



BREXIT – Pharma Implications & Adopting the Change

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ABSTRACT

The United Kingdom (UK) has left the European Union (EU), and the transition period after Brexit comes to an end on 31st December 2020; from 1st January 2021, the Medicines and Healthcare Products Regulatory Agency (MHRA) will be the UK's standalone medicines and medical devices regulator. This change will impact the manufacturers for registration of clinical trials for pharma and devices, licensing, life-cycle management of existing marketed products in the UK, Marketing Authorizations, and changes in packaging and labeling information. This event would also impact the handling of centrally authorized products (CAPs) and its conversion to UK Marketing Authorizations (MAs). Moreover, handling of Active Substance Master Files (ASMFs) and Certificates of Suitability (CES), Reference Medicinal Products, IT systems, and pharmacovigilance procedures are also likely to get impacted due to Brexit. These regulatory changes by MHRA will require the pharma and medical device manufacturers to adapt swiftly as per MHRA prescribed timelines and ensure a smooth transition to new procedures. For a seamless transition, companies need to plan and execute with additional resources, ensure there is no impact to existing product portfolio, and utilize automation to reduce the operational spend on these process changes.

This whitepaper will provide insights into some of the critical impacts, subsequent process changes required, timelines, and various automation areas where companies can reduce the spending.



INTRODUCTION

Brexit has been one of the key talking points in the industry for the last few years, and finally, MHRA has released the guidelines of transition and post-transition period due to the No-Deal scenario. The transition period comes to an end on 31st December 2020, and the new guidelines will be in effect from 1st January 2021 unless there is any negotiation or extension between UK and EU during the transition period. The overall impact of Brexit will be visible across industries, and life sciences companies marketing their products in the UK will have to comply with the new guidelines. Pharma is the 3rd largest industry in the UK and contributing 10% of the UK GDP with more than 200,000 direct employments. The impact of Brexit for pharma and medical devices will be across clinical trials, licensing, importing and exporting of products from the UK, pharmacovigilance practices, pediatrics submissions, life-cycle management of products, IT systems to manage the interactions, etc. The transition from the EU allows the UK to offer fully independent regulatory decisions for both devices and pharmaceuticals, both nationally and in joint work with other international regulators. Stakeholders need to get ready for new rules from 1st January 2021.

Companies have to invest a lot to analyze the changes, find the gap in existing procedures, plan for Brexit changes, operationalize the changes in the current process, and effectively transition knowledge across the value chain. They also need to ensure there is no impact on existing marketed portfolios in the UK and Europe, supply chain issues are addressed before the changes are in effect, and ensure compliance to guidelines from regulators. These time and energy-consuming activities will require a skilled Regulatory team, operational resources to track and implement the changes, document the changes in existing SOPs, and train the existing team, suppliers, vendors, and other 3rd party teams on the changes.

Besides, the change management exercise will also challenge the manufacturers with increased paperwork caused by custom bottlenecks, increased lead time for products to reach in EU, new timelines due to added process for UK licenses, the challenge of transportation of goods, establishment of intellectual property and its governance, data

sharing and security.

These testing times also provide an opportunity for manufacturers to test innovative solutions to address near-term challenges as well as plan for long-term challenges. Some of the tactical solutions will be to have a grip on the high volume of activities due to label change requirements, use of digital-enabled processes to address efficiency in supply chain working and tracking, use of RPAs, and machine-readable solutions to convert existing legacy submission to MHRAs specific eCTD submissions.



KEY CHANGES: PROCEDURAL CHANGES & ITS IMPACT ACROSS R&D AND REGULATORY VALUE CHAIN



Clinical Trial Registration & Public Disclosure:

- Manufacturers have to continue and use existing international registers like ISRCTN registry or <https://clinicaltrial.gov> to ensure the public is aware of the clinical trial undertaken by the company and critical parameters and progress of the clinical trial.
- For trials where the EU and UK are involved, the record will continue to exist in the EU clinical trials register.
- Publish trial results within six months of the end of the trial for pediatric studies and 12 months for non-pediatric studies.
- A short confirmation email has to be communicated with MHRA once the result gets published in a public register and submit a final report to the Ethics committee within the same timeframe.

