GLOBAL CLINICAL SUPPLIES GROUP

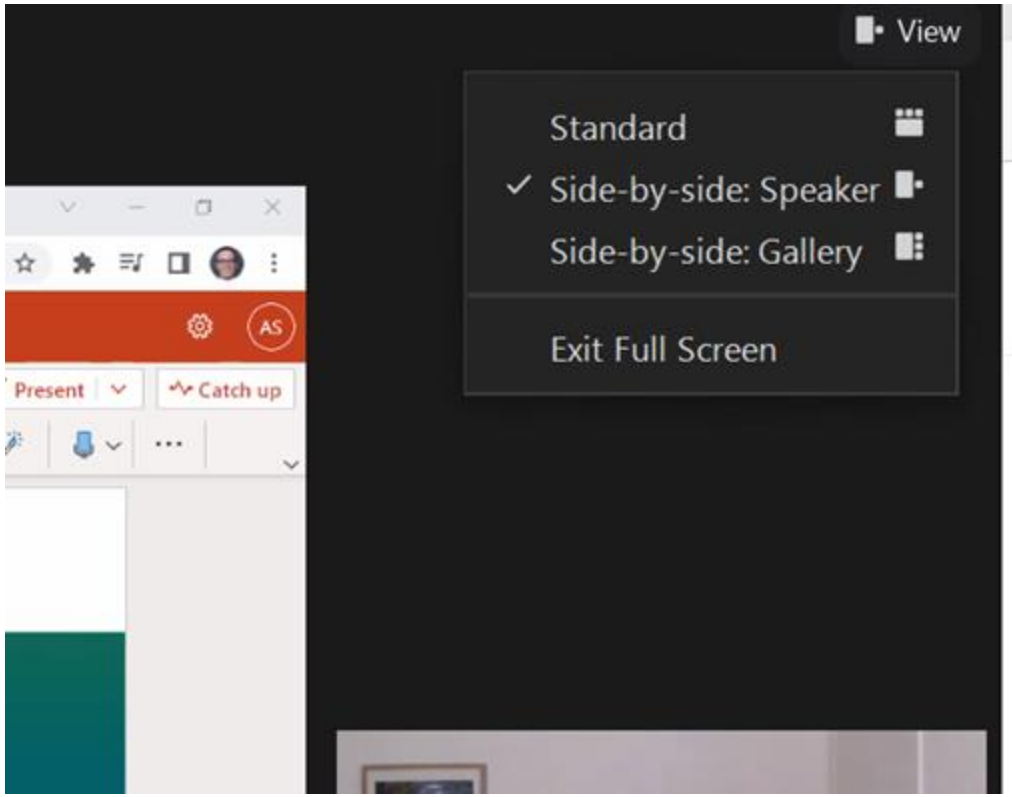
Asia-Pacific Clinical Supplies Webinar Series

30 SEP 2022, 2PM (1400) SGT

Recent Developments in the Global Regulatory Landscape

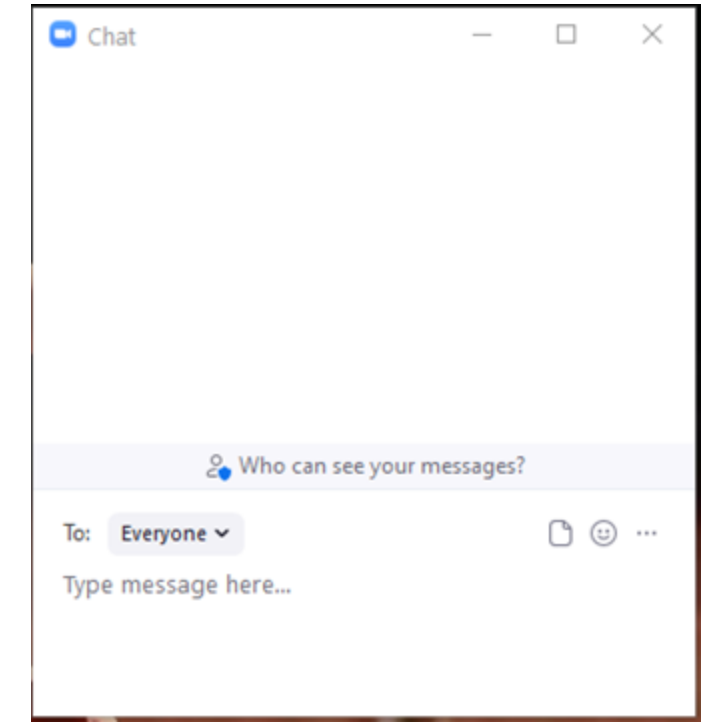
How to Get the Most Out of This Webinar

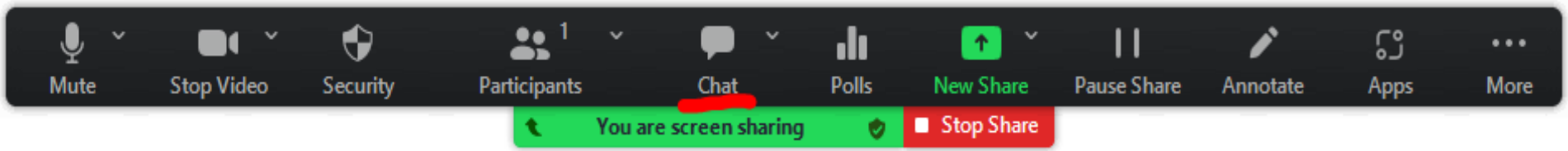
- GCSG website www.mygcsg.com
- Speaker view



How to Get the Most Out of This Webinar

- Ask questions!
- Please type your questions in the Chat Box
- Networking! Connect on social media eg LinkedIn, then follow up after webinar





Today's Agenda

- GCSG - Who are we and what do we do
- 1st Speaker: EU Clinical Trial Regulation by Frances Smith
- 2nd Speaker: QP Expectations and Responsibilities for Drug Products in Europe/UK by Harry Berlanga
- Panel Discussion: Virtual Audits
- Post Webinar Survey
- Closing Remarks and Upcoming GCSG Events

GCSG – Who Are We

- Member-run
- Not-for-profit
- Dedicated to clinical supplies
- Professionals involved in all aspects of the clinical supply chain
- Our first conference was held in 1988
- Global presence
- Largest clinical supplies organization in the world

GCSG Board of Directors

Steve Jacobs - Chairman
(Global BioPharm Solutions, US)

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Executive Director (US)

Global Clinical Supplies Group Organizational Overview

GCSG Asia-Pacific E-Team

Richard Rossi - Lead

Global Cold Chain & Strategic Projects Director

(CRYOPDP, Australia)

Chan Liu

Comparator Strategist Lead

(Pfizer, China)

Masako Ota

Clinical Supply Manager

(Kyowa Kirin, Japan)

Arishma Narayan

Senior Quality Manager

(Akesa Pharma, Australia)

Puvi Bala

Clinical Supply Chain Professional

(UK)

Mervin Sulistyo

Value Engineering Consultant APAC

(World Courier, Singapore)

Linda Kim

Founder & CEO

(Cold Chain Platform, S Korea)

Takuya Kitami

Country Director - Japan

(4G Clinical, Japan)

Celin Ong

VP, Cell and Gene APAC

(Marken, Singapore)

GCSG – Our Aim

- Provide a forum for open discussion
- Share knowledge and industry best practices
- Educate those who are new to our industry
- Provide solutions to problems
- Networking!

