# Latest Updates on QP Responsibilities and Quality Expectations in the EU and Israel

CRISP Meeting

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Presented by:

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# Agenda

Identify pharmaceutical legislation updates specific to IMPs, focusing on:

- EU Directives and Regulations
  - Clinical Trials Directive
  - Falsified Medicines Directive
  - GDP Directive
- EU GMP Guidelines
  - Chapters 1, 3, 5, 6, 7, 8
  - Annexes 2, 16
- QP Declaration template
- New requirements for QP Release in Israel
- Assess the impact, if any on the
  - QP
  - Sponsor

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# CLINICAL TRIALS DIRECTIVE

# Clinical Trials Directive Update

- Proposal issued July 2012
- Intended to replace the CT Directive 2001/20/EC
- Driven by the significant decline (25%) in the number of trials conducted in the EU between 2007 and 2011

*'Proposing to cut red-tape and bring patient orientated research back into Europe.'*

*'Restore the EU's competitiveness in clinical research ….for the ultimate benefit of patients.'*

# Intention

- Simplified Authorization Procedure
  - Fast and thorough assessment by all Member States (MS)
  - One single assessment outcome
  - Individual MS appoint body or bodies in charge of assessment
    - Assessment is fully independent
    - Based on necessary expertise
  - Regulatory Authorities in EU countries work together and are held to the same time frame when approving CT

# Intention

- Simplified Reporting Procedures
  - Prevents submitting largely identical information on the CT to various bodies and MS
- Commission to conduct controls in MS and other countries
  - Ensure rules are being supervised and enforced
- New rules for CT that are conducted outside the EU but referred to in a CT application
  - Proposal provides for compliance with regulatory requirements
    - At least equivalent to those in the EU
    - Rules on transparency

# Intention

- Takes the legal form of a Regulation - SIGNIFICANT CHANGE!
  - Current Directive is subject to interpretation in different MS
  - Ensures that the rules for conducting trials are identical throughout the EU
  - Vital to ensure that in authorizing and supervising the conduct of a CT, MS use identical rules
- Legislative proposal to be discussed in the European Parliament and in the Council

# Impact

- Out for consultation
  - Due for implementation 2016
  - Content not finalized and therefore subject to change
    - Likelihood of timely agreement on the content is questionable
    - Industry at large is not optimistic

- No immediate impact for the QP or Sponsor

- Potential benefits
  - Simplifies CT submissions and reporting
  - Recognizes the need for flexibility
  - Should reduce costs for our customers (e.g. administration fees)
  - Harmonization between MS advantageous when conducting multinational CT
    - e.g. labeling requirements identical for all countries

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# FALSIFIED MEDICINES DIRECTIVE

# Directive 2011/62/EU

# Falsified Medicines Directive
# Directive 2011/62/EU

- Published 01 July 2011 as Directive 2011/62/EU
- First provisions of the Directive were to be implemented by MS- 02 January 2013
- Not all MS have confirmed that the requirements have been transposed into national law
- Predominantly impacts pharmaceutical companies involved in commercial manufacture
  - Less significance to those involved in Clinical Trials
  - Pertinent elements of relevance

# Falsified Medicines Directive
# Directive 2011/62/EU

- Substantially changes the EU framework concerned with the supply of licensed medicines

- Introduces
  - Concept of brokering for finished medicinal products
  - Requirement for brokers to be registered in their EEA Member State
  - Requirement for a wholesale dealer's license for export of medicines to third countries

- Extends existing obligations for wholesale dealers and provides new obligations, in particular reporting any suspected falsified medicines

- Formalizes expectations regarding the manufacture and importation of APIs from the EEA or non-EEA countries
  - Extensive details provided within the Directive but these are not applicable to IMPs

# Falsified Medicines Directive
# Directive 2011/62/EU

- Formalizes the:
  - Expectation that manufacturers of the medicinal product will verify the authenticity and quality of APIs and excipients used
  - Obligation for manufacturers to inform the Competent Authority and MA Holder should information become available that products may be falsified
    - Whether distributed through the legitimate supply chain, or by illegal means

# Falsified Medicines Directive
# Directive 2011/62/EU

- Formalizes the:
  - Requirement for internet companies selling medicines to be registered and for them to display a common internet logo on their website
    - Not yet fully operational
  - Requirements for the outer packaging of certain commercial medicines to include unspecified safety features to verify the authenticity of the medicine
    - Exact requirements to be specified in delegated act due 2014

# Falsified Medicines Directive
# Directive 2011/62/EU - Impact

- Predominantly applicable to commercial products

- With regards to IMPs
  - Relevant to
    - Comparator product
      - Origin of material
      - Security of supply chain
      - Authenticity of product
        - » Assurance provided by presence of security features
      - Use of brokers, wholesale dealers etc…
    - Excipients used in IMPs
      - Encapsulation e.g lactose

