JAPAN

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Overview of EU Regulatory Framework and Brexit Implications

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Presenter

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Agenda

- Overview of EU Pharmaceutical and Regulations
- Current live regulatory topics
- Implications of Brexit

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OVERVIEWS

Overview of EU Pharmaceutical Regulation

- Directive 2001/83
  - What is a medicinal product? By presentation or function – treatment of disease
  - All medicinal products must have a marketing authorisation
  - Abbreviated routes and exemptions
  - Requirements – toxicology, etc clinical
- Regulation 726/2004
  - Centralised medicines regime
  - European Medicines Agency
- Clinical Trials 2001/20
  - To be replaced by a new Regulation 2014/745 in December 2021
  - New hub and database

Overview of EU Pharmaceutical Regulation (cont)

- Paediatric use
  - PIP
  - Exclusivity
- Orphan Medicines
  - Exclusivity
- Advanced therapy medicinal products
  - Cell products
- Pricing and Reimbursement
  - National competence
- Law and guidance – Notice to Applicants
  - E.g. pharmacovigilance

Overview of EU Medical Device Regulation

- What is a medical device?
  - an article, material etc, together with any software, intended by the manufacturer for use in relation to a disease/the anatomy/ physiological process, or control of conception with a principal intended action other than by pharmacological, immunological or metabolic means.

- What is an IVD Device?
  - a reagent, kit, instrument, etc intended by the manufacturer to be used *in vitro* for the examination of human specimens, including blood and tissue for the purpose of providing information on a physiological or pathological state, a congenital abnormality, the compatibility of donations, or to monitor therapeutic measures,

Overview of EU Medical Device Regulation (cont)

- Previous legislation – Medical Device Directive 93/42/EC
  - to ensure the free movement of goods, while providing a high level of protection and ensuring devices perform as stated by the manufacturer.
  - provides the **essential requirements** that medical devices and accessories covered by it must comply with, and it outlines the conformity assessment procedures.
  - need for a Notified Body (NB) depends on the Class (I, IIa, IIb or III) of the device.
  - NBs - private organisations entrusted by regulatory authorities to award/police CE marks.
  - no NB for Class I unless with a **measuring function** ("*devices which measure physiological parameters…and display or indicate its value in a unit of measurement*") or sterile.
  - for Class I the manufacturer performs and documents the conformity assessment.
  - need for the company to register with its local competent authority
- New legislation - May 2021 – Medical Devices Regulation (EU) 2017/745 (MDR)

Overview of EU Medical Device Regulation – New Law

- New regulations on vigilance and post-market surveillance for national authorities and economic operators, include a new EU EUDRA database (launching May 2022).
- Economic operators – not just manufacturers but also distributors, importers, suppliers and Authorized Representatives have regulatory responsibilities.
- Software requirements must be evaluated to determine potential classifications.
- Stricter NB requirements with new MDR designation required. Unannounced audits by NBs to take place.
- UDIs to be introduced for traceability on all medical devices and labels.
- Stricter rules on clinical, performance evaluation, and clinical investigations will require review of clinical strategy and post-market clinical follow-up plans.
- Safety and performance requirements replace Essential Requirements with compliance through risk management, testing, technical studies etc.

Overview of EU IVD Regulation

- Move from list-based approach to risk-based approach
- Four risk categories: A (low risk) to D (high risk)
- Conformity amended to reflect the new classification rules
- More manufacturers need to use a Notified Body - 80/20 > 20/80
- Process of performance evaluation defined and required throughout the lifetime of the device

Overview of EU IVD Regulation (cont)

- New requirement to provide a body of clinical evidence; required reports
  - Scientific validity, analytical performance, clinical performance
- Post market performance follow-up new requirement
- Unique Device Identifier (UDI)
- Requirement re post-market surveillance (PMS) and PMS plan - incident reporting/trending
- New requirements in technical documentation will mean audit and updates to all technical files
- Summary of Safety and Performance for Class C & D