Frances Smith

Regulatory Compliance Manager, Almac Clinical Services

Monitor and assess global regulations impacting Clinical Services facilities to ensure compliance

20 years experience in clinical packaging and distribution

MS in Quality Assurance and Regulatory Affairs from Temple University in Philadelphia, PA

GCSG Regulatory E-Team member

EU Clinical Trial Regulation 536/2014

Difference between EU Directive and EU Regulation

Directive 2001/20/EC

- No force of law on its own
- Each member state creates their own law based on the directive
- Introduces variation between member states

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Regulation EU No. 536/2014

- Has force of law by itself
- No individual member state laws
- Ensures consistency in application of law across EU

EU Clinical Trial Regulation 536/2014

- Passed April 16, 2014
- Goal is to streamline conduct of clinical trials in EU through:
  - Consistent application of requirements
  - Development the Clinical Trial Information System (CTIS)
- CTIS took longer to develop than expected, and was further delayed by Brexit and Covid-19
- System development completed in 2020, then an independent audit of the system commenced
- Audit completed in early 2021 and notice published in the Official EU Journal on July 31, 2021
- CTIS go-live and full applicability of CTR was 6 months after this notice, on January 31, 2022

Impact of EU CT Regulation on CTA

Directive 2001/20/EC

- 27 Member States = 27 applications
- Each member state evaluates and provides individual feedback
- Results in variation of the CTA between member states; Sponsor has to maintain each individual CTA

Regulation 536/2014

- 27 Member States = 1 application through Central CTIS Portal
- Single Decision on Part 1 of the CTA
- Central CTIS portal also used for Modifications and Clinical Trial reporting
  - Facilitates streamlined communication between Sponsors and EU Member States
- Public access to CTIS facilitates increased transparency of clinical trial conduct and results

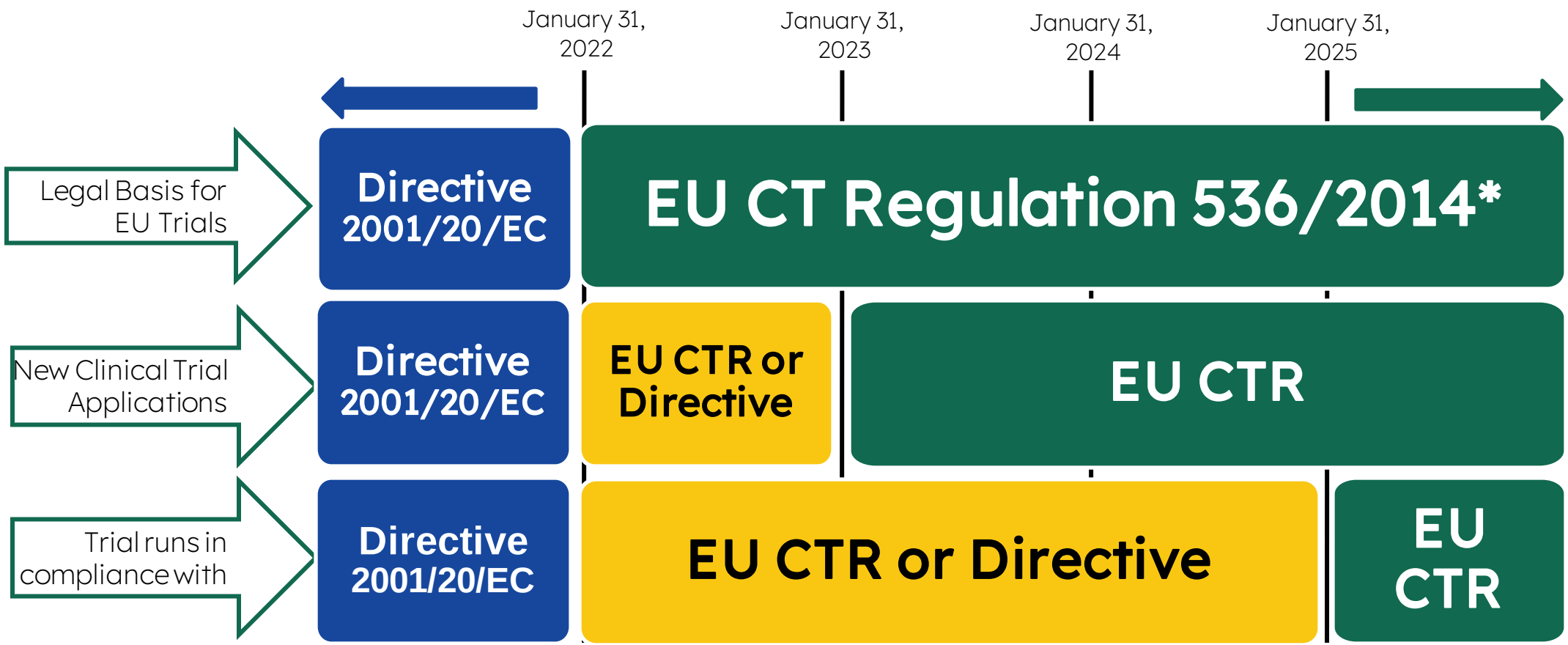
CTA Part 1

- Introduction/Cover Letter/EU Application
- Protocol
- Investigator's Brochure
- GMP Compliance of IMP
- Investigational Medicinal Product Dossier (IMPD)/Auxiliary Medicinal Product Dossier
- Pediatric Investigation Plan (PIP)
- Labeling of the IMP

CTA Part 2

- Recruitment arrangements
- Subject Information/Informed Consent
- Suitability of Investigator/Facilities
- Proof of Insurance, Financials, etc.