Change of trial sponsor/ legal representative:

- **The UK will require the sponsor or legal representative of a clinical trial to be in the UK or country on an approved country list,** which would initially include EU/European Economic Area (EEA) countries.
- For the sponsors from the rest of the world having the legal representative established in the UK and there are sites elsewhere in the EU/EEA, the sponsor will need to assign an EU/EEA legal representative for these sites via a substantial amendment to the relevant EU/EEA competent authorities.
- No amendment submission to MHRA is required where the sponsor or legal representative for an ongoing trial is established in the EU/EEA as the UK will continue to accept this.
- No amendment will need to be submitted in the UK if the sponsor retains the UK legal representative for the UK study. Similarly, if a sponsor remains in the UK and has a legal representative to cover EU/EEA sites, the amendment is not required to be submitted in the UK.

Investigational medicinal product (IMP) certification and importation:

- If the holder is required to be included for importation to an ongoing trial, a substantial amendment should be submitted to the MHRA to include the details of the MIA(IMP) holder performing the 'supply chain oversight' role within 1 year of 1 January 2021.
- This means that **for up to 1 year after 1 January 2021, IMPs may be supplied direct from the EU/EEA MIA(IMP) holder to the ongoing Great Britain trial site without the GB MIA (IMP) oversight process.**

Licensing Procedures:

From 1 January 2021, the MHRA is introducing changes to national licensing procedures, including procedures to prioritize access to new medicines that will benefit patients, an accelerated assessment procedure, and new routes of evaluation for novel products and biotechnological products.

Accelerated Procedure:

- MHRA will introduce an accelerated procedure and will reach its opinion on the approvability of marketing authorization applications within 150 days of submission of a valid application. The Accelerated Assessment option is available for good quality new marketing authorization applications for both new and existing active substances and submitted directly to the UK.
- Eligibility will also include those applications seeking an orphan MA approval in GB and those submitted for conditional and full marketing authorization, as well as approvals submitted under exceptional circumstances.
- The assessment process will run in two phases totaling 150 days, with an intervening clock-off period between phase I and phase II. Assessment phase I, including CHM consultation, will be completed 80 days after the clock start.
- Any questions arising from the initial assessment will be raised with the applicant and should be addressed in the clock off period of up to 90 days. Phase II assessment will begin on receipt of the applicant's responses.
- Assessment in phase I will also address eligibility for grant of orphan status or a conditional MA. Based on these assessments, the MHRA will provide an opinion on the approvability of the product by day 150, and if positive, will grant the MA.

Rolling Review route:

- Applications for any new active substances including, biological products that wish to obtain a marketing authorization in GB based on submission of a 'full dossier' to MHRA, are eligible for a rolling review. Similar biological applications (biosimilar products) are also eligible for a rolling review.
- The process is a phased, modular, iterative approach to the evaluation of marketing authorization applications.
- The quality, non-clinical, and clinical modules may be submitted separately or in combination depending on the individual circumstances as data becomes available. It is expected that each module will be near completion to avoid multiple iterations of assessment of the same module.

- Each assessment phase will progress independently, and any questions raised will offer the applicant the opportunity and time for a comprehensive update of the modules before the final submission.
- The final phase will involve the submission of a complete application, including updated versions of the modules evaluated previously.

Community marketing authorization procedure for the next two years:

- For two years from 1 January 2021, Great Britain will adopt decisions taken by the European Commission on the approval of new marketing authorizations in the community marketing authorization procedure.
- Applications should include all information provided to EMA during the licensing procedure and should be accompanied by all iterations of the CHMP assessment report, including the final CHMP opinion. A declaration of conformity of the Great Britain application with the dossier approved by the European Commission.
- Marketing authorization applications should be submitted to MHRA following receipt of the CHMP opinion and will be determined following confirmation of notification of the EC decision.

