

Questions for the March 2010 PQG MHRA discussion Meeting – Master With answers

	Q No	Person	Subject	Questions	Answers
	1.1	1	Product contamination	What are the thoughts of MHRA on how to ensure the quality of APIs from China etc post the Heparin incident and what more can the authorities do rather than rely on the QP?	<p>MHRA are working closely with other European Competent Authorities and Mutual Recognition partners to provide an increased surveillance program of APIs in 3rd Countries. The inspection of API sites by authorities is targeted towards product types regarded as higher risk and where information provided to authorities is incomplete or raises concerns about evidence of GMP compliance e.g. QP declarations, and CEP applications. The future compliance strategy for APIs is being discussed on a global basis including the future role of Competent Authorities. However at present the regulations still, not unreasonably, requires manufacturing Authorisation holders/QPs as users of the APIs to only use API sources that they have proven to comply with EU GMP Part II.</p> <p>The MHRA initiated a project in 2009 to consider this. It must however be remembered that the legislation currently requires the Manufacturing authorisation holder to only use API which have been manufactured in accordance with GMP. It remains our expectation that this assurance can best be obtained by on-site audits carried out by properly trained auditors. The declaration which is required to assure the regulators of this control is signed by the QP but this does not mean that they have sole responsibility.</p>

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	2.1	5	GDP	When a company distribute products using carriers with “Hubs”, should the sender carry out any extra steps to satisfy the regulators?	<p>For ambient products the sender should have knowledge of the transport arrangements and assess the risk presented to the product. This assessment should be completed before entering into any third party agreement with the distributor and can be performed either physically or via documented communication with the carrier involved. Details of any physical assessment of the hub should be fully documented.</p> <p>Where distribution is contracted out responsibility for the quality of the medicines being distributed rests with the sender until they are received as acceptable by the customer.</p> <p>The hubs should be included in subsequent audits of the distributor by the sender.</p> <p>The same situation applies for cold chain products where products are shipped in specialised packaging or in temperature controlled vehicles. If cold chain products are placed in a refrigerator at any hub it will need to be licensed and the sender should confirm that this is the case.</p>

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	2.2	20, 5	GDP	<p>In distribution it is common practice to use multi-drop carriers; one lorry takes the goods to a transport depot and another delivers them (with possibly a third doing a long haul between depots); it is not uncommon for the goods to be held briefly at the depot for the next lorry or held overnight for the morning.</p> <p>So how long must the goods wait at the depot before this becomes storage and requires a wholesale licence? What about deliveries that leave on a Friday for Monday delivery?</p>	<p>If the goods are held at any point during the distribution chain for longer than 36 hours the site at which they are held will need to be licensed.</p> <p>Before entering into a contract with a potential distributor, it is the responsibility of the sender to ensure that the company is able to provide appropriate delivery arrangements to ensure that consignments are protected and transported within the stated temperature parameters <u>throughout the entire journey</u>.</p> <p>Companies should only be dispatching deliveries on a Friday for Monday delivery if they are using a carrier that has a Licensed distribution network.</p> <p>Cold Chain If cold chain products are placed in a refrigerator at any hub it will need to be licensed and the sender should confirm that this is the case.</p>