Transitional Arrangements from Directive to CTR



*Directive 2001/20/EC was repealed by the EU CTR when it entered into force (Articles 96 & 99)
Transitional provisions are laid out in Article 98

Transitional Arrangements from Directive to CTR

31-Jan-2022

- Clinical Trial Information System (CTIS) is Live
- New trials can be submitted in CTIS (to run under CTR) or directly to EU member states (to run under the Directive)
- Existing trials can continue under Directive

31-Jan-2023

- End of first transition period
- All new trials must be submitted in CTIS (to run under CTR)
- Existing trials can continue under the Directive or transition to CTR

30-Jan-2023: Last date to submit under Directive 2001/20/EC
Trial can be approved after this date

31-Jan-2025

- End of second transition period
- All clinical trials must be transitioned to the CTR
  - Allow time for transition application to be approved in CTIS), as it must be approved before the end of the transition periods

What Trials Must Transition to EU CTR?

Transition is Optional

- Trial being conducted under the Directive that will complete in all EU Member States prior to January 30, 2025
  - End of study must be submitted to all EU member states
  - Study may still be active outside the EU
- Update to EMA Q&A document advises careful consideration before transitioning a trial to avoid unnecessary transition applications

Trial must transition to CTR

- Trial being conducted under Directive 2001/20/EC and the sponsor wants to add an EU member state after January 31, 2023
- Trial that that is still active in any EU member states on January 30, 2025

Timing of transition

- Can be initiated at any time
- Transition must be approved by January 30, 2025
  - Requires Substantial Amendment to align existing documents under the Directive (e.g., Protocol, IMPD)
  - After Substantial Amendment is approved, then trial can be submitted in CTIS for approval

Impact of CTR on Non-Investigational Medicines

Directive 2001/20/EC

- Called Non-Investigational Medicinal Products (NIMPs)
- Medicines that are administered to patients in the study but are not the subject of the study:
  - Rescue Medications
  - Challenge Agents
  - Background Treatments
  - Concomitant Medications
- These are defined under the Directive, however there are not many controls

Clinical Trial Regulation 536/2014

- Now called Auxiliary Medicinal Products (AxMPs)
- Carry the same definitions, but CTR clarifies that they must be necessary for the conduct of the study:
  - Rescue Medications ✓
  - Challenge Agents ✓
  - Background Treatments ✓
  - ~~Concomitant Medications~~ Not AxMPs
- CTR introduces Authorised and Unauthorised AxMPs
- Strict Controls for Unauthorised AxMPs

Auxiliary Medicine (AxMP) Requirements under CTR

Authorised AxMPs

- Clear direction in CTR that authorised medicines should be used as AxMPs
- Includes central EU authorised medicines or Member State concerned authorised medicines
    - Member State concerned is an EU Member state that is participating in the trial
- Suggested labelling for authorised AxMPs in Annex VI – many interpretations of true requirement to label authorised AxMPs
- Will likely require a clinical label to ensure appropriate language (e.g. French authorised AxMP being used in Germany)

Unauthorised AxMPs

- The use of an unauthorised medicine as an AxMP must be justified in the Clinical Trial Application
    - CTR is clear that cost is not an acceptable justification
- Strict controls in place for unauthorised AxMPs
- Required labelling for unauthorised AxMPs in Annex VI
- Traceability, Returns and Accountability must be equivalent to unauthorised IMP
    - Medication Numbers on label
    - Full returns and accountability arrangements

Impact of CTR on Trial Master File Retention

- CTR introduces and standardizes the requirement of 25-year retention of the Trial Master File (TMF)
- The TMF is all the documents and data required to reconstruct the conduct of the trial
- Sponsor is responsible for retention, however retention can be outsourced to a third party
  - Written agreements should be in place
- EU guidance "Recommendation on the content of the trial master file and archiving" is currently being updated
- Sponsors can reference ICH E6_R2 for guidance on TMF contents (Section 8)

Impact of Clinical Trial Regulation on Clinical Label Text

- Clinical Label Text Requirements are found in Annex VI of the CTR
- Harmonises label text across EU Member States
- Includes required text for:
  - Unauthorised Investigational Medicinal Products (IMPs) and AxMPs
  - Authorised IMPs/AxMPs (Article 67)

- Original version of Annex VI required the expiry date to be printed on all primary containers, with no allowance to omit
  - This requirement caused significant concern among Sponsors

Revision of Annex VI

- The European Commission adopted a revision to Annex VI on September 6, 2022
- Expect it to be published in official EU Journal in November 2022, will be fully applicable 20 days later
- Revisiion re-aligns allowance for expiry date omission with EU Annex 13
    - Small immediate container or when immediate container will remain with outer
    - In both scenarios, expiry date must appear on the outer container label

Impact of CTR on Good Manufacturing Practice for IMPs

- The CTR introduces new laws and guidelines for Good Manufacturing Practice for IMPs
- This causes a further fragmentation of Good Manufacturing Practice in the EU
- This also illustrates the move from the use of Directives to Regulations in the European Union

New GMP framework for Investigational Products

Delegated Regulation 2017/1569

- Effective on the same date as the EU CTR (January 31, 2022)
- Includes QP responsibilities that were left out of the EU CTR
  - Imported product must be manufactured under GMPs equivalent to those in EU
  - Manufacturing must comply with Clinical Trial Authorisation
- Includes arrangements for inspections