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SOME LIVE EU REGULATORY ISSUES

Health technology Assessment/Reimbursement

- 100+ regional/national HTA bodies recommend medicines and other health technologies that should be financed or reimbursed
  - Patient access to novel medicines for patients
  - Pressure on healthcare budgets
- Cost effectiveness and cost utility analysis is often represented as an incremental cost-effectiveness ratio (ICER) in Euros per Quality Adjusted Life Year (QALY)
- Considered against an upper limit of what the payer will pay for a QALY
- National autonomy subject to EU Transparency Directive 89/105
- European Network for Health Technology Assessment (EUnetHTA)

Health technology Assessment/Reimbursement (cont)

- Draft Regulation on Health Technology Assessment concerned at varying criteria and parallel assessments
- The EC has proposed four areas of cooperation to address the challenges highlighted above:
  - Joint clinical assessments (JCA)
  - Joint scientific consultations (JSC)
  - Identification of emerging health technologies
  - Voluntary cooperation
- These will cover all new/existing active substances EMA's centralised marketing authorisation
- Centralised JCA will focus on the Relative Efficacy Assessment and not economic parameters. Any pricing and reimbursement negotiations remain the remit of the individual member states.
- A new permanent body will be established to conduct the assessments
- Consideration and assessment prior to CHMP opinion
- Process moving toward mandatory MS cooperation from 2026 following a transition period

Adaptive Pathways

- EMA Adaptive pathways – timely access to new medicines through iterative development, conditional approvals and involvement of patient/ HTA bodies
- Timelines
  - EMA pilot project - March 2014 - August 2016
  - 62 applications - 6 of the applicants had received parallel advice from EMA and HTA bodies
  - Final report on lessons learned in August 2016

Orphan Medicines

- Orphan medicines – Regulation 141/2000
  - Procedure for orphan medicine designation
  - Incentives for the development and placing onto the market of orphan medicines
  - Includes 10 years' market exclusivity (+2 years for paediatric orphan medicines) against from similar medicines with similar indications
- Revision of the EU's legislation on orphan and paediatric' medicines - 141/2000 and 1901/2006 on paediatric use ')
  - It is proposed to revise both regulations to address unmet needs through more tailored incentives medicines addressing the specific needs of children and patients with rare diseases are developed.
  - Impact assessment ended on 6 January 2021. 12-week public consultation.

Promotion and Transparency

- EU legislation– Directive 2001/83 VIIIa. National enforcement
- Detailed and further provisions through EFPIA/national codes
- No POM advertising to the public except approved vaccination campaigns
- No 'excessive and ill-considered' promotion on public health
- To encourage rational use and not exaggerate properties
- Primacy of the medical profession
- Protecting healthcare budgets
- Inducements and hospitality
- Sunshine law equivalents on HCP benefits – some laws (France etc), otherwise codes

Regulatory Framework for Advanced Therapy Medicinal Products including Cell Therapy

- Worldwide **450** companies developing gene therapies and more than **1,000** clinical trials with **20+** new ATMPs filings are expected in Europe pa over the next 5 years
- EMA's own regulatory strategy for 2025 to prioritise cell-based therapies at the top of the list of the "transformational research that is having a significant impact on the regulatory science agenda"
- ATMP Regulation 1394/2007 established a novel legislative framework for advanced therapies
  - Gene Therapy Medicinal Product
  - Somatic Cell Therapy Medicinal Product
  - Tissue Engineered Medicinal Product and Combination ATMP
- Requires a centralised MAA for all ATMPs within the EU and formed a new Committee for Advanced Therapies (CAT)
- Continuing issues around adapting existing EU regulation to cell therapy/ATMPs

Regulatory Framework for Advanced Therapy Medicinal Products including Cell Therapy (cont)

