Introduction

Brexit from a pharmaceutical perspective

Marie Gårdmark
Director Division of Licensing
Brexit

• A regulatory challenge for Europe
• EMA to relocate to Amsterdam
• Business continuity plan to ensure operational continuity
• MPA active in discussions with our ministry, HMA and EMA about the future
• Need to re-distribute workload between agencies
• MPA takes over part of UK workload
Brexit – how do we prepare?

• Capacity
• Financing
• Communication
The redistribution of UKs product portfolio was finalized on 4 April 2018. The new (Co)-rapporteurships were communicated to MAHs on 30 April 2018.

The new (Co)-rapporteurs will only take full responsibility for the re-allocated medicinal products as of 30 March 2019. MHRA/VMD will be accountable for the medicinal products until 29 March 2019.

However, the new (Co)-rapporteurs will handle, from Q4 2018 onwards, post-authorization procedures still under evaluation after 30 March 2019.
Overall redistribution of UK portfolio human applications (from EMA)
Brexit
European perspective

Christer Backman
Office of the Director General
Where are we?

✓ Withdrawal date 29 March 2019 (11.00 p.m. UK time)
✓ Withdrawal agreement
  • Agreement post Brexit relationship 25 November
  • Transitional period
Future relationship with UK

• explore the possibility of cooperation of United Kingdom authorities with Union agencies such as the European Medicines Agency (EMA)

but

UK will not act as leading authority from 30 March 2019 regardless of Transitional agreement
Preparation on EU level

EMA
HMA
CMDh
CMDv
Eur Com
Scope

• Centralised procedures
  – Capacity - Yes
• MRP/DCP
  – Capacity - Yes
• Inspections – Com view on GMP-certificates
• Clinical trials
• OMCL
• Availability
Relocation of EMA

- Preparation for both the temporary premises (Spark building) and the final premises (EMA building) is on track and according to plan;

- A visit of the MB delegation to both construction sites took place on 7 November 2018 and the MB delegation was reassured about progress made; a report will be presented at the December Management Board meeting.

- EMA continues to monitor the staff retention situation; feedback from early movers is positive.
Impact of Brexit on medicines availability (CAPs)

Results of the Survey

- High response rate: 91%
- The results of the survey showed that 58% of the 694 CAPs were “on track” with their regulatory planning to ensure that the marketing authorisations remain valid once the UK becomes a third country.
- Based on the survey results, EMA was concerned about potential supply shortages for 108 medicines (88 human and 20 veterinary) which had one or more manufacturing sites located in the UK only without any other current alternatives, hence these medicines were considered to be “at risk” of supply disruption or shortages in the EU, if changes were not submitted and implemented in due time.

![Bar chart showing the number of products and activities in different categories.](chart.png)

- Number of products: MAH 400, QPPV 335, PSMF 376, BR 119, QC 41, Importation 18.
- Responses received: MAH 383, QPPV 305, PSMF 361, BR 104, QC 37, Importation 9.
Impact of Brexit on medicines availability (CAPs)
Revised number of CAPs “at risk” of supply

- Follow-up meetings with MAHs of the “at risk” medicines:
  - **Follow-up meetings** for 108 medicines were organised with 54 MAHs (45 human and 9 veterinary) during July-September 2018. These included MAHs that did not reply to the survey.
  - Plans are changing for a number of companies since the launch of the survey; many companies have stated that they will make the necessary changes **before 30 March 2019**
  - **31** medicines (19 human and 12 veterinary) are currently considered “at risk” and may have potential supply issues

*as of 26 October 2018. This number is likely to change when updated information from MAHs becomes available
Impact of Brexit on medicines availability (CAPs)

Criticality Assessment

- All products considered as “at risk” will undergo a **criticality assessment**
- The methodology is based on the [Criteria for classification of critical medicinal products for human and veterinary use](#), adapted to the context of Brexit, and foresees two parts:

  **PART A**: CHMP/CVMP with the support of EMA will look at **therapeutic use**, i.e. the medicinal product is an integral part of the treatment for or prevention of a disease, which is life-threatening or irreversibly progressive, or without which the public and animal health could be severely harmed.