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# GDP DIRECTIVE

# 2013/C 68/01

# GDP Directive - 2013/C 68/01

- Previous guide was in place for 19 years (4 page document)
  - Many of the requirements had been expanded at a local level and incorporated into national guidance
- Revised Guidelines on GDP to reflect more complex supply chains of the 21st Century – similar to the current EU GMP guide
- Published on 7 March 2013
  - Adopted 7 September 2013
- Various organizations affected, e.g.
  - Pharmaceutical companies, Wholesale Distributors, Logistics Centers, Couriers, and Brokers
- Impact on these organizations depends on the:
  - Size, culture, and existing Quality Systems

# GDP Directive - 2013/C 68/01

- Divided into chapters:
  1. Quality Management
  2. Personnel
  3. Premises and Equipment
  4. Documentation
  5. Operations
  6. Complaints, returns, suspected falsified Medicinal products, and Medicinal Product Recalls
  7. Outsourced Activities
  8. Self-Inspections
  9. Transportation
  10. Specific Provisions for Brokers

# GDP Directive - 2013/C 68/01

## Chapter 1: Quality Management

Increased emphasis on:

- The Quality System
  - New expectations regarding:
    - Change Control, CAPA, and Quality Risk Management

- Management review and monitoring to facilitate continuous improvement
  - Requires a formal process for review of the Quality System periodically to include for e.g.
    - Complaints, deviations, CAPA, change control, audit findings, performance indicators
    - Outcome to be documented and communicated internally

- Quality Risk Management to be applied
  - Level of effort commensurates with the level of risk

# GDP Directive - 2013/C 68/01

## Chapter 2: Personnel

- Defines the requirement for:
  - Responsible Persons (RPs)
  - Organizational charts, job descriptions, staff training

- Key new areas
  - RP may delegate duties but not responsibilities
    - 12 routine duties defined
  - Staff to be trained in GDP with regular training for the RP
  - A requirement for personal hygiene to be considered

# GDP Directive - 2013/C 68/01

## Chapter 3: Premises & Equipment

- Significant changes
  - Expanded requirements for
    - Temperature mapping
    - Use of electronic inventory systems
    - Qualification and validation of equipment
  - Key new areas
    - Records for equipment repair, maintenance, and calibration required
    - Validation of computer systems

# GDP Directive - 2013/C 68/01

## Chapter 4: Documentation

- Greater emphasis on how documentation should be managed and controlled, e.g.
  - SOPs, instructions, contracts, records

- Key new areas
  - Documentation should be in a language understood by personnel
  - Emphasis of version control and ensuring documentation is up-to-date

# GDP Directive - 2013/C 68/01

## Chapter 5: Operations

- Significant emphasis on checking the legitimacy of suppliers and customers
- GDP now extends to cover export
- Key new areas
  - Verifying the supplier is compliant with GDP
  - Due diligence checks on the supplier
  - Monitoring sales to identify misuse or diversion of medicines
  - Requirement for First Expiry First out, rather than FIFO
  - Stock inventories should be performed regularly
  - Exporting medicines out of the EEA requires a wholesale authorization and full GDP is applied

# GDP Directive - 2013/C 68/01

## Chapter 6: Complaints, Returns, Suspected Falsified Medicinal Products, and Medicinal Product Recalls

- No significant change to previous requirements
- Guide suggests 10 days as an acceptable time limit to return medicines that have been outside the licensed chain
- MHRA will maintain its existing guidance on the acceptance of returns to sellable stock
- Stolen medicines cannot be returned to stock

# GDP Directive - 2013/C 68/01

## Chapter 7: Outsourced Activities

- Requirements for contracts between parties where GDP has been outsourced
  - Consistent with current MHRA expectations
- Contracted out activities should be audited as part of management review
- Audits by independent external experts may also be useful
  - Cannot be used as a substitute for self-inspection

# GDP Directive - 2013/C 68/01

## Chapter 8: Self Inspections

- Greater emphasis on how self inspections are conducted and recorded

- Key new areas
  - Self inspections can be carried out by staff other than RP
  - Independent external audit is recommended
  - Reports should be subject to CAPA principles

# GDP Directive - 2013/C 68/01

## Chapter 9: Transportation

- Expanded requirements to control distribution

- Key new areas:
  - Medicines to be shipped within label conditions
  - Temperature excursions should be reported and investigated
  - Risk assessments of delivery routes to identify when temperature control is needed
  - Dedicated vehicles to be used where possible
    - Procedures to cover use of non dedicated vehicles.
  - A contract to be in place with transporters as required by Chapter 7

# GDP Directive - 2013/C 68/01

## Chapter 10: Specific Provisions for Brokers

- New requirements not previously covered
  - Provides a definition for Brokers

    *"Person involved in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another"*
  - By definition, brokers do not procure, supply, or hold medicine

# GDP Directive - 2013/C 68/01

## Chapter 10: Specific Provisions for Brokers

- Indicates requirement for broker
  - To be registered
    - Permanent address and contact details in the MS where they are registered
  - To notify the CA of any changes without unnecessary delay

- Embraces requirements of the Falsified Medicines Directive
  - Requirements applicable to wholesale distributors apply
    - Quality and documentation systems in place
    - Retention of records of sales between other parties to ensure those products are authorized for sale in EU

# GDP Directive - 2013/C 68/01 - Impact

- Impact on Sponsors & QP depends on their:
  - Sub-contractors within the supply chain
    - Establishment, development, and robustness of their existing Quality Systems
    - Suitability and development of their processes, premises, and equipment
    - Visibility and oversight of suppliers and customers to safeguard the supply chain
  - Expert knowledge of product stability and shipping routes to justify minimum shipping requirements during transportation

- Question- Temperature control and monitor or not?
  - If not-why not?