- 2016-2020 advanced therapies clinical trials in EU **+2%** compared with **36%** and **28%** in US and Asia respectively
- Gene therapies considered genetically modified organisms so must also comply with GMO regulation – different EU GMO national authority decisions may vary
- Temporary COVID derogation – Regulation (EU) 2020/1043
- CTR does not cover environmental/biosafety issues so determined at MS level

EU Product Liability

- Product Liability Directive 85/374 – nationally implemented
- Strict/no-fault liability. based on defectiveness
- "Producer"
- "Defect"
- "Damage" and causation
- Defences – including development risk; regulatory compliance
- National competencies including development risk and damage ceilings
- Higher level? *Boston Scientific (Case C-503/13)*
- Relative lack of use? – issues around class actions, legal fees and contingencies, judge/jury, damages levels and cross-border actions

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BREXIT IMPLICATIONS

Impact of Brexit on the UK/EU Life Sciences Industry

- Background
- What does the 'deal' cover and/or exclude?
- Some examples of specific ramifications
- What does the future hold?

UK Legislation and Guidance

- Draft amendments to UK Regulations published January 2019 approved
- Aim to replicate the current arrangements so far as possible
- UK will continue to rely on EU Guidance
- MHRA will be a 'stand-alone' agency
- 50 Guidance Notes
- UK to continue to follow EU GMP, GDP etc but UK may diverge over time:
  - Commission is driving fragmentation of GMP
  - MHRA and PIC/S do not agree with proposed structural changes
  - If PIC/S diverge from EU then UK may follow PIC/S

Immediate Logistic Consequences

- EMA was headquartered in London till 1 March 2019 - now Amsterdam
- 25% + staff and contractor losses
- Moved into the temporary offices in the Spark building from 11 March 2019
- Official address is that of the permanent building - Domenico Scarlattilaan 6,1083 HS Amsterdam.
- Massive extra work due to Brexit
  - Move of Centralised Procedure MAHs
  - New Centralised Procedure owners
  - New RMS for DCP/MRP MAs
- UK MHRA provides >30% of EMA's scientific expertise and conducted 25% of EMA's inspections
- EMA needed to assign this work to other Member State Competent Authorities

EU-UK Trade and Cooperation Agreement - Pharma

About		
• Agreement on 24 December 2020. Not 'once and for all'. Establishment of Working Group • Mutual recognition of GMP inspections of facilities for medicinal products and GMP documents		
What the Agreement Entails		
• Each party may conduct its own inspection on reasoned notice and any material change not considered adequate by the other party, allows it to terminate the cooperation	• No provision for the mutual acceptance of batch testing certificates but UK will accept EEA batch testing and Qualified Person certification until 1 January 2023	• Nothing on mutual recognition of regulatory regimes. Products will be regulated in the UK separately from the EU, and companies will need to comply with both sets of requirements
• No customs on medicinal products originating in an EU member state (or Turkey) or the UK	• Each party may determine its own position in relation to exhaustion of intellectual property rights	• Each party shall provide a period of additional patent protection (an SPC)
• Each party to protect CCI submitted to obtain an MA against unfair commercial use		

Some UK Responses

- 'Grandfathering' rights:
  - Centrally authorised products will automatically be given UK MAs
  - Can opt out but if not converted cannot market in UK after 31 October 2019
- MAHs have 1 year from Brexit to give MHRA baseline data for converted MAs.
- New MA applications go to MHRA which can use normal national 210/180 day procedure or 3 new procedures :
  - A 67-day assessment of new applications for products containing new APIs or biosimilars which have received an EMA CHMP positive opinion
  - A full accelerated, 150-day, assessment for new active substances
  - A 'rolling review', for new active substances and biosimilars

Some UK Responses (cont)

- Applications in progress on Brexit day:
  - MHRA to 'take into account' EU decisions
  - CAPs to be submitted for UK MAA
- Generic MAAs
  - UK will no longer have access to data on EU reference products so need UK reference
  - Existing MAs will remain valid
- Orphans – new UK regime