Life-cycle Management:

Variation Procedure

- The procedures detailed under Chapter IIa of Variations Regulation (EC) No 1234/2008, which specifically applied to variations to purely national Marketing Authorizations, will be incorporated into UK law from 11pm on 31 December 2020, and as such continue to apply to both pending and new variations to purely national UK Marketing Authorizations, from 1 January 2021.
- All Marketing Authorizations authorized in the UK by the MHRA before 1 January 2021 will be national (UK). Any pending and new variations will therefore only be processed to a conclusion after 1 January 2021 as national variations, where the relevant national procedures will be followed.

Change to finished product:

- A change in finished product manufacturing site, including as appropriate primary and/or secondary packaging site, should be submitted under the relevant sub-change code under B.II.b.1 and be suitably supported.
- This includes the submission of a copy of the relevant Manufacturing Authorization or as appropriate a valid good manufacturing practice (GMP) certificate issued by the UK, or a GMP certificate (or an equivalent document) from the competent authority of a country on the approved country for a batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the USA).

Change to importer/batch release site/quality control site:

- A change in importer/batch release site and/or quality control site should be submitted under the relevant change code under B.II.b.2 and be suitably supported.

Importer/batch release:

- The change should be supported by including a copy of the relevant Manufacturing Authorization or a valid GMP certificate issued within the last three years (as issued by the UK or a country included on the approved country for import list (currently EU/EEA Member States)).

Quality Control site change:

- The change should be supported by including a copy of the relevant Manufacturing Authorization or a valid GMP certificate (as issued by the UK or a country included on the approved country for a batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the USA)).

Change of Marketing Authorization Holder (MAH):

- A change of MAH, such as from a company outside the UK to one established in the UK, cannot be done as a variation. That change requires the submission of a Change of Ownership application. It should be noted that from 1 January 2021, the MAH will have 24 months to comply with rules on the establishment in the UK.

Change to the location of the Pharmacovigilance Systems Master File (PSMF) or the Qualified Person for Pharmacovigilance (QPPV):

- As the MHRA will no longer have access to the Article 57 database, any change to the QPPV or location of the PSMF should be submitted under change code C.I.8.a (Type IA IN), provided the conditions and documentation requirements can be fully met.
- The QPPV for UK authorized products must be established in the EU or UK on day one, and the PSMF for the UK authorized products must be accessible electronically from the UK at the same site at which reports of suspected adverse reactions may be accessed.

Implementation of the outcome of referrals and procedures concerning PSUR or PASS:

- From 1 January 2021, the MHRA will be carrying out their assessments, the outcomes of these assessments will be published together with advice on implementation. Where a variation is required will usually be a Type IA.
- Where the procedure has been finalized before 1 January 2021, the outcomes concerning any required variations will be processed based on the decision already taken. Depending on the nature of the required changes, the variations should be submitted under the relevant main change codes of C.I.3 or B.V.b (usually type IA).

Summary of approach to variations

Variation	Positive CHMP Opinion Stage before exit day	MHRA assessment	Fee payable	Include in Initiating Sequence
Type IA: (i) Submitted to EMA before 1 January 2021 and not rejected or, (ii) submitted to EMA on or after 1 January 2021 and not rejected before data submission date	N/A	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type IB: Submitted to EMA but not granted before 1 January 2021	Yes	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type IB: Submitted to EMA but not granted before 1 January 2021	No	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type II: Submitted to EMA but not granted before 1 January 2021	Yes	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type II in clock stop: Submitted to EMA but not granted before 1 January 2021, And in clock stop	No	Yes, assessment of replies	No	No: Separate Submission needed along with or after Initiating Sequence (either minimal or complete)
Type II in clock stop: Submitted to EMA but not granted before 1 January 2021, And before procedure first clock stop	No	Yes	Yes	No: Separate Submission needed along with or after Initiating Sequence (either minimal or complete)
Type IB/II variations: Submitted to EMA on or after 1 January 2021	N/A	Yes	Yes	No: Separate Submission needed along with or after Initiating Sequence (either minimal or complete)

