 12 months (“annual report”) after implementation.</p> <p>In addition, this administrative requirement will have an unnecessary impact on resources on both industry / regulators. This will result in 1000s of variations being submitted/received in only 2 months, causing a major burden while there is no risk for patient safety involved. It is preferable to have this more spread over the period of a year, to make sure that variations that do have an impact on patient safety are not jeopardized.</p> <p>CMDh to clarify the reasons for changing this general approach, as it is a fundamental part of the European regulatory framework, and for stipulating the 2 month period – taking into account the definitions and application of the implementation and notification date.</p> <p>In some cases, it may happen that a variation to submit a new testing site cannot be done yet (because data for the technical transfer cannot be completed yet), but UK site already needs to be removed because of the 2 month period, resulting in a dossier with no QC testing site .. Would this be acceptable?</p> <p>Two months for informing the Authorities is a recommendation from CMDh and not a strict legal requirement. However, if those sites are used, a company becomes a non-compliant.</p>	

	<p>Industry is fully conscious that a UK testing/ batch release site cannot be used any longer if there is no transitional agreement. For large companies that use a lot of UK sites, spreading the removal over several months would help to handle thousands of variations more rationally and to prioritise the most important.</p>	
<p>Bioequivalence Studies using UK comparator</p>	<p>We are very grateful that CMDh updated guidance dated 19 June 2018 included a revision regarding acceptance of Bioequivalence Studies using a UK comparator: <i>“For Marketing Authorisation Applications submitted prior to 30 March 2019 for group procedures MRP/DCP that include a biostudy with the UK reference product as comparator, and where the study has been completed prior to 29 March 2019, will be accepted.”</i></p> <p>However, there are some cases where the studies (with the UK sourced reference product, authorized by the European procedure) <u>were finalised before Brexit</u> but cannot be submitted i.e. due to on-going Data Exclusivity (expiry shortly after Brexit).</p> <p>The Reference product which has been <u>sourced from the UK to perform BEQ / comparability studies</u> has been authorized in accordance with the EU legislation in place/ Acquis Communautaire and the Reference Product has been approved in at least one EU 27 Country <u>from the same European procedure (CP/ DCP/ MRP)</u>. Thus, we believe that studies finalised before Brexit with a UK sourced reference product will be accepted even if they are used/ filed after Brexit (the same principle as for the RUP).</p> <p>CMD informed about the discussion with the EC. The EC was not willing to change their interpretation. In case of the transitional period agreed, the issue will be solved and studies will be accepted.</p>	
<p>Art 126a for MT/CY/IS</p>	<p>It is not very clear what the final solution is on how authorisations granted based on Art 126a will be handled. Could CMDh clarify this?</p> <p>It is not yet very visible to the industry how small MSs, which use the procedure under Art 126a quite extensively, will handle this in practice. How can we have better clarity? Should we approach the MSs individually?</p> <p>CMDh replied that there is no EU approach yet. Topic to be discussed again at next F2F meeting in November 2018.</p>	