  **PART B**: EMA will liaise with MSs with respect to the **availability of therapeutic alternatives** for each medicinal product, e.g. other products in the same class or even other classes, and generics.

EMA is closely monitoring the medicines considered critical and evaluating potential mitigation measures to minimise any disruptions in supply.

HMA/EMA workshop on availability of authorised medicines, 9 November 2018
HMA Brexit TF

- **BTF mandate:** to ensure a coordinated approach within the network to safeguard regulatory continuity.

- **Key players:**
  - EMA (CAPs)
  - CMDh/v
  - HMA/EMA Task Force on Availability of authorised medicines
  - HMA Brexit Task Force
  - National Competent Authorities (all NAPs).
HMA Brexit Task Force

- Mapping Brexit-related availability risks for NAPs proves difficult due to large number of products and MAHs, national particularities and labor-intensive nature of mapping list of essential/critical products.

- Therefore currently no coordinated European effort to map Brexit-related availability risks for NAPs.

- Instead MAHs have been informed to report to member states affected regarding any potential shortages for essential products- specific cases will be reviewed by EC and CMDh & CMDv.
Change of RMS

Adam Andersson
CMDh alternate, Regulatory Department
Current situation

- Approximately 500 UK procedures in MRP/DCP where SE is CMS (400 human, 100 vet)

- SE has capacity to accept more RMS-ships
UK PRODUCTS TO BE REDISTRIBUTED WITHIN THE EEA-29
(Each pharmaceutical form and strength counted separately)
(HUMAN MP ONLY: 4323)

RMS switch pending *
1670
39%

RMS switch done/ongoing in CTS (after 01/04/2018)
1451
33%

RMS switch agreed in Brexit tool
1202
28%

*including
20 (0.5%) recorded 'Requests' and
48 (1.1%) 'Rejections by CMS'
following MAH contact

(Current situation 2018-11-06)
RMS switches **received from UK** since 01/04/2017
(total:1451; CTS data of 06/11/2018)
When to change?

• Transfer of RMS-ship can only be conducted when no other regulatory activity is ongoing

• Contact the desired new RMS even if procedures are ongoing.

• Do not wait!
How to change? (1)

- Contact the MPA via RIC@lakemedelsverket.se

- Information to be provided according to the CMDh template: http://www.hma.eu/90.html
How to change? (2)

• The MPA will make a product-specific decision based on the current resource situation

• Intention to respond to all transfer requests within 3 weeks
Problem: Ongoing procedures

• For several products with UK as RMS, procedures are ongoing or applications submitted but not yet started

• UK prioritizes procedures where RMS transfer requests are pending
Problem: No CMS accepts

- If all CMS in a procedure declines the RMS-ship, contact the CMDh or CMDv
- The CMDh/v will appoint a new RMS
At Brexit: RMS change not completed

- No regulatory action can be conducted until a new RMS has been appointed (variation submissions etc.)
At Brexit: Ongoing procedures

• UK can no longer act as RMS

• Ongoing procedures will be stopped
Ongoing DCPs

• The application can be withdrawn and resubmitted with a new RMS

• SE as RMS: Fee reduction equal to the already paid fee for the initial application

• SE as CMS: 50 % fee reduction

• Mention in the cover letter that the resubmission is due to Brexit and specify the previous procedure number

• Final decision on the fee taken after the application has been submitted
Brexit related changes – nationally authorised products (NP, MRP, DCP)

Christin Olofsson
CMDh member, senior expert Regulatory Department
Impact on activities currently based in UK

• MAH (and local representative) must be established in the EU/EEA

• Some activities must be performed in the EU/EEA, e.g. pharmacovigilance, batch control (unless MRA), batch release

• MPA recommendation: **Act now!**

• In case of no-deal these changes must be implemented before 30 March 2019. We will not know in time if there will be a withdrawal agreement.
Where to find information?

Brexit-related guidance for companies is continuously published:

- CMDh [http://www.hma.eu/535.html](http://www.hma.eu/535.html)
What if I am a marketing authorisation holder established in the UK?