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# EU GMP GUIDELINES

# CHAPTERS 1, 3, 5, 6, 7, 8

# EU GMP Guidelines

Chapters

1. Pharmaceutical Quality System – Recently revised and effective
2. Personnel - In draft for consultation-changes not extensive
3. Premises and Equipment- In draft for consultation
4. Documentation – Recently revised and effective
5. Production- In draft for consultation
6. Quality Control -In draft for consultation
7. Outsourced Activities- Recently revised and effective
8. Complaints and Product Recall - In draft for consultation
9. Self Inspection- No change

- Written with commercial manufacture in mind but principles to be applied to IMPs
  - Not just Annex 13

# Chapter 1: Pharmaceutical Quality System

- Published in September 2012; effective 31 January 2013
- Title changed to “Pharmaceutical Quality System” to integrate with the principle of ICH Q10
- Applies now to veterinary medicinal products as well as human medicinal products
- Main changes include:
  - Reference to the Pharmaceutical Quality System
  - Continuous improvement and change management
  - Supply chain management
  - Senior management responsibilities
  - Deviations and CAPA

# Chapter 1: Pharmaceutical Quality System

- Contains an extensive list of items that the PQS should ensure
  - New items listed under the QA section

- Pertinent aspects include:
  - Verification that each delivery is from the approved supply chain
  - Establishment of processes to assure the management of outsourced activities
  - Consideration of results for product and processes monitored, taken into account
    - During batch release
    - In the investigation of deviations
    - With a view to taking PA to avoid potential deviation occurring in the future
  - Continual improvement facilitated through the implementation of quality improvements appropriate to the current level of knowledge

# Chapter 1: Pharmaceutical Quality System

- Arrangements in place for the evaluation and approval of planned changes considering
  - regulatory notification
  - approval where required

- Effectiveness checks following implementation of a change to assess impact

- Appropriate level of root cause analysis (RCA) using quality risk management principles during the investigation of
  - Deviations
  - Suspected product defects
  - Other problems

# Chapter 1: Pharmaceutical Quality System

- True root cause to be determined
- When true root cause cannot be determined:
  - Consider most likely root cause and address
  - Human error should be justified
    - Verify process, procedural, or system-based errors have not been overlooked
  - Appropriate CAPA to be identified
  - Effectiveness of CAPA to be monitored and assessed according to Quality Risk Management principles

# Chapter 1: Pharmaceutical Quality System

- Fundamental that…

  *"Senior management has the ultimate responsibility to ensure effective PQS is in place… Senior management leadership and active participation in the PQS is essential."*

- Periodic management review, with the involvement of senior management is specified

- Expectation that the PQS

  *"… should be defined and documented. A quality manual or equivalent documentation should be established and contain a description of the quality management system including management responsibilities."*

# Chapter 1: Pharmaceutical Quality System

- Impact
  - Changes are significant
  - Dependant on company and maturity of existing PQS
    - May already apply the principles of ICH Q10?
      - Compliant with Chapter 1
  - Involvement of the whole organization is critical
    - QP needs to be assured that the PQS encompasses the entire organization

# Chapter 3: Premises and Equipment

- Draft published for consultation on 17 January 2013
  - Predominantly to address the risks of cross contamination in shared facilities
- New requirements added:
  - Cross contamination should be avoided for all products by
    - Appropriate design and operation of manufacturing facilities
    - Providing dedicated facilities (if applicable)
  - Measures for prevention should commensurate with the risks
  - Assessment should include:
    - Toxicological evaluation of the product being manufactured
- Impact
  - Important when assessing sites of manufacture outside of EEA to ensure standards equivalent to EU GMP are applied
  - Greater emphasis on risk management

# Chapter 5: Production

- Draft published for consultation on 17 January 2013
  - Predominantly to align with the proposed requirements of Chapter 3 and address the risks of cross contamination
- New requirements added:
  - Sections 26 -28: Changes introduced for the qualification and oversight of suppliers to ensure starting materials are produced in accordance with GMP
    - Inclusive of supply chain traceability
  - Section 33: Inserted to clarify and harmonize expectations of manufacturers regarding the testing of starting materials
  - Section 68: Introduces guidance on notification of restriction in supply
- Impact
  - Knowledge of supply chain essential
  - Greater emphasis of GMP requirements from the onset

# Chapter 6: Quality Control

- Draft published for consultation on 17 January 2013
  - Greater emphasis on the need to investigate OOS, anomalous & OOT results

- New requirements added:
  - Includes the requirement for a procedure for OOS / OOT results
  - Introduces the requirement for test method validation & transfer
  - Requires test methods which were not originally validated, e.g. pharmacopoeial methods to be verified for intended use
  - Requires reference standards to be certified, qualified & verified as suitable for intended use
  - Details specific instruction regarding the preparation, verification & disposal of culture media