Decentralised and Mutual Recognition procedures

- UK was Reference Member State (RMS) for approx. 3000 DCP/MRP MAs
  - New RMS in EU is needed
  - If UK is RMS MA holder will need to move to a legal entity in another EU Member State
- Some Member States have offered to re-register for free if they are a Concerned Member State

Retesting and QP – UK Position

- Role of QP already in UK law (SI 2012/1916)
  - UK to retain the role post-Brexit
  - EU and EEA countries 'white listed' - UK to continue to recognise EU QP release
- QP certifying UK product or product imported into UK from outside of EU/EEA must reside in UK
- QP for product imported from EU/EEA can reside in a country on the 'white list'
- Batch testing - UK to accept testing performed in EEA
- QP and testing arrangements may change in future - MHRA will consult and give minimum of 2 years' notice on changes
- Applies to both IMPs and commercial products

Falsified Medicines

- Came into effect 9 February 2019
- UK stakeholders would no longer be able to comply with the requirement to verify and authenticate all relevant medicines.
- There will be no obligations on the UK supply chain to affix the safety features or to scan packs of medicines.
- Packs already affixed with FMD safety features will continue to be accepted in the UK, provided that they are in line with other UK packaging requirements.
- In the interests of public safety, the Government will evaluate the options for a future UK falsified medicines framework, taking into account the investment already made by stakeholders.

Clinical Trials – EU Position

- CT Regulation 536/2014 implemented after Brexit so no UK access to new 'portal'
- UK sponsors need legal entity in EU for trials in the EU or legal representative
- IMPs will need to be QP certified in EU
  - 70% of EU IMPs are currently QP certified in the UK
- Submission of CT information
  - UK-specific trial information will no longer to be submitted to EudraCT.

Clinical Trials – UK Position

- New CT Regulation will be implemented after the UK leaves EU - UK will not have access to new portal or EudraCT database
- UK will continue to accept existing CT approvals (regulatory and IEC)
- Sponsor can be based in UK or an approved country (initially EEA)
- UK will align with the parts of the EU's CTR legislation that are within the UK's control including possibly adopting the same CTA format?
- IMPs need not be recertified if from an approved country (initially EEA)
- Importers of IMPs into UK will require an MIA (IMP)
- IMPs certified in EEA will not need to be recertified if QP oversees compliance
- Publishing trial results and safety reporting – no immediate changes

Pharmacovigilance in the UK

- UK MHRA would assume oversight
  - Individual case safety reports (urgent and non-urgent)
  - Periodic safety update reports
  - Risk management plans
  - Post-authorisation safety studies
- New submission portal developed
- Sharing with EEA of data and systems would cease
- All individual and periodic update reports to MHRA including from 3rd countries
- GPhP would continue to apply but may be reviewed

Parallel Trade

- UK has decided to continue Parallel Trading
  - UK will unilaterally align to the EU/EEA exhaustion regime from Brexit day
  - Long term options will be reviewed and subject to consultation
- UK will convert all currently approved Parallel Distribution Authorisations of CAPs into UK parallel import licences
- EU has made no comparable commitments

Pricing and Reimbursement

- Very little harmonisation at EU level – 'subsidiarity'
- Transparency Directive 89/105
- Proposed HTA Regulation
- Reference pricing
- Limited impact

Medical Device Implications

- Medical Devices – 3 Directives (e.g. 93/42/EEC), MD Regulation 2017/745 –
  - CE-marking
  - NBs – free circulation
- 45% of all Medical Devices CE marked in Europe use UK NBs
- 70% of Non-EU Based Manufacturers use UK NB services
- Where UK Notified Body used - EU position is that UK Notified Bodies lost their status as EU Notified Bodies from 31 October 2019
- BSI achieved designation as a Notified Body in the Netherlands - ISO 13485 Accreditation