Detailed Commission Guidelines for GMP of IMP

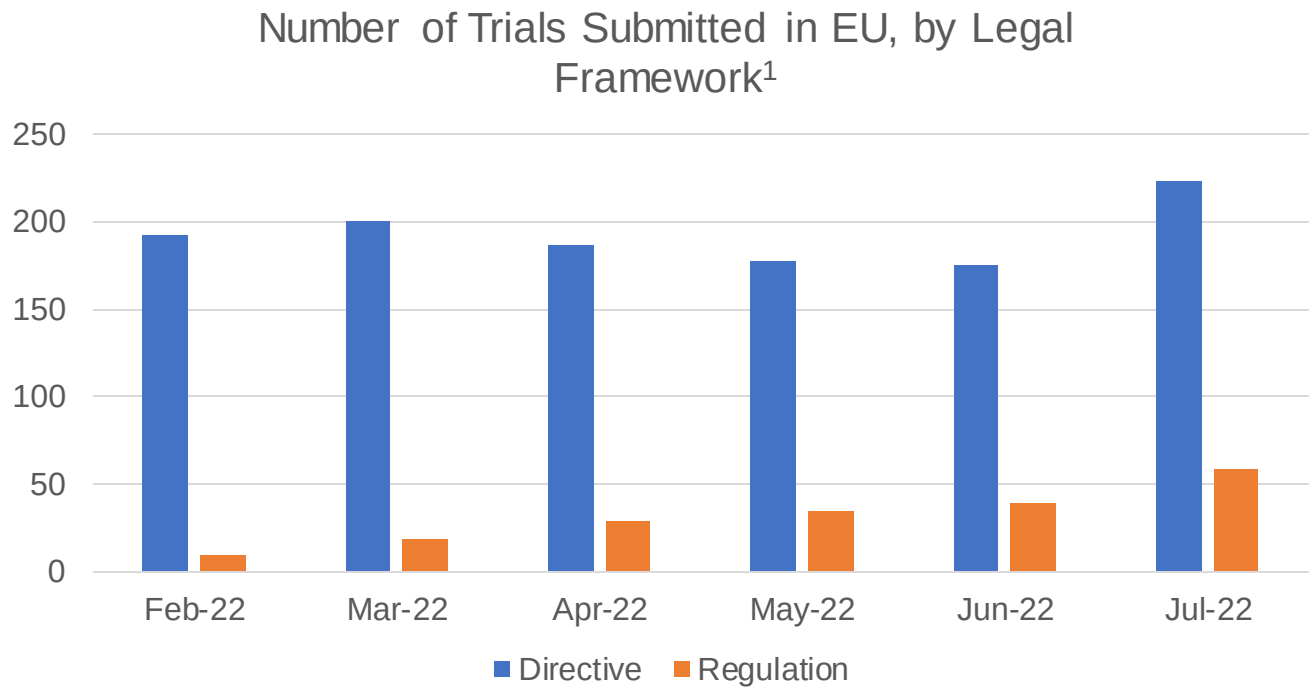
- Replaces Annex 13
- GMP requirements are largely the same, but some changes have been made
- Expiry Update labels must contain the new expiry date, repeat the batch number **and** repeat the trial reference number
- New template for IMP Batch Release available on Eudralex Volume 10
- Shipping section with 2-step release process was removed, but this is brought back in the EU Guideline for handling and shipping of IMP (EMA/INS/GMP/258937/2022)

Global Impact of new EU GMP for IMP framework

- PIC/S (Pharmaceutical Inspection Cooperative Scheme) has updated Annex 13 in the PIC/S GMP Guide to align with the new EU Guidelines
- PIC/S Annex 13 update was effective February 1, 2022 and includes:
  - 25 year retention of the Trial Master File
  - Label text requirements aligned with Annex VI of EU CTR but not identical
    - Leaves flexibility to justify the omission of the expiry date
  - Expiry update label requirements aligned with new EU Guidelines – expiry update label should state new expiry date, repeat the batch number and repeat the trial reference number
- The update removes the following items, also mirroring the EU Guidelines:
  - Definition of Non-Investigational Medicinal Product
  - Shipping section (which removes the 2-step release procedure)

Sponsor Adoption of EU Clinical Trial Regulation

- As of July 31, 2022 sponsors are still submitting a majority of Clinical Trial Applications under the Directive
- Applications under the Regulation, in the Clinical Trial Information System are steadily increasing



1. EMA KPIs Clinical Trials (31-Jul-2022)

Final thoughts: Looking Ahead

- The next major milestone is the end of the first transition period on January 30, 2023
- Sponsors are still working through adopting the use of CTIS and how to apply the requirements of the CTR
- EMA is consistently updating their Q&A document to provide additional direction to sponsors
- Positive decision on the revision of Annex VI (clinical label text requirements) is important to sponsors

Helpful Links

1. Eudralex Volume 10 (Clinical Trial Guidelines)
2. EU Clinical Trial Regulation Questions & Answers (Version 6.2 September 2022)
3. EU Clinical Trial Regulation 536/2014 (Annex VI Label Text pages 72-74)
4. Commission Delegated Regulation 2017/1569
5. Detailed Guidelines for GMP of IMP
6. Guidelines on Sponsor Responsibility for Shipping and Handling of IMP
7. Revision of Annex VI
8. CTIS Sponsor Handbook

Frances Smith

Regulatory Compliance Manager, Almac Clinical Services

Monitor and assess global regulations impacting Clinical Services facilities to ensure compliance

20 years experience in clinical packaging and distribution

MS in Quality Assurance and Regulatory Affairs from Temple University in Philadelphia, PA

GCSG Regulatory E-Team member

Questions?

Harry Berlanga BSc(Hons) MSc CBiol MSB

Senior Director for Quality & Qualified Person,

Thermo Fisher Scientific

GCSG Regulatory E-Team Lead

Thermofisher, Oversee Quality org at 6 sites in the clinical trials division

QP Status under Permanent provisions in UK

Chartered Biologist with over 20 years experience of Commercial Sterile & Solid dose, Clinical Manufacture, Packaging and Distribution

QP Expectations & Responsibilities for Drug Products in Europe/UK

Understanding the QP Role, Legal and Routine Duties, Code of Conduct

QP Legal Duties

- Comply with EU/UK Law
- Delegate legal duties to another QP only (Formalised under QP to QP agreements)
- Certify a batch meets GMP and requirements of a CTA (Clinical Trial Application) or Marketing Authorization Application (MAA)
- Cannot release a batch unless it has been certified and certify on a register