According to Directive 2001/83/EC the marketing authorisation holder must be established in the Union. Through the EEA Agreement this is extended to include also Norway, Iceland and Liechtenstein.

For national authorised medicinal products the marketing authorisation holder will therefore normally need to transfer its marketing authorisation to a holder established in the Union (EEA). This means that the addressee of the marketing authorisation decision changes to the new addressee. (NEW:) The transfer of the marketing authorisation must be fully completed and implemented by the marketing authorisation holder before 30 March 2019.
How are MA transfers and change of local representative dealt with in Sweden?

- National notification
- Information including form available on our website:
  - Innehavare av godkännande för försäljning och ombud
  - Change of MAH and Local Representative
- No separate fee
- Normally handled within 90 days
MA transfers - Parallel sales of packs with old and new label in Sweden

- Regarding new packaging the following applies to change of address of MAH, change of name of MAH and transfer of MAH:

- A new MAH is to commence production of the new labelling within six months from the date of labelling approval.

- As soon as the new labelling has begun to sell the new MAH is advised to submit a letter to the Medical Products Agency (mah.ombud@mpa.se) containing information about the start of sales date. The Medical Products Agency allows six months of coexisting sales of products with the old and new label.
Transfer of MA – Summary of PhVig System

• In case of transfer of a MA in one or more MS the new summary of the pharmacovigilance system (human) or DDPS (veterinary) of the new MAH has to be submitted to all MS concerned via MRP variation (type IA\textsubscript{IN} notification, C.I.8.a, or under category C.II.7 as applicable)

• *Exception:* A variation to submit the summary of the pharmacovigilance system will **not be necessary** in cases where the MA is transferred within companies belonging to the same parent company and the same PSMF will continue to be used

(CMDh/v Q&A on variations no. 2.8)
• What if my Qualified Person for Pharmacovigilance (QPPV) resides and carries out his/her tasks in the UK?

• According to Article 8 of Directive 2001/83/EC, the qualified person responsible for pharmacovigilance must reside and carry out his/her tasks in the Member State of the Union (EEA). The QPPV will therefore need to change his/her place of residence and carry out his/her tasks in the Union (EEA) or a new QPPV residing and carrying out his/her tasks in the Union (EEA) will need to be appointed. Changes in the QPPV, including contact details (telephone, and fax numbers, postal address and email address) may, for medicinal products for human use, be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline C.I.8).

For MPs for veterinary use, a C.I.9 variation is needed (CMDv Q&A no. 3)
What if my Pharmacovigilance System Master File is located in the UK (PSMF)?

According to Commission Implementing Regulation (EU) No 520/2012, the PSMF must be located within the Union (EEA). The supervisory authority for pharmacovigilance is the competent authority of the Member State in which the pharmacovigilance system master file is located. The marketing authorisation holder will therefore need to change the location of the PSMF to a Member State within the Union (EEA). Changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline C.I.8).
CMDh/v practical guidance Q&A no. 7

• How to classify Brexit-related changes impacting on the manufacturing activities for my medicinal product?

• Each batch of finished product must be certified by a Qualified Person within the EEA before being released for placing on the market in the EEA or for export. Certification can only be performed by a Qualified Person of the manufacturer and/or importer who is identified in the marketing authorisation and is located in the EEA (see EudraLex, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 16: Certification by a Qualified Person and Batch Release).

• Also the site for batch control (where each batch undergoes full qualitative analysis, a quantitative analysis of at least all the active substances and other tests necessary to ensure the quality of the products in accordance with the requirements of the marketing authorisation) needs to be located in the EEA or a country covered by a mutual recognition agreement. For products manufactured outside the EEA, also an authorised importation site in the EEA is required.
CMDh/v practical guidance Q&A no. 7, cont.

- Products that only have batch release and quality control testing sites for finished product in the UK will have to change the batch release and testing sites. For products that have other batch release and testing sites the MAH may choose to delete the site(s) or may choose to replace them. For finished products manufactured in the UK an importation site (in EEA) will need to be introduced.