- Impact
  - Important when assessing testing sites outside of EEA to ensure standards equivalent to EU GMP are applied

# Chapter 7: Outsourced Activities

- Published September 2012, effective 31 January 2013
  - Title changed from Contract Manufacturer and Analysis to Outsourced Activities to extend the scope
  - Principles of ICH Q10 incorporated

- New requirements added:
  - Contract Giver is now responsible for:
    - Reviewing and assessing the records and the results related to the outsourced activities
    - Ensuring by himself, or Contract Acceptor's QP, that products /materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the MA

- Impact
    - Sufficient oversight of outsourced activities
    - Ensure contracts are in place with vendors and service providers

# Chapter 8: Complaints and Product Recalls

- Draft published for consultation on 17 January 2013
  - Major re-write aimed to
    - Reflect quality risk management principles when:
      - Investigating quality defects / complaints
      - Making decisions regarding product recalls
    - Emphasizes the need for Quality defects to be investigated, root cause established, and CAPA implemented
    - Clarify expectations and responsibilities in relation to the reporting of quality defects to the Competent Authority

# Chapter 8: Complaints and Product Recalls

- New requirements added:
  - Specifies the need for:
    - Sufficient, trained and experienced personnel to be responsible for:
      - Managing complaints / quality defects and investigations
      - Deciding and implementing actions to be taken to manage risk
      - The management of interaction with Competent Authorities
  - Details a list of items to be included in a Quality Defect investigation
  - Defines the expectation for:
    - Investigations
    - Decision making
    - Root cause analysis
    - Determination of CAPA

# Chapter 8: Complaints and Product Recalls

- Recall section updated to include:
  - Any retrieval of product from the distribution network as a result of a Quality defect should be regarded and managed as a recall
  - For IMPs all sites should be identified and the countries of destination should be notified
  - A requirement for Sponsors to implement a procedure for the rapid unblinding of blinded products
  - Consideration should be given to different markets and their requirements
  - Any decision not to initiate a recall, e.g. shortage of an essential medical product, must be justified
  - A requirement to challenge the effectiveness of recall procedures both within and out of office hours

# Chapter 8: Complaints and Product Recalls

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- Impact
  - Sponsor to have robust quality procedures in place to investigate quality defects and complaints
  - Robust recall procedure in place with proven effectiveness
  - Clear communication pathways in place to communicate with necessary personnel e.g. QP, Competent Authority
  - Processes to be assessed during supplier qualification and routine audits and self-inspections

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# EU GMP GUIDELINES

# ANNEXES 2, 16

# Annex 2: Biological Products

- Published September 2012, effective 31 January 2013
  - Major revision offering sound practical and detailed guidance on most areas
    - 5 pages to 31 pages
  - Adopts the principles of risk management
- New requirements added:
  - Guidance now takes account of Part 2 of Eudralex vol IV GMP for Active Substances
  - Range of regulated biologicals has increased significantly
  - Includes
    - Part A – General guidance
    - Part B – Specific guidance on selected product types

- Impact
  - Significant impact on the manufacture of biological products
  - Provides clearer guidance on the requirements

# Annex 16: QP Certification and Batch Release

- Revised version of Annex 16 is in preparation
  - Concept paper out for comment until 15 November 2013
    - Recognizes the lack of harmonization in requirements between Member States e.g.
      - What is the minimum a QP must personally carry out when certifying a batch?
      - What are the pre-requisites for relying on statements from persons other than fellow QPs?
      - How is the control strategy and batch certification release process linked?
      - What are the expectations for QPs reviewing batch records manufactured by third parties in third countries?
      - What knowledge should a QP have about the site (s) involved in the manufacturing of a batch?
      - What actions are expected from a QP when a batch cannot be certified and therefore released?
      - Sampling and testing of batches produced outside the EU/EEA
      - Dealing with minor deviations from marketing authorizations

# Annex 16: QP Certification and Batch Release

- Concept paper
  - States implications of new legislation related to API, excipients, and finished product to the batch certification and release procedure should be explored
  - Ensure guideline is up-to-date concerning IMPs

- Most contentious area: QP discretion when dealing with minor deviations from the details in MA
  - Reflection paper has been
    - Misinterpreted in some cases
    - Lacks clarification
    - How will this be adopted for IMPs?

# Annex 16: QP Certification and Batch Release

## Impact

- Additional areas where clarification is required
  - The QP's position in an organization's structure
  - The physical location of the QP
  - Independence of the QP from the Head of Production Manager and/or Quality Control
  - The QP's role in product defects and related investigations

- Concept paper states that these questions are not related to the batch certification activity itself
  - Not in the scope of Annex 16
  - Should be addressed in future revisions of applicable chapters or in Q&A section on EMA's website

- Draft guidance for public consultation was due December 2012
  - Date missed - expected 2014

# Annex 16: QP Certification and Batch Release

- Draft proposal yet to be issued
  - Will require further consultation following release
  - Indicates
    - Complexities of the QP release process
    - Difficulties in establishing and defining specific requirements
    - Demonstrates reluctance to commit to specifics
      - Instead the decision is left to the QP
        - Positive?
        - Negative?

