International Developments and their impact on GMP and Manufacturers

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All opinions expressed are my own and not those of my former employer, EMA
EU-USA MRA – Highlights (1)

- Arose from the “Mutual Reliance Initiative”
- Salvaged from TTIP
  - Amendment to the 1998 MRA, which was non-operational
- Extensive scope of product types
  - Provision for further extension in future
- Includes pre- and post- approval inspections
- FDA has recognised the equivalence of the EU system
  - Evaluation of national implementation and capability ongoing
    ⇒ According to a schedule laid down in the agreement
EU-USA MRA – Transition phase

- As of 1 November 2017: Transition Phase
  - All EU Member States able to recognise “GMP Documents” issued by FDA
  - FDA able to recognise “GMP Documents” from member states that it has assessed as capable
  - 19 member states already confirmed as capable
    - Milestone 1 December 2018: 1 member state assessment outstanding
  - Next Milestone 15 July 2019
    - Capability assessment to be completed for the remaining member states
    - Decision on inclusion of veterinary products

- Import testing of US products will be waived on 15 July 2019 provided all member states are found capable at that time
- UK would continue to benefit until end of any Brexit transition period
EU-USA MRA
EU Member States determined as capable by US-FDA (as of today)
Capability assessment result awaited
EU-USA MRA - Benefits for Authorities

- Firm legal basis enhances existing collaboration
- Optimal utilisation of GMP inspection resources
  - Facilitates risk based approach
  - Option available to recognise extra-territorial inspections
- Improvements to 2-way exchange of information
  - e.g. Rapid Alerts and non-compliance
EU-USA MRA – Benefits to Industry

- Reduction of inspections in EU by FDA and by EU Inspectorates in USA
- QP can rely on release decision by US counterpart
  - QP must still perform batch certification
- Batch testing waived (but not yet)
  - Subject to all member states being assessed as capable
- EU GMP certificates in support of EU MA submissions not needed for manufacturers in USA
  - Export Certificate issued by FDA
  - Pre-existing “valid” EU GMP Certificates may be used
News on other MRAs (on GMP)

- **Canada**
  - GMP included within CETA
  - Provisionally in force since 21 September 17
    - Little practical change from original MRA
    - New option for mutual recognition of extra-territorial GMP inspections

- **Japan**
  - Steriles, biologicals and APIs within scope from 17 July 18
Brexit

- What do we know?
  - The United Kingdom becomes a Third Country on 30 March 2019
Brexit Timetable

EU approval of draft 25 Nov 18

EP vote early 2019

Council approval

Withdrawal Agreement Declaration on Future Framework

Brexit Day 30 Mar 2019

Unless postponed

Transition ends 31 Dec 20 unless extended

Negotiations on future relationship

Transition

“Hard Brexit”

UK Parliament vote 11 Dec 2018

Delay Brexit New agreement Withdraw art. 50
## From 1 April 2019: Marketing Authorisations

<table>
<thead>
<tr>
<th>Issue</th>
<th>No Withdrawal Agreement</th>
<th>During Agreed Transition Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EU-27</td>
<td>UK</td>
</tr>
<tr>
<td><strong>MAH in EU-27</strong></td>
<td>No change</td>
<td>UK contact point. Change to UK MAH by end 2020*</td>
</tr>
<tr>
<td><strong>MAH in UK</strong></td>
<td>Invalid</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Existing CAP</strong></td>
<td>No change</td>
<td>Converts to UK PL</td>
</tr>
<tr>
<td><strong>New MA Applications</strong></td>
<td>No change</td>
<td>Must apply separately to UK</td>
</tr>
<tr>
<td><strong>Safety Features</strong></td>
<td>No change</td>
<td>Legislation repealed</td>
</tr>
</tbody>
</table>

*No corresponding date yet set for VMAs
## From 1 April 2019: GMP-related Issues

<table>
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<tr>
<th>Issue</th>
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<th>During Agreed Transition Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU-27 Manufacture</strong></td>
<td>Test/QP in EU-27</td>
<td>No change</td>
</tr>
<tr>
<td><strong>EU-27 Manufacture</strong></td>
<td>No change</td>
<td>EU QP recognised UK WDA* converts to MIA</td>
</tr>
<tr>
<td><strong>3rd Country (non-UK) Manufacture</strong></td>
<td>No change</td>
<td>Test/QP in UK unless from MRA</td>
</tr>
<tr>
<td><strong>Inspections</strong></td>
<td>EU can inspect in UK</td>
<td>Not specifically confirmed</td>
</tr>
<tr>
<td><strong>UK APIs</strong></td>
<td>WC from MHRA</td>
<td>No change</td>
</tr>
<tr>
<td><strong>EU APIs</strong></td>
<td>No change</td>
<td>Not yet clarified</td>
</tr>
</tbody>
</table>

*If imports from EU*
What will the future look like?

Post December 2020:

- UK free to create own GMP rules
  - Counter-productive in age of harmonisation
- MHRA likely to focus influence at PIC/S
  - Can EU cede lead in GMP guidance applicable in EU?
- EU-UK MRA on GMP
  - Part of future trade deal to avoid trade barriers
    - Should include recognition of extra-territorial inspections
What will the future look like? (2)

- UK government wants MHRA to “participate fully in EMA”.
  - Political Declaration on future framework states “Parties will explore the possibility of cooperation”
  - Participation in non-centralised procedures?

- UK free to make own trade deals with third countries
  - Could include MRAs on GMP
    ⇒ Incompatible with full EMA participation
What if there is no deal?

- In 2016 all stakeholders told by EC to prepare for UK becoming a Third Country on 29 March 2019
- Some stakeholders have not heeded this advice
  - Short-term medicines supply disruption possible in April 2019
- UK technical notes published
  - Pragmatism and flexibility to minimise any disruption to inward UK supply from EU-27
  - Many EU-27 member states may not be prepared
    - UK is a major source of medicines to EU-27
- In the medium to longer term
  - Trade arrangements develop between UK and EU and the rest of the World
Impact of Brexit on EMA

- In the process of moving from London to Amsterdam
  - Fully operational in temporary location by end March 2019
- Significant loss of staff (possibly 30%)
  - Resignation
  - Short-term contract staff ineligible for employment in NL
- Deployment of resources into relocation exercise
- Phase 3 of business continuity plan on 1 Oct 18
  - Almost all but core functions stripped back
  - Development of non-ICH guidelines ceases except 7 guidelines including
    - Reflection Paper on GMP and MAHs
    - GMP Annex 1
    - GMP Annex 21
Contrary to widespread belief, “Fiscal Import” was **not** the driver for Annex 21.
ICH

- ICH Q12 (Lifecycle Management)
  - Step 2b: Deadline for public comments 18 December 2018
    ⇒ Comments to EMA from EU stakeholders

- ICH Q13 (Continuous Manufacturing)
  - Concept Paper awaited

- ICH Q14 (Analytical Method Development and Validation)
  - Concept Paper awaited
Thank You