A detailed table with the different scenarios and their corresponding variation classification is given.
CMDh practical guidance Q&A no. 10 (CMDv no. 9)

• When should I submit Brexit related type IA (“do and tell”) variations that have to be implemented before 30 March 2019?

• Certain changes that have to be fully implemented before 30 March 2019 can be submitted as type IA variations. Considering the regulatory nature of type IA variations (“do and tell”), and in order to avoid the need to implement such changes even earlier, it is acceptable that corresponding notification of type IA variation(s) is submitted no later than within 2 months after 29 March 2019 provided that the MAH is established in the Union (EEA) by that time.

• Type-IA variations requiring immediate notification (‘IA\textsubscript{IN}’) must in any case be notified (submitted) immediately following implementation of the change.

• The MAHs are reminded that actual implementation of such changes must in any case take place before 30 March 2019, irrespective of the variation type.
How does UK’s withdrawal from the Union affect the name of the product in UK mentioned in the package leaflet?

After 29 March 2019, the mentioning of the name of the product in UK in the package leaflet (Article 59(1)(g) of Directive 2001/83/EC) will become obsolete.

The deletion of the name of the product in the UK in the package leaflet will need to be incorporated as part of a future regulatory procedure (e.g. variation, renewal and the earliest opportunity after 29 March 2019 should be used) affecting the package leaflet, but no separate notification according to Article 61(3) of Directive 2001/83/EC is expected.
Grouping Brexit related changes

- CMDh/v Examples for acceptable and not acceptable groupings for MRP/DCP products:

- Acceptable groupings:
  - After a member state has triggered an Art. 50 procedure of the Treaty on European Union several changes to the finished product might be necessary, e.g. changes to MAHs, manufacturers for batch release, new summary of pharmacovigilance system (human)/pharmacovigilance system (veterinary) in case of MAH transfers or changes in the product names etc. While the transfer of the MA to a new MAH is an independent purely national application all other changes related to the consequences of this Art. 50 procedure, may be grouped in one application according to the highest variation type for the single changes.
UK reference product for generic and hybrid applications

Christin Olofsson
CMDh member, senior expert Regulatory Department
• The Q&As reflect the situation in case the withdrawal agreement with the transitional period is not agreed

• Could be subject to change
Information about the reference medicinal product in the application form – 3 sections

• Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA *This section defines the reference medicinal product chosen for the purposes of establishing the expiry of the data protection period.* => CMDh Q&A no. 13

• Medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product (ERP) => CMDh Q&A no. 10

• Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies => CMDh Q&A no. 11
How does UK’s withdrawal from the Union affect the Global Marketing Authorisation (GMA) concept?

The concept of global marketing authorisation within the meaning of Article 6(1) of Directive 2001/83/EC covers the initial marketing authorisation and all subsequent developments of the original medicinal product, irrespective of their authorisation procedures, namely variation or grant of a separate MA. The GMA is accompanied only by a single regulatory data protection period which applies both to data relating to the original medicinal product and to data presented for any subsequent developments. That regulatory data protection period begins with the grant of the initial marketing authorisation in the Union (EEA).

Marketing authorisations granted before 30 March 2019 by the UK can still be considered as the initial marketing authorisation.

=> can continue to be used in the first section of the AF
UK product as ERP – CMDh Q&A no.10 (CMDv Q&A no.8)

- How does UK’s withdrawal from the Union affect my generic or hybrid marketing authorisation or application based on a reference product authorised in the UK?
  - A generic or hybrid application in accordance with Article 10 of Directive 2001/83/EC refers to information that is contained in the dossier of a reference medicinal product (RefMP) that is or has been authorised in the Union (EEA).
  - Generic/hybrid marketing authorisations granted before 30 March 2019 referring to a RefMP authorised by the UK (UK RefMP) remain valid. **(NEW:)** Applications need to be submitted well in advance in order for the national competent authority to be able to grant the national marketing authorisation before 30 March 2019. Applicants should take into account that in case of a DCP or MRP the national decisions of the Member States are adopted within 30 days after the "end of procedure" (i.e. agreement of the concerned Member States in accordance with Article 28(4) or Article 29(3) or decision of the Commission in accordance with Article 34(1) of Directive 2001/83/EC), subject to the applicant providing high quality national translations of the product information within seven days of the "end of procedure".
  - Generic/hybrid applications for which marketing authorisations will be granted after 29 March 2019 should refer to a RefMP that is or has been authorised in a EU-27 Member State or a contracting state of the EEA. **(NEW:)** Applicants are advised to take this into account already at the time of submission of the application.
UK product in BE studies – CMDh Q&A no.11 (CMDv Q&A no. 9)

• Can medicinal products used in bioequivalence studies be sourced in the UK?