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# QP DECLARATION TEMPLATE

# QP Declaration Template

- To recap - QP Declaration:
  - Signed by QP, confirming…manufacturing sites to be used outside of the EEA operate to standards equivalent to EU GMP
  - Protocol and Product specific
  - Submitted as part of the CTA to the relevant Competent Authority
  - QP is taking personal responsibility for certifying the sites

# QP Declaration Template

- Updated template published by EMA 30 April 2013 for implementation 30 October 2013
- QP confirms that the IMP manufactured in a third country meets EU GMP standards for IMPs
- Verified by either
  - A personal on-site audit
  - An audit conducted by a third party
    - e.g EU Competent authority, EMA, country with a Mutual Recognition Agreement in place
  - Another QP employed by the importer
- If no audit has been performed, a brief justification and explanation should be provided
  - Detail how the QP knows that standards at least equivalent to EU GMP are being followed at the site

# QP Declaration Template - Impact

- Emphasizes the importance to ensure visibility of entire supply chain including testing sites
  - Optimize the supply chain and reduce complexity
- Previously testing facilities were evaluated during the supply chain assessment
  - Were not detailed on the QP Declaration except when submitting to CZ and Sweden
  - Now a requirement
    - Emphasizes the importance of streamlining the number of testing sites in the supply chain to ensure visibility and oversight of any subcontracted testing
    - In the event of a change in testing facilities – updated QP Declaration required
- Justification needs to be provided when an audit has not been performed
  - Will a pending audit be accepted by the Competent Authority?

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# QP Release in Israel

# QP Release in Israel - Background

- Israeli legislation recently aligned with EU legislation with regards to manufacture and importation of IMPs

- Published EX-012/01 on 14 Apr 2013
  - Implementation date of 01 Jul 2013
  - To be applied initially to all Phase III studies commencing 01 Jul 2013
  - Extended to 01 Oct 2013 to accommodate Form 7
    - Document authorizing the conduct of a CT at named investigator sites in Israel
- Legal requirement that a QP (i.e. a Responsible Pharmacist) in Israel will:
  - Release every batch
    - Locally manufactured
    - Imported

# QP Release in Israel - Background

- Assessment of legislation by Almac highlighted challenges and raised concerns
- How would this work in practice?
  - Timelines for implementation
  - Scope (Phase I, II or III)
  - Sharing of documentation (nature, confidentiality, and associated timelines)
  - Sampling requirements (purpose and expectation)
  - Technical Agreements (parties involved, complexity, and establishment)
- Where do responsibilities lie?
  - QP, Israeli QP, Non EU Authorized Person, Sponsor
- Could this be detrimental to the conduct of trials in Israel?

# QP Release in Israel - Background

- Questions compiled and forwarded to:
  - Almac managed depots in Israel
  - Israeli Ministry of Health (MOH)
  - Responses sought and meeting convened with Israeli MOH (09Jul2013)
- Meeting held with Head of GMP Inspectorate at Ministry of Health
  - Responsible for implementation of the legislation
- Open discussion of the perceived challenges
  - Each question addressed in turn
  - Identified scenarios not previously considered during generation of the legislation (e.g import of product from non- EU countries)
  - Almac's input sought and opinion valued regarding possible resolutions

# QP Release in Israel - Background

- Feedback welcomed and deemed most beneficial
  - Regretful that scenarios presented had not been apparent / considered previously during the consultation period as this would have influenced the legislation
  - Requested summary of the questions and answers discussed to:
    - Share with:
      - Colleagues
      - The industry via publication on the Israeli MOH website
    - Provide clarification before legislation would be next updated

# QP Release in Israel - Background

- MOH clarified the purpose, scope, and intention
  - Mimic elements of an already established process for IMPs (as in the EU) to:
    - Provide visibility of the supply chain
    - Determine responsibilities
    - Ensure accountability
    - Ultimately to protect the patient
  - Acknowledges ‘primitive’ CT application process
    - Foundation to build on
    - Applicable to Phase III initially, however expectation is that the provisions would be applied by Israeli manufacturing sites for all phases

# QP Release in Israel - Background

- Not intended to:
  - Deter sponsors from conducting CTs in Israel
  - Result in duplication of effort if 'authorized persons' in the supply chain have already performed verification
  - Introduce entirely new concepts

- Consideration not given fully to material coming from non-EU countries
  - Non-EU processes are not aligned with the new Israeli requirements
    - No equivalent
      - QP Statement of Release
      - PSF
      - Documented evidence that all aspects have been verified as required

# QP Release in Israel - Background

- Following visit and follow-up telecons:
  - Questions and answers document compiled by Almac
  - Published on Israeli MOH website week commencing 02Sep2013
    - http://www.health.gov.il/hozer/ISCP_03092013.pdf

# What aspects of the legislation are relevant?

- NOT concerned with sections applicable to manufacture and testing in Israel
  - Activities at the logistic center limited and are outside the scope of manufacture