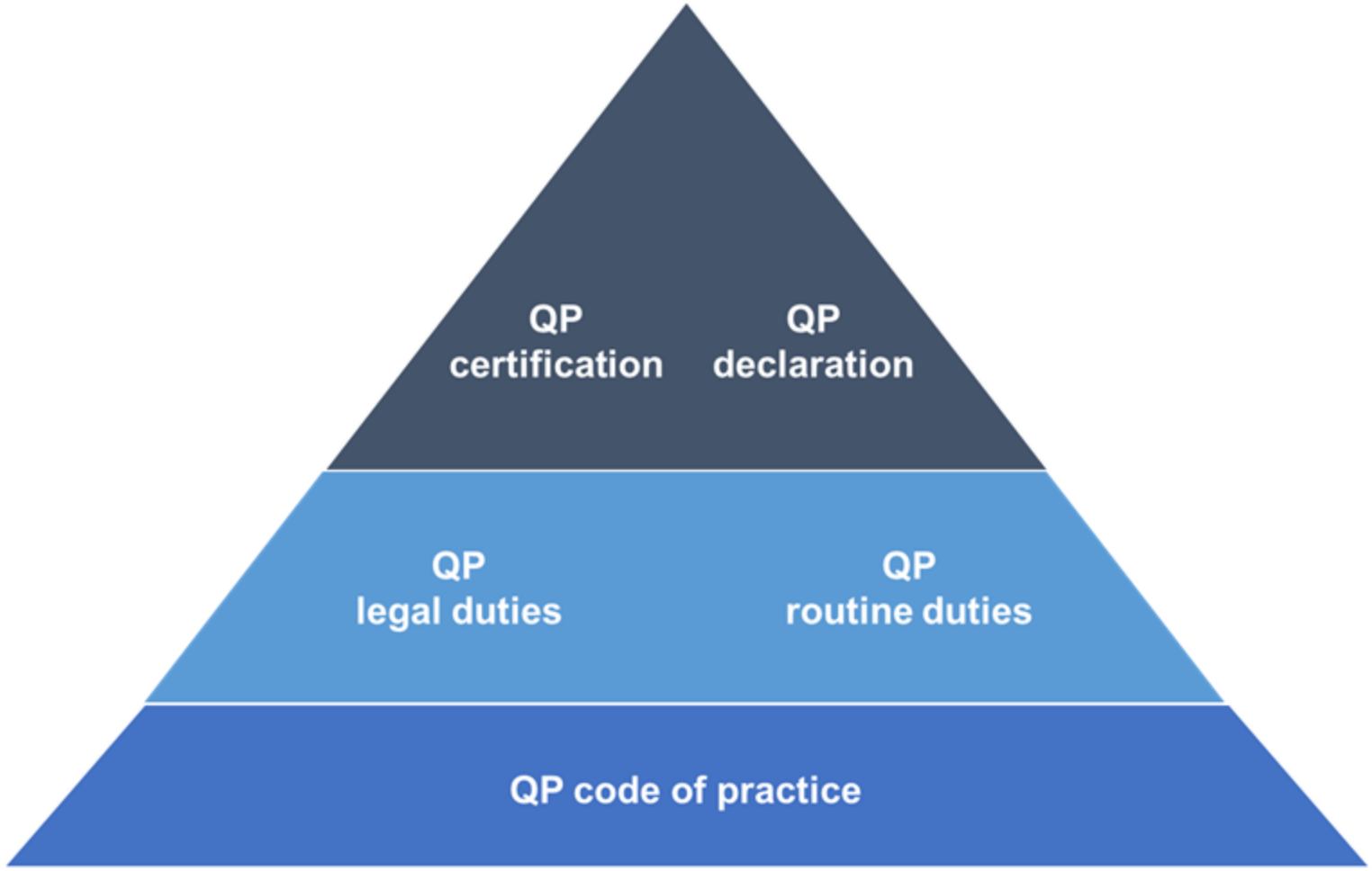
QP Routine Duties

- Delegate their duties to other professionals in the supply chain
- Have oversight of the Pharmaceutical Quality system
- Keep track that all areas are up to date and compliant using KPIs, Audits etc

QP Code of Practice

- Abide by a code of practice
- Educational requirements and experience are defined at a high level in the EU Directives. These are interpreted slightly differently in different member states
- They must only represent themselves on licenses that they have intimate experience of the formulation & technology
- Certain member states restrict QPs to particular dosage forms e.g blood and Advanced Therapy Medicinal Product (ATMP) in Germany

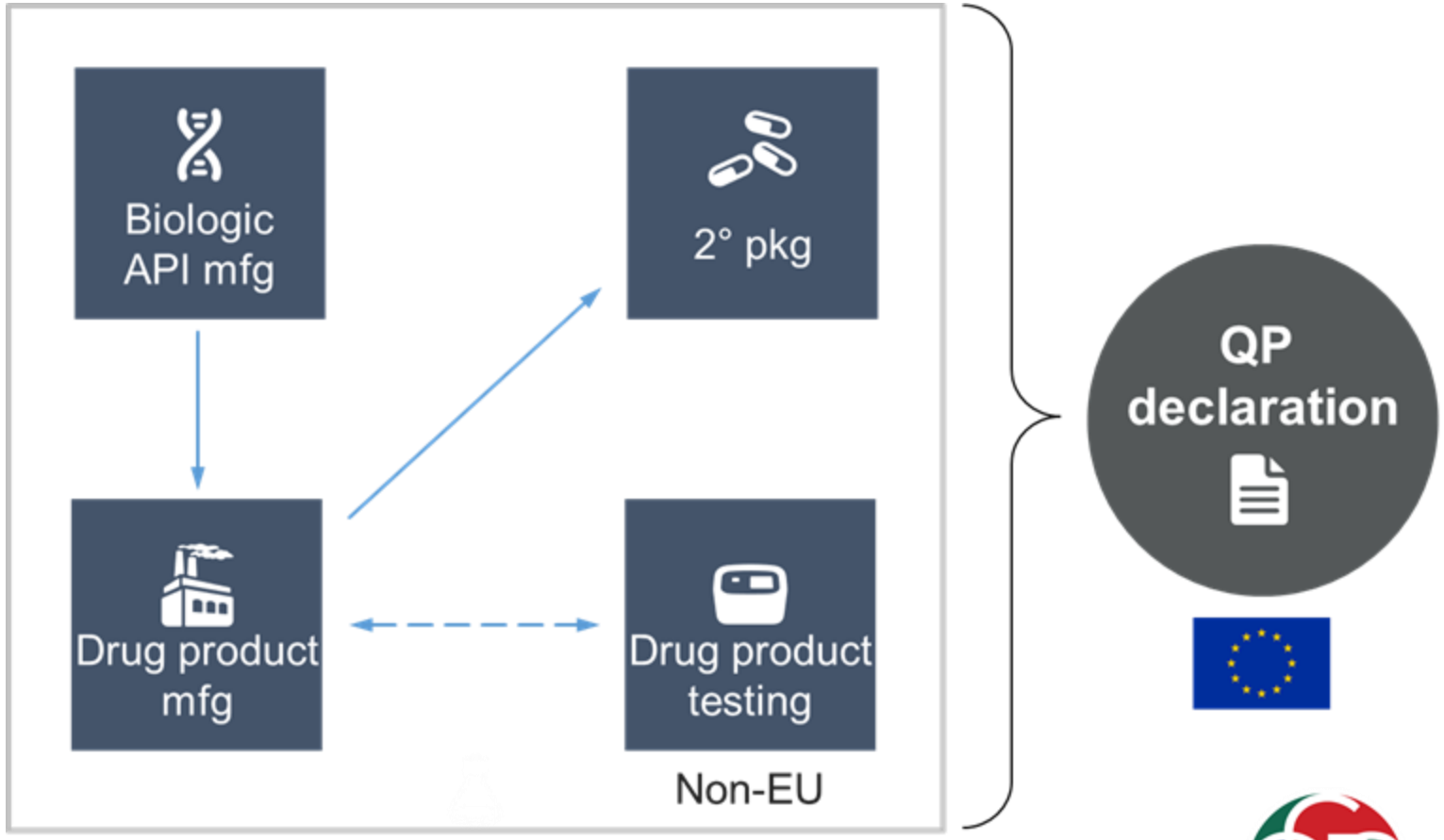
Understanding the QP Role, Legal and Routine Duties, Code of Conduct



The QP declares, based on evidence, that sites in the supply chain operate to a standard of GMP at least equivalent to EU GMP