• Bioequivalence studies that have been conducted with a medicinal product sourced in the UK can be used in generic/hybrid marketing authorisation applications only if the marketing authorisation for that application will be granted before 30 March 2019.

• *Important footnote* =>
In exceptional cases where bioequivalence studies are intended for use in new applications which will be submitted before 30 March 2019 and if these bioequivalence studies have been already completed the national competent authorities will accept submission of such studies in order to avoid unnecessary repetition of studies in humans or animals.

Furthermore, in order to avoid unnecessary repetition of studies in humans or animals, applications to extend an existing national marketing authorisation of an EU27 Member State to more EU27 Member States via the mutual recognition procedure (including so-called "repeat use procedure") may be submitted also after 29 March 2019 provided that the applicant is able to demonstrate that the medicinal product used for the studies has been authorised and the batches used for the studies have been released while the UK was a Member State of the Union.
Brexit info 2018-11-26

Virve Reiman-Suijkerbuijk
Head of the unit
Inspektion av Industri och Sjukvård
New organisation per 2017-01-01

GMP/GDP-group

GVP/GCP-group

KANSLI Compliance Office
Our assignment

- GXP inspections and supervision
- Support to normative work from EU Directive and regulations to national legislation and guide lines
- Co-operation with other authorities and associations both nationally and internationally
- Implementing of changes by training and information
- Participation on relevant conferences as speakers
- Dialogues with actors within industry and healthcare – daily telephone line, response questions per mail registrator, bookable industry dialogues, training days for QP´s and RP´s,
Responsibility for GXP inspections and supervision

- National program for GMP inspections of all manufacturers of medical products regardless registration path Nat, DCP, CAP
- GMP inspections of IMPs, ATMP, PET products, active substances
- Inspections in 3rd country (EMA, voluntary, EDQM, WHO)
- National program for procurement and manufacturing within hospitals/healthcare – PET, blood centers, tissue and cell establishments, dialysis
- National program for manufacturing at pharmacies (ex tempore, dose dispensing, radio pharmaceuticals) and distribution of medical products to hospitals
- National program for GDP inspections of all wholesalers and distributors
- GCP inspections of Clinical Trials, nationally and internationally
- GVP inspection of Pharmacovigilance on supervisory basis nationally
Responsibility for Compliance group

- Often the first contact – receiving of notifications and allocation of incoming cases
- Guidance in notified quality defects cases, assessment and evaluation of complaints, approval of recalls
- Co-operation at risk situations caused by quality
- Assessment of GMP status at renewals of application or changes in MA medicines
- Assessment and co-ordination of exemptions regarding GMP/GDP
- Administration and authorisation of national permissions
- Administration of MIA/WDA and GMP- and GDP certificates EudraGMDPDatabase
Change of competent authority for assessment of medical device with a ancillary medicinal substance

Anna Mäkinen Salmi, Regulatoriska enheten
Consequences of Brexit

• For medical devices with an ancillary medicinal substance the quality, safety and efficacy of the medicinal substance should be assessed by a competent authority within EU/EEA

• For those products which have been assessed by MHRA need to be transferred to another competent authority within EU/EEA
Process for change of competent authority

• The notified body completes and submits the Request form to registrar@lakemedelsverket.se
  – Product Information should be included

• The MPA will respond by e-mail whether the request can be accepted (based on the availability of required expertise).

• To complete the transfer all documentation submitted to the competent authority and the assessment report should be submitted to RIC@lakemedelsverket.se
  – A confirmation that all documentation has been sent should be included