- Focus on sections pertinent to importation:
  - License obligations for the Israeli logistic centers
    - GMP requirements in Israel
    - Israeli QPs (i.e. Responsible Pharmacists)
    - Material to be received from a recognized country which has been released by a QP or an Authorized Person
      - Allowance detailed within the guideline to permit import of material from an unrecognized country
        - » Must be released by a QP or an Authorized Person
    - Direct to site shipments no longer permitted

# Licensing Requirements

**Importers in Israel must:**

- Be inspected by the Israeli MOH
- Have a GMP certificate
- Licensed - Manufacturer / Importers Authorization (MIA)
  - Valid for 5 years, updated following audit if needed
  - To include:
    - ✓ Over-labeling secondary packaged product
    - ✓ Package adjustment – addition of an accessory to the package (e.g. expiry update label)
    - ✓ Sub-contracted activities (e.g. labs)
    - ✓ Named Israeli QPs

# Licensing Requirements

To obtain an MIA they must have a Quality System that incorporates the principles of GMP

- Documentation control and retention
- Deviation and CAPA management
- Quality / Technical Agreements
- Sample retention (as applicable)
- Appropriate facilities and equipment (validated as applicable)
- Sufficiently trained personnel, including QPs
  - Job descriptions and organizational charts

# QP / Responsible Pharmacists

QP at site of importation is responsible for:

- Verifying that manufacture and testing of the Product is in compliance with:
  - GMP
  - Product specification file
  - Clinical trial protocol
  - Random code
  - Labeling requirements to Annex 13 and the Israeli guidelines and administration procedure (no. 14)

- Recertifying the product for use in the trial

# QP / Responsible Pharmacists

- What is the purpose of this recertification?
  - Assurance that the product has been manufactured and tested in accordance with GMP
  - Sites involved in the supply chain have been assessed
  - Compliance has been verified
  - Someone is accountable for each stage
    - No gaps with regards to responsibility
  - Ultimately patient safety assured

# QP / Responsible Pharmacists

- Legislation dictates significant amount of documentation required
  - Key Concerns:
    - Provision of such (availability, timelines, confidentiality)
    - Duplication of responsibilities

- Aim of the discussion with the Israeli MOH was to simplify the process
  - Leverage on checks performed by Authorized Persons upstream
  - Reduce the workload and documentation requirements
  - Streamline the importation process

# Documentation Requirements

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## Elements of the PSF

- ✓ Specifications and analytical methods
- ✓ Manufacturing methods
- ✓ IPC tests and methods
- ✓ Label text
- ✓ CT protocol
- ✓ Random codes
- ✓ Quality / technical agreements
- ✓ Stability results
- ✓ Storage and transport conditions

## Manufacturing Site Information

- ✓ GMP 'Certification' for all sites provided on a declaration

**No change in existing documentation requirements HOWEVER shipments to be temperature monitored and controlled**

## Lot Specific Documentation

- ✓ C of A's for all input lots (except for licensed material, if not available)
- ✓ Lot linking documentation
- ✓ Pedigree documentation
- ✓ Unblinding documentation
- ✓ Authorized person declaration for comparator products
- ✓ Declaration of product certification by authorized person overseas
- ✓ Deviations

## Importation Documentation

- ✓ Proforma Invoice
- ✓ Shipping Documentation
- ✓ Approved Form 7

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# How will this be achieved?

# Recognized Countries

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EU Member States


USA


Canada


Switzerland


Norway


Iceland


Australia


New Zealand


Japan


Israel

****Unrecognized Countries – any other country****

# Elements of the PSF Required by the Israeli QP

1. Specifications and Analytical Methods
2. Manufacturing Methods
3. IPC Tests and Methods
4. Labelled Text
5. Certificate of Analysis
6. Batch Certificate
7. Quality / Technical Agreements
8. Stability Results
9. Storage and Transport Conditions