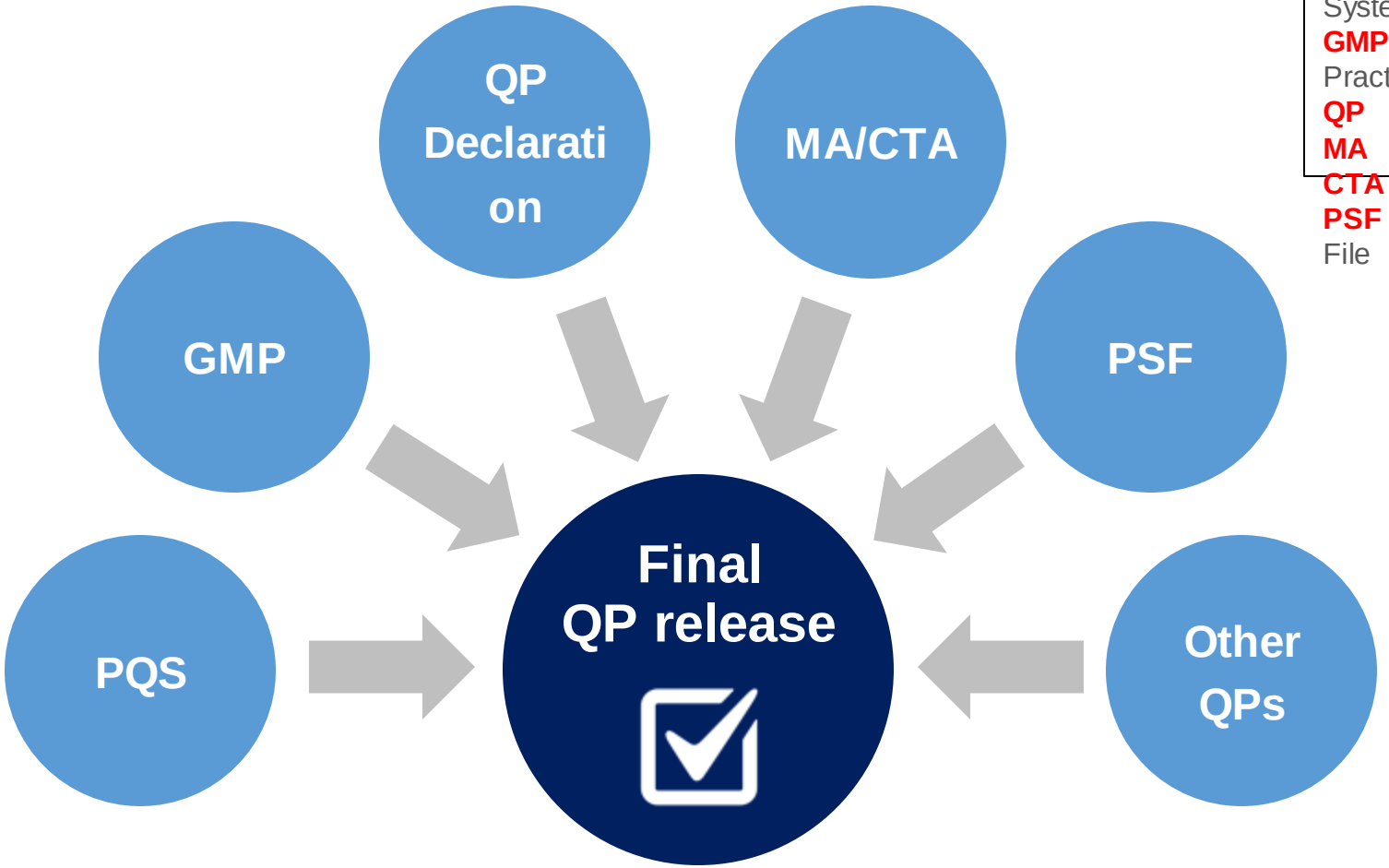
QP Declaration

- The QP declares that all sites operate to a standard of GMP at least equivalent to EU GMP
- Includes manufacturing, packaging and release and stability testing sites including any contract laboratories (including drug substance if a biological product)
- The QP has to list the evidence that the declaration is based on
  - Appropriate Audit evidence
  - EudraCT number
  - Protocol
  - IMPD- supply chain



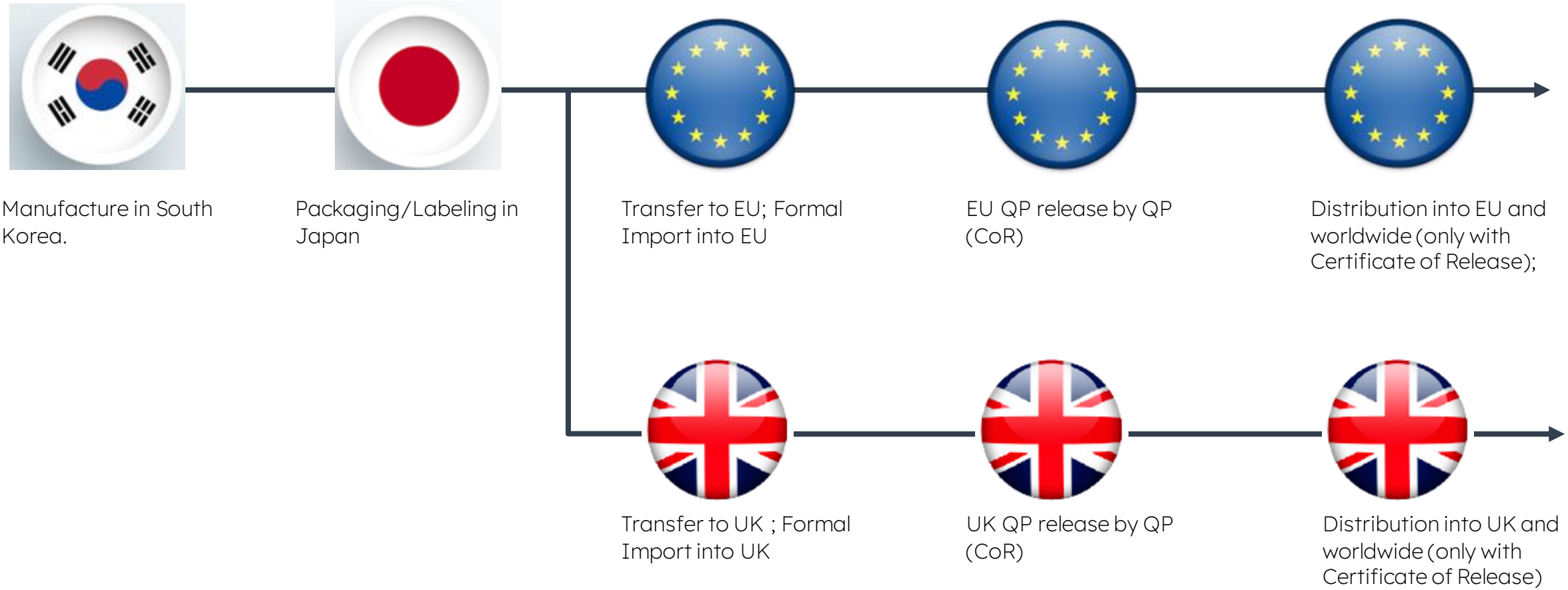
QP Release Duties; A Summary

PQS	Pharmaceutical Quality System
GMP	Good Manufacturing Practice
QP	Qualified Person
MA	Marketing Authorization
CTA	Clinical Trial Agreement
PSF	Product Specification File