Medical Devices – UK Position

- UK will accept EU NB approved medical devices for a limited time
- UK NBs will be afforded a new legal status and to recognise their pre-31 October 2019 approvals
- UK device vigilance autonomy
- UK has in place provisions partly mirroring the new EU device regulation 2017/745
- From 1 January 2021 all devices will need to be registered with the MHRA
  - within 4 months for class III and IIb implantables and IVD list A
  - within 8 months for class IIa, class IIb non-implantables and IVD list B and self tests
  - Within 12 months for class I and class A IVDs and self-certified IVDs

Regulatory impact across therapeutic classifications

Medicines

Centralised
- UK cannot be MA holder
- UK cannot be Rapporteur

MR/DCP
- UK cannot be RMS
- UK cannot be CMS

National
- UK cannot be MA holder for EU market (CEE and Mediterranean Islands)

Medical Devices

UK cannot be **Legal manufacturer** for medical devices marketed in EU

UK **Notified Body** not acceptable for medical devices marketed in EU → need to move to EU Notified Body

Cosmetics

UK cannot be **Responsible person** for Cosmetics marketed in EU (impact on PIF address / label)

Country of origin cannot show EU if Cosmetics manufactured in UK → need to change to "made in UK" – label impact

What Changes and What will Happen in the UK?

- The pharma sector is the UK's 3rd largest in the UK adding $19B to economy
- The industry has relied to a large extent on harmonized procedures in the EU, cross-border processes, goods and value chains
- To replace access to Horizon 2020, IMI, ERC etc the UK government pledged to continue R&D investment post-Brexit, rising to 2.4% of GDP by 2027
- No mutual regulatory recognition. Hence UK effectively now a third country for the EU although the UK provides for transitional measures – MHRA guidance.
- MHRA has joined the Access Consortium (with Australia, Canada, Singapore and Switzerland) and looks to build its relationship with the EU and EMA
- Difficulty of Northern Ireland Protocol – transition till 2022. Then what?

Upcoming Session – Life Sciences Growth Series

Timothy J. Corbett

Dr Joachim Heine

Mike Pierides

Omar Shah

Chris Warren-Smith

Morgan Lewis

WHEN

Thursday, October 14, 2021
4:00pm JST / 3.00pm CST / 8:00am BST

The life sciences industry is undergoing transformation across the globe and facing challenges and opportunities arising from the COVID-19 pandemic. In addition, the United Kingdom's exit from the European Union has brought significant changes for the industry in relation to issues including pharmaceutical and medical device regulation, antitrust and competition, and corporate transactions.

Please join us for a two-part webinar series on key legal, employment, and regulatory trends and issues impacting the European life sciences market.

This first session will focus on corporate, commercial, antitrust, and litigation considerations.

Other Upcoming Sessions – Life Sciences Growth Series

Date / Time	Title	Speaker(s)
Thursday, November 18, 2021 5:00pm JST / 4:00pm CST / 9:00am BST	European Life Sciences Perspective: Current Trends and Brexit Implications – Part 2 (Employment, Data Privacy, Regulatory)	Louise Skinner, Lee Harding, Paul Ranson
Tuesday, November 30, 2021 8:00 pm EST / 5:00 pm PST Wednesday, December 1, 2021 10:00 am JST / 9:00 am CST	Patenting digital therapies – crossroad of life science and technology	Janice Logan, Brett Lovejoy
Wednesday, December 8, 2021 9:00 pm EST / 6:00 pm PST Thursday, December 9, 2021 11:00 am JST / 10:00 am CST	Governance constructs considerations in Japan-US cross-border strategic alliances and collaborations	Suzanne L. Filippi
Tuesday, December 14, 2021 8:00 pm EST / 5:00 pm PST Wednesday, December 15, 2021 10:00 am JST / 9:00 am CST	Using AI in Pharma R&D and Clinical Testing—Regulatory and Legal Issues for the US landscape	Kathleen Sanzo, Jacqueline R. Berman, Nancy Yamaguchi, Jitsuro Morishita

Coronavirus COVID-19 Resources

We have formed a multidisciplinary **Coronavirus/COVID-19 Task Force** to help guide clients through the broad scope of legal issues brought on by this public health challenge.