**Reduce**

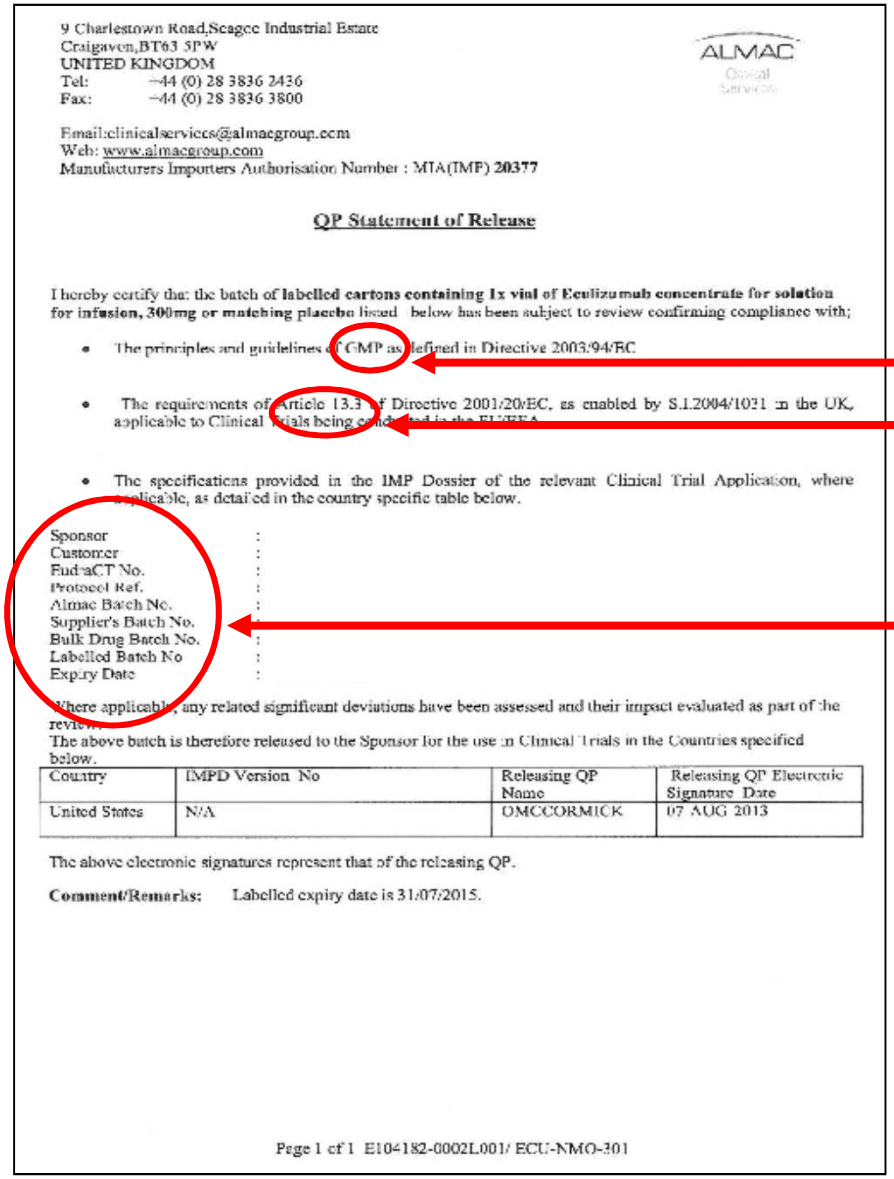
## Documentation to meet the requirements

1. QP Statement of Release, compliant with Annex 13
   - Inclusive of lot linking information

   **or**
   - Authorized Person Statement of Release
2. Responsibilities clearly defined in TA between:
   - Almac and the Depot
   - Almac and the Sponsor

- ✓ Together these provide confirmation that all required checks have been performed
- ✓ Negates the need to provide elements of the PSF to the QP in Israel
- ✓ Fulfills the requirements

# Example of QP Statement of Release



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Craigavon,BT63 5FW
UNITED KINGDOM
Tel: +44 (0) 28 3836 2436
Fax: +44 (0) 28 3836 3800

Email:clinicalservices@almacgroup.com
Web: www.almacgroup.com
Manufacturers Importers Authorisation Number : MIA(IMP) **20377**

**QP Statement of Release**

I hereby certify that the batch of **labelled cartons containing 1x vial of Eculizumab concentrate for solution for infusion, 300mg or matching placebo** listed below has been subject to review confirming compliance with;

- The principles and guidelines of GMP as defined in Directive 2003/94/EC
- The requirements of Article 13.3 of Directive 2001/20/EC, as enabled by S.I.2004/1031 in the UK, applicable to Clinical Trials being conducted in the EU/EEA
- The specifications provided in the IMP Dossier of the relevant Clinical Trial Application, where applicable, as detailed in the country specific table below.

Sponsor :
Customer :
EudraCT No. :
Protocol Ref. :
Almac Batch No. :
Supplier's Batch No. :
Bulk Drug Batch No. :
Labelled Batch No :
Expiry Date :

Where applicable, any related significant deviations have been assessed and their impact evaluated as part of the review.
The above batch is therefore released to the Sponsor for the use in Clinical Trials in the Countries specified below.

| Country | IMPD Version No | Releasing QP Name | Releasing QP Electronic Signature Date |
|---|---|---|---|
| United States | N/A | OMCCORMICK | 07 AUG 2013 |

The above electronic signatures represent that of the releasing QP.

**Comment/Remarks:** Labelled expiry date is 31/07/2015.

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**GMP Compliant**

**PSF Compliant**

**Lot Specific Information**

# Manufacturing Site Information

1. GMP 'Certification' for all sites provided on a declaration
   - Includes sites of:
   - Drug Product Manufacture
   - Packaging
   - Testing

Reduce

## Documentation to meet the requirements

1. GMP certificates for all sites involved in the supply chain
2. Single 'Pedigree Document' to be supplied with first shipment for each protocol signed by a QP
   - Providing details of:
     - Each site in the supply chain
     - Certification to appropriate standards of GMP
   - Responsibilities clearly defined in the Technical Agreement
   - Depot to be informed of any changes in the Supply Chain

✓ Single document

✓ Negates the need to provide multiple GMP certifications for each site in the supply chain