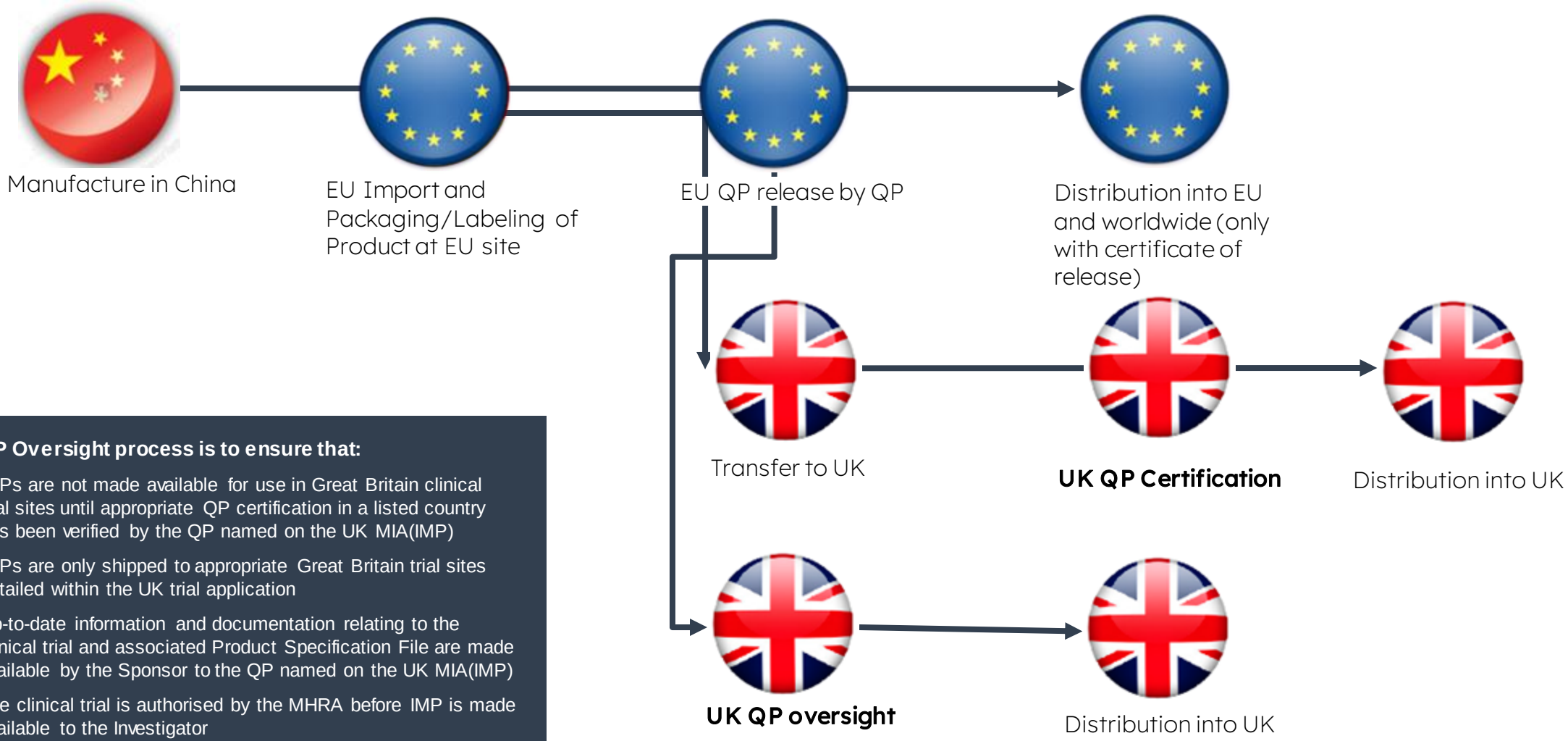


Underpinned by QP to QP agreement and QTA

Option 1: EU/UK Supply– Manufactured/Packaged/Labelled outside of EU

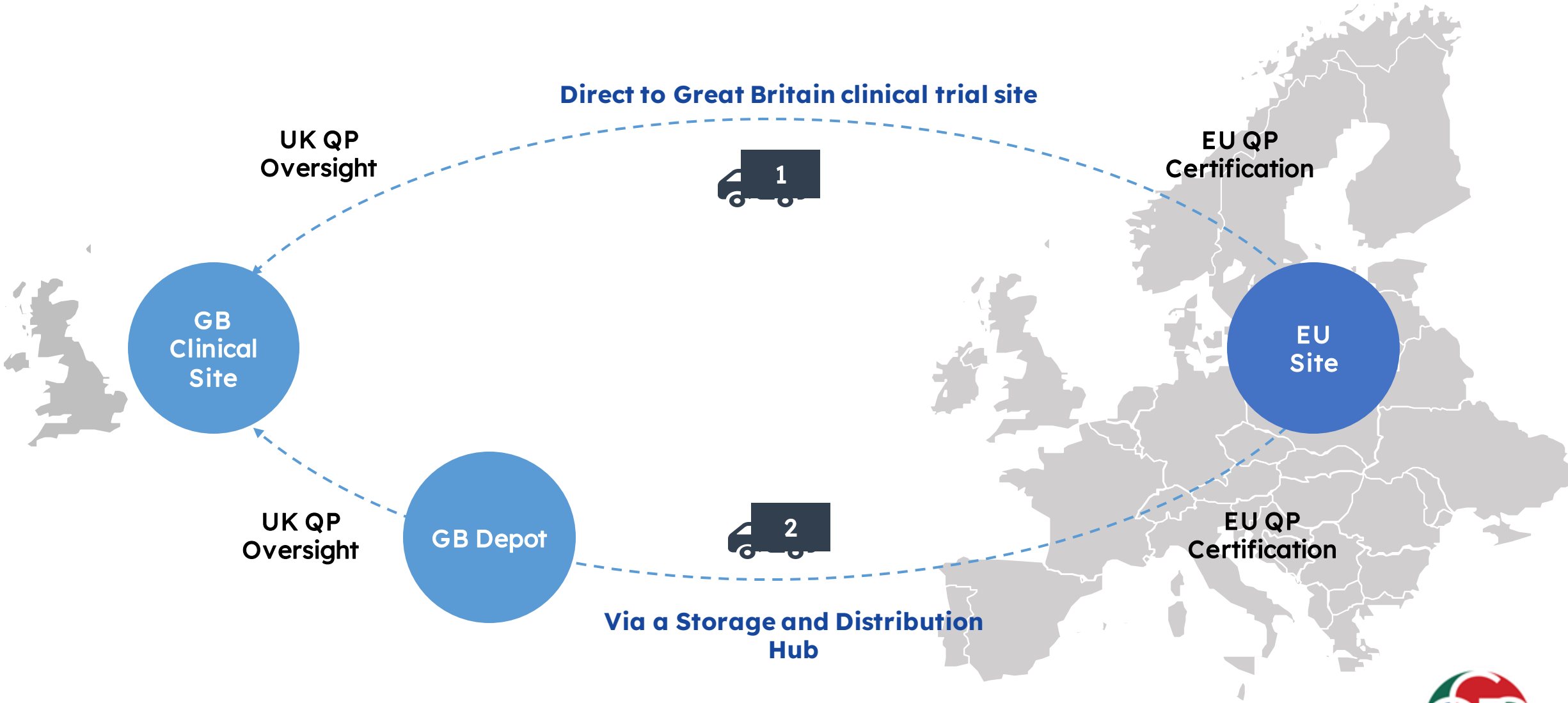


Option 2: EU/UK Distribution– Packaged/Labelled in the EU



The QP Oversight process is to ensure that:

- IMPs are not made available for use in Great Britain clinical trial sites until appropriate QP certification in a listed country has been verified by the QP named on the UK MIA(IMP)
- IMPs are only shipped to appropriate Great Britain trial sites detailed within the UK trial application
- Up-to-date information and documentation relating to the clinical trial and associated Product Specification File are made available by the Sponsor to the QP named on the UK MIA(IMP)
- The clinical trial is authorised by the MHRA before IMP is made available to the Investigator



Both routes require the oversight of a UK MIA(IMP) holder and QP

Harry Berlanga BSc(Hons) MSc CBiol MSB

Senior Director, Quality & Qualified Person,

Thermo Fisher Scientific

GCSG e-Regulatory Team Lead

Thermofisher, Oversee Quality org at 6 sites in the clinical trials division

QP Status under Permanent provisions in UK

Chartered Biologist with over 20 years experience of;

Commercial Sterile & Solid dose

Clinical Manufacture, Packaging and Distribution

Questions?

Panel Discussion on Virtual Audits

A SHORT POLL ON VIRTUAL AUDITS

Our Panellists

Frances Smith

Regulatory Compliance Manager,

Almac Clinical Services

Harry Berlanga

Senior Director, Quality & Qualified Person,

Thermo Fisher Scientific

Richard Rossi

Global Cold Chain & Strategic Projects Director

CRYOPDP, Australia

Celin Ong

VP, Cell and Gene APAC

Marken, Singapore

Richard Rossi

Global Cold Chain & Strategic Projects Director

CRYOPDP, Australia

Over 20 years of experience in diagnostic pathology, clinical trial storage and logistics management across Australia, Singapore and Japan

GCSG Asia Pacific E-Team Lead

Virtual Audit Panellist

Celin Ong

VP, Cell and Gene APAC

Marken, Singapore

14 years of experience in the pharma industry

Registered Pharmacist in Singapore, Australia and Malaysia

Focused on global clinical trial distribution for the past 10 years

GCSG Asia Pacific E-Team Member

Virtual Audit Panellist

Virtual Audits

- QP Audits
  - Required for QP declarations
  - Every 3 years for all sites
  - RA used during COVID
- Competent Authority Inspections
  - Stop/Pause or refer to Virtual Inspections during COVID
  - Now Hybrid Inspections?

International Coalition of Medicines Regulatory Authorities (ICMRA)
Covid-19 Working Group: Remote GCP and GMP Regulatory oversight inspections

Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic

MHRA remote inspection: What you should know

11 SEPTEMBER 2020