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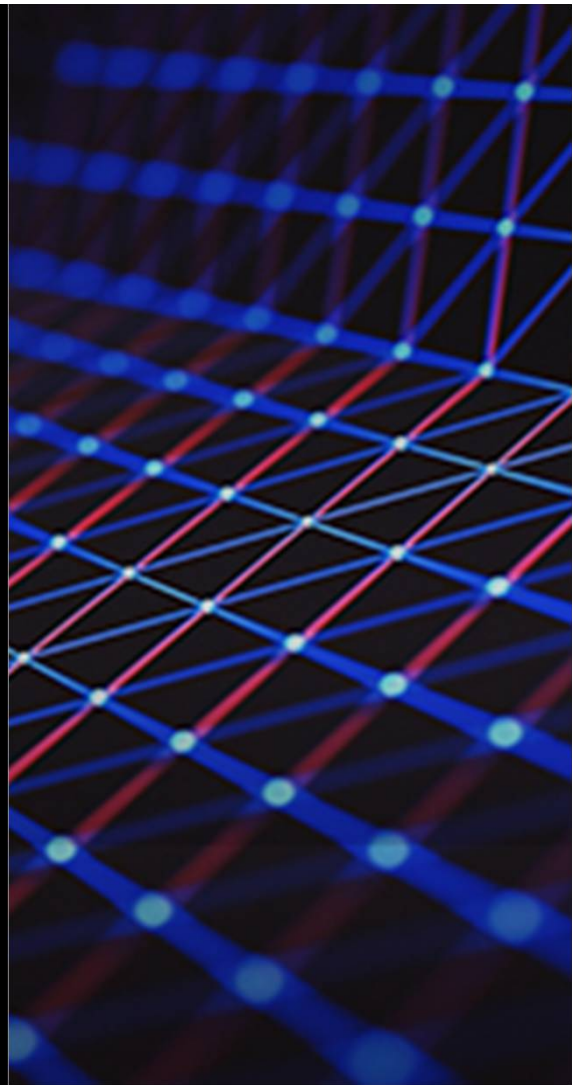
To help keep you on top of developments as they unfold, we also have launched a resource page on our website at **www.morganlewis.com/topics/coronavirus-covid-19**

If you would like to receive a daily digest of all new updates to the page, please visit the resource page to **subscribe** using the purple "Stay Up to Date" button.



Biography

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Paul Ranson is a consultant who focuses on the regulatory and commercial needs of the pharmaceutical, biotechnology, and medical devices sectors. Paul's regulatory experience covers both marketing authorization-related matters and market access, pricing, and reimbursement issues. His commercial work is concentrated on transactions with a high degree of industry specificity including collaborations and outsourcing transactions.

As a result of his experience, Paul is a frequent speaker at conferences on a variety of topics including licensing, health technology assessment and various regulatory topics including during 2015 the Informa EU Pharmaceutical Law Forum in Europe and BIO and ISPOR in the United States. He has written some 10 reports on pharmaceutical and medical device regulatory issues and has authored/co-authored numerous journal articles.

Biography

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Motonori Araki primarily advises on mergers and acquisitions (M&A), commercial transactions, intellectual property licensing, and international dispute resolution. Moto has worked with clients across all industries with a focus on life sciences and technology, representing major US and Japanese companies in cross-border transactions and regulatory matters. His M&A work includes representing buyers and sellers on cross-border transactions and covers structuring, documenting, and negotiating transactions. Moto serves as the office managing partner of the firm's Tokyo office as well as the leader of the firm's Tokyo corporate and business transactions practice.

Our Global Reach

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Asia Pacific
Europe
Latin America
Middle East
North America

Our Locations

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