Renewals:

Converted EU MAs from 1 January 2021

- For renewals, converted EU MAs are treated as if they were granted on the date on which the corresponding EU MA was granted. The converted EU MA will therefore have the same renewal date in the UK as in the EU. In general, the MHRA will not consider renewals to converted EU MAs before at least a minimal initiating sequence and related documentation (the “data submission package”) has been received.
- The date on which the minimal or full initiating sequence is received is referred to as “the data submission date”.
- From 1 January 2021, MAH should continue to submit your renewal applications 9 months before they expire.
- The requirements for renewal submissions will remain the same for products authorised in the UK and should include the same documents currently required in the EU as detailed in the following guidance:
 - CAP renewals and annual reassessments
 - Renewals for products authorised through MRP or DCP procedures
 - The MHRA will continue to accept the reduced submission requirements for renewals of MAs for products authorised under Article 10.1 as set out in the CMDh Best Practice Guide on processing renewals in the MRP/DCP.

Renewals for MAs granted via unfettered access

- Where you have a Great Britain-only MA granted via the Unfettered Access route, an application to renew the MA should be submitted in line with the above guidance.
- Where the MA has remained in line with the EU or Northern Ireland MA we will accept the same renewal application as submitted to the EU and a reduced fee will be applied.

Registering new packaging information for medicines from 1st January 2021

- Once MAH have been issued with new Marketing Authorisation (MA) to convert a previously EU-wide to a MA for Great Britain, MAH will have no later than 24 months after the end of the transition period to establish and register a Great Britain presence for the MA. This will include submitting amended artwork for approval to accommodate the following new administrative information:
 - Name and address of Marketing Authorisation Holder (MAH) or representative
 - Great Britain MA number
 - Name and address of product manufacturer for batch release

Actions to take once you have been issued an MA

- MAH will have a further 12 months (36 months in total from 1 January 2021) to ensure all stock released to market is in compliant packaging. This additional time allows for assessment of your submission(s) and time for implementation in the production schedule.
- MAH may need to amend the labeling and/or the patient information leaflet (PIL) to take account of new information as a result of a variation application submitted between the grant of the new MA and 24 months from 1 January 2021. In such cases, the changed artwork which accompanies that variation application should include the new administrative information at that earlier time.
- If MAH is making changes to the labeling and/or the PIL as a consequence of a variation application, MAH should submit the full colour mock-ups as part of the variation submission. These will be assessed and approved as part of the variation procedure. Normal fee arrangements apply.
- If MAH is only changing the name and address of the marketing authorization and/or the manufacturer for batch release (stated in the PIL) you may do this as part of a Better Regulation of Medicines Initiative (BROMI) notification. Normal fee arrangements apply.

- If MAH is making any other changes to the statutory information or the pack design (which are not consequential to a change to the Summary of Product Characteristics (SmPC)), MAH will need to submit the artwork for full assessment to the Product Information Quality Unit under change code P2. Normal fee arrangements apply.
- Packs containing the Falsified Medicines Directive (FMD) safety features would still be accepted in the UK, provided that they are in line with other UK packaging requirements.
- Multi-language packs - The MHRA will continue to allow multi-country packs, including packs with more than one language on the pack and/or in the PIL, provided that the entirety of the information is compliant with the UK requirements.

KEY CHALLENGES FOR PHARMA TO IMPLEMENT THESE CHANGES

The additional workload on existing Regulatory function – Along with the existing marketed portfolio work requirements, the existing group of the team will be burdened with extra efforts required for tracking, planning, and implementing the Brexit specific changes to the process.