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Authorities test Hybrid Inspections

The ICMRA (International Coalition of Medicines Regulatory Authorities) is a voluntary association of medicines regulatory authorities around the world for overarching strategic coordination and advocacy, particularly in regulatory matters. The EMA is also a member.

One objective is to improve coordination between regulatory authorities in the review of CMC submissions, e.g. through submissions of information in the same format (e.g. according to the harmonised standards of ICH M4Q, M8, etc.) and the same standards for sponsor submissions. Now there are two pilot projects in this regard; one on a possible cooperative assessment in the CMC area and one on the implementation of hybrid inspections*.

The two pilots are being conducted under the auspices of ICMRA to assess the feasibility and potential for further collaboration and convergence between regulators on specific data expectations and assessment

Hosting Audits: In Person versus Virtual

In Person

- Technology needs typically minimal
- Live tour is more interactive, allows direct communication with area experts
- Typically have controlled copies of standard documents such as SOPs, facility controls, validation, etc.
- Can review original documentation where available, ability to compare multiple documents
- Easier to support multiple auditors assessing separate topics

Virtual

- Need reliable meeting and secure document sharing platform
  - Conduct a technical test before the audit
- Tour may be pre-recorded or live, but interaction with area experts is limited
  - Wi-Fi coverage in warehouse/production areas can be challenging
- Sharing electronic documentation only
  - Need detailed scope and clear understanding of what the auditor wants to review
  - Pre-load as much documentation as possible to the portal
  - May need to scan hard copy documentation to allow auditor review
- Auditor will likely request documents to review ahead of audit
  - Must decide what will be shared - will be different for a client audit than for a regulatory authority audit

POST WEBINAR SURVEY

Updates

- European conference is held annually in Oct: Croatia in 2022
- **SAVE THE DATE: 24Feb2023 (Friday) Asia Pacific Webinar Series on IRT and Forecasting**
- US conference is held annually in April
- Our first Asia Pacific face-to-face conference is planned for 2024 - Watch this space…
- Access to Discussion Forum and past conference materials (for members)

In Closing…

- Thank you for your attendance, questions, comments and feedback
- Please share your experience with your managers and colleagues
- Sign up to our newsletter!
- Consider volunteering
- Job Board https://mygcsg.com/jobs/
- Contact: asiapac@mygcsg.com
- Network!

THANK YOU FOR JOINING OUR JOURNEY