✓ Provided once unless changes occur in the supply chain

✓ Fulfills the requirements

# Example of Pedigree Document

**Authorised Person – Pedigree Document**

Sponsor Name & Address: ***Detail name & address of the Sponsor responsible for the trial***
Protocol Ref.: ***Detail the Protocol / Study number***
Product Name & Dosage Form: ***Detail the product name and dosage form***
Product Strength / Potency: ***Detail the product strength / potency***
Package Size: ***Detail the contents per vial / bottle / blister***

**Site(s) of Drug Product Manufacture:**

| Name & Address | Establishment Number or Equivalent | Activities carried out at this site |
|---|---|---|
| ***Detail site name and address*** | ***Detail the establishment or licence number pertaining to the site*** | ***Summarise the activities performed at the site for the above mentioned product, e.g. manufacture of tablets*** |
| | | |

**Site(s) of Drug Product Testing:**

| Name & Address | Establishment Number or Equivalent (if applicable) | Activities carried out at this site |
|---|---|---|
| ***Detail site name and address*** | ***Detail the establishment or licence number pertaining to the site (if applicable)*** | ***Summarise the activities performed at the site for the above mentioned product, e.g. .final release and stability testing*** |
| | | |

**Site(s) of Drug Product Packaging & Labelling:**

| Name & Address | Establishment Number or Equivalent | Activities carried out at this site |
|---|---|---|
| ***Detail site name and address*** | ***Detail the establishment or licence number pertaining to the site*** | ***Summarise the activities performed at the site for the above mentioned product, e.g. secondary packaging and labelling*** |
| | | |

I certify that the above referenced Investigational Medicinal Product to be used in this clinical trial, has been / will be manufactured, tested, packaged and labelled at the named site(s) in accordance with national standards of Good Manufacturing Practice.

Signed: _____ Date: _____

***Detail the name of the Authorised Person***
Authorised Person

***Note: Highlight text in Bold and Italics to be deleted and replaced as appropriate.***

**Product identifiers e.g., Description, Sponsor, Protocol**

**Manufacturing site with details of license number and activities performed**

**Testing sites with details of license number and activities performed**

**Packaging and labeling sites with details of license number and activities performed**

**Certification by QP or Authorized Person**

# Lot Specific Documentation

1. C of A's for all input lots (except for licensed material, if not available)
2. Authorized Person Declaration for Comparator Products
3. Declaration of Product Verification by Authorized Person (if applicable)
4. Lot Linking documentation
5. Deviations
6. Pedigree documentation
7. Unblinding documentation

**Reduce**

**Documentation to meet the requirements**

1. C of A's for all input lots (except for licensed material, if not available)
2. Authorized Person Declaration for Comparator Products
3. QP / Authorized Person Statement of Release
   - Lot linking documentation
   - Deviations
4. Pedigree documentation
   - Study specific, provided once unless changes occur in the supply chain

✓ Responsibilities clearly defined in the Technical Agreement to make unblinding documentation available on request

# Benefits of Buy-In to the Process

- Documentation requirements greatly reduced
  - Pedigree Document for first shipment
  - Statement of Release
- Sharing of proprietary information restricted to Almac and the Sponsor
  - Confidentiality maintained
- Facilitates timely assessment of compliance in advance of importation
  - Not a rate limiting step later
- Avoids duplication of effort
  - Leverages on preceding efforts
  - Overall costs reduced
- Documents standardized and consistent
  - Reduced complexity at the depot
- Expert knowledge in the legislation

# Impact

- Raising awareness of the need to:
  - Identifying new Phase III studies due to start on or after 01 Oct 2013 in Israel to ensure they comply
  - Ship all supplies to and within Israel under temperature controlled and monitored conditions (new requirement)
    - Will impact shipping costs
    - Shipping instructions currently in place
    - Instructions in place with Logistic Center
  - Provide the necessary documentation
    - Complete and accurate to address the requirements
    - Timely (in advance of shipping to mitigate against delays)
  - Use Almac templates - essential to benefit and mitigate against the need to provide the logistic center with significant volumes of documentation

# Impact

- Raising awareness of the need to:
  - Update associated TAs to ensure responsibilities are clearly defined
- Clarification required regarding the phase of trial to which the legislation applies
  - Phase I, II, III for ongoing studies need not apply
  - Phase III studies commencing after 01 Oct 2013 must apply
  - Phase I and II new studies after 01 Oct 2013
    - GMP and GDP expectations must apply
    - Documentation requirements –may apply?

# Summary

Discussed pharmaceutical legislation updates specific to IMPs, with focus on:

- EU Directives and Regulations
  - Clinical Trials Directive
  - Falsified Medicines Directive
  - GDP Directive
- EU GMP Guidelines
  - Chapters 1, 3, 5, 6, 7, 8
  - Annexes 2, 16
- QP Declaration template
- New requirements for QP Release in Israel
- Assess the impact, if any on the
  - QP
  - Sponsor

# Summary

- Active with respect to updates
  - Directives
  - GMP Guidelines
  - Annexes
  - Legislation
- Predominantly written
  - With commercial product in mind but expected to apply the principles to IMPS
  - To encompass
    - The principles of ICH Q9 and Q10
    - Updates to related Directives
  - To provide greater clarification
    - Questionable if this is always achieved

# Questions?


**Contact Info:**

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