Converting existing legacy EU submission to UK specific MA – Tracking and ensuring all document gaps are filled before the conversion to UK MA will be time-consuming for the RA function, and a lot of effort will be required over a period of time to ensure complete compliance to new regulations.

Label changes and allied process changes – In addition to local representation, there would be a requirement to change the existing process for UK marketed products. Administrative changes are required to be made to the labels and the required submission needs to be done to the agency. This will lead to more number of variation submissions and increase the workload of the team.

Increased lead time for products to reach in EU – Change in the existing operating model will lead to additional paperwork caused by customs clearance, regulatory submission requirements, etc.; this will lead to increase lead time for products to reach in EU if the manufacturing facility is in the UK. This is a big challenge for products having a lower shelf life.

Documentation of changes in existing process SOPs – To ensure compliance and track the compliance of teams involved in Brexit changes, it would be very important to update all relevant SOPs that will be affected due to Brexit changes. The Quality Assurance function will be very important to ensure these compliance tasks are updated and followed across the board.

Supply Chain challenges – New regulations on border checks can lead to increased paperwork and processes. Manual processes can be a cause of concern until digitally sound processes are implemented.

Data Sharing and Security – A critical challenge which the regulators are trying to address is data sharing and cross leveraging of information between the EU and UK. One of the challenges will be of base-line data that needs to be submitted to MHRA for product changes/ variations.



KEY SOLUTIONS TO ADDRESS THESE CHALLENGES:

Use of automated solutions for operational tasks – Key automation by use of AI and RPA enabled technologies can address automation of operational tasks like label changes, comparisons, review process. This automation can help to reduce manual efforts required for a high volume of label change requirements expected from the Brexit changes.

RPA enabled solutions for submission and data re-usability – Robotic automation and machine-readable content can help in build automation and re-usability of submissions, which can reduce the overall submission preparation and review timelines and increase the speed of submission to the agency.

Intelligence-driven processes – R&D operational processes need to be more agile and intelligence-driven to ensure such changes will have a limited impact on day-to-day operations and do not incur high operational spending. One of the starting points to enable such practice is embedding Regulatory Intelligence as a practice across all R&D and Regulatory process and technology. It is important to be proactively addressing issues rather than building.

Digital processes for complete supply chain tracking and operating – Use of digital infrastructure to operationalize supply chain processes including documentation, package serialization/ tagging using tagging technology, storage of data using cloud platforms, tracking & operating through digital platforms, and analytics-driven reporting. Digital processes will ensure reducing the lead time of supply chain operations from manufacturing site to consumer is reduced and generate data insights on customer usage patterns, supply chain inventory, product information, and feedback.



CONCLUSION

Brexit as an event will bring disruptions in the process across UK and EU processes and can also lead to the harmonization of processes for matured markets. There is an enormous potential for technology to play in the Regulatory processes and enable stakeholders with intelligence-driven decision-making abilities and reduce the operational spend for the manufacturers. With multiple changes expected across Life Sciences industries in the coming days, the approach of long term & agile systems and processes will ensure a highly compliant and stable R&D process for the pharma and life sciences industry.



REFERENCES

<https://www.gov.uk/government/collections/mhra-post-transition-period-information>



ABOUT TATA ELXSI

Tata Elxsi, a part of Tata Group, is amongst the world's leading providers of design, engineering, and regulatory compliance services. With 15+ years of experience in catering to healthcare & life sciences companies, Tata Elxsi has built a strong services and solutions portfolio that adds value at every stage of the customer's product development lifecycle.

We offer end-to-end regulatory service portfolio for global pharma companies to help them increase agility and lower operational costs while ensuring compliance with ever-changing global industry standards and requirements. We have extensive experience with regulatory agencies like FDA, EMA, PMDA, MHRA, BfArM, and other leading health agencies.

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