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	2.3	13	GDP	<p>Given the increasing attention given to GDP by the MHRA what is their view on the following issues;</p> <ol style="list-style-type: none"> 1. The control and monitoring of temperature for products requiring ambient storage conditions, from manufacturer to pharmacy/hospital, especially given the recent cold snap in Europe. 2. Are there any plans to review/harmonise the requirements for inbound checks at wholesalers/distributors for products distributed in the EU so as to provide a clarity between the role of the releasing QP and the Responsible Person/Pharmacist. e.g Belgium requires Administrative release by a pharmacist of EU inbound products even though they have been released by a QP in the EU. 3. Are there any plans to look at harmonisation of 'Returns' policies in the EU for pharmaceutical products returned from Wholesaler, Pharmacies and Hospitals for reintroduction in to the supply chain. The MHRA currently stipulates up to 5 days as long as assurance can be given of correct storage. 4. MHRA view and feedback on the recent issue highlighted in the US regarding pallets treated with 2,4,6 tribromophenol (TBP). Implications for EU and thoughts re pallets treated with Me Bromide. 	<p>1. For ambient products the sender should have knowledge of the transport arrangements and assess the risk presented to the product. This assessment should be completed before entering into any third party agreement with the distributor and can be performed either physically or via documented communication with the carrier involved. Details of any physical assessment of the hub should be fully documented.</p> <p>Where distribution is contracted out responsibility for the quality of the medicines being distributed rests with the sender until they are received as acceptable by the customer.</p> <p>Before entering into a contract with a potential distributor, it is the responsibility of the sender to ensure that the company is able to provide appropriate delivery arrangements to ensure that consignments are protected and transported within the stated temperature parameters <u>throughout the entire journey</u>.</p> <p>2. Not that we are aware of - this question may relate to the use of control reports and in the UK we have determined that these are not applicable for holders of Wholesale Dealers Licences.</p> <p>3. The GDP guidance is currently being reviewed and revised. MHRA have not yet had sight of the final draft therefore we are unable to comment on this specifically. Once agreed the revised text will be issued for public consultation.</p> <p>4. A recall in the USA by McNeil for various consumer products has been blamed on contamination from wooden pallets by 2,4,6 tribromophenol (TBP). This preservative is not Licensed in the EU and we would therefore not expect this to become a problem in the UK. If complaints were received concerning odour of a product we would expect a the investigation to look into the possibility of pallet contamination.</p>

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	3.1	23	IMP	Please clarify the rationale for the release of unlicensed products by the 'quality controller' rather than a QP.	(Nothing to do with IMPs as far as I can see). The distinction between licenced medicinal products and unlicenced medicines (usually "specials") is fundamental. One of the legal responsibilities of a QP is to certify batches against the marketing authorisation. Unlicenced medicines are manufactured and supplied against a specific clinical need and do not have an MA. The ultimate responsibility lies with the prescriber. There is therefore no need for QP certification and therefore no need for the holder of an MS licence to have a named QP. Some certification/release by an independent body is still however a requirement of GMP and this falls to the "QC" department and suitably trained personnel.
	3.2	23	IMP	Where a commercial QP qualified under the permanent provisions of 2001/83/EC is applying for nomination on an IMP licence, what is the MHRA's expectation for additional education and training?	Such a QP should be knowledgeable of the aspects of GMP which are particular to IMP manufacture and control. Some experience in an IMP unit would be expected. Also, a theoretical training course is desirable. Note that the experience may be picked up at a previous employer. The bottom line is that the QP should feel that they have knowledge and experience sufficient to be able to discharge their duties and responsibilities.
	3.3	20	IMP	If a manufacturing site is producing a specific product only for export markets, is it necessary to name the testing site on its MIA or is it sufficient that the proposed testing site is an MIA holder authorised as the testing site on the product licence of the equivalent product for the UK market?	(Not IMP related) The contract testing site should be named on the MIA. This is not required if the testing site is outside the UK (should be listed on the SMF). The QP is required to certify export products as having been made in accordance with GMP. QC is part of manufacture so the site should be named.
	3.4	20	IMP	Can a contract giver provide final QP certification of IMPs assembled at a Phase I clinical trial unit? If so, what are the pre-requisites to support this activity?	This is permissible but the following is required: The contract giver needs their own MIA(IMP). The named QP needs to have sufficient knowledge and documentation to be able to certify the batches against EUGMP and the contents of the CTA and the PSF. The technical agreement between the two parties needs to lay out the various duties and responsibilities accordingly.

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	3.5	6	IMP	Where a batch of Investigational Medicinal Product (IMP) has a variation from registered details which would NOT constitute a substantial amendment to the IMPD, please can MHRA confirm that, in the absence of a specific variation process for IMPs, these may be assessed in accordance with the principles in the EMEA Reflection paper (EMA/INS/GMP/227075/2008). I.e. if the conclusion of an appropriate evaluation is that the deviation/non-compliance does not materially affect the Safety or Efficacy of the batch, then the QP may decide to release the batch and that no notification to MHRA is required in order to do so.	Any deviation should be discussed with the Trial Sponsor as it is their duty to determine whether an amendment is substantial or not. If necessary advice should be sought from the CTU. If the deviation is agreed to not be substantial the QP may consider the certification of the IMP. Any deviations will be documented, however and investigated as part of normal GMP.
	3.6	6	IMP	Re. revised Annex 13 paragraph 37 which relates to the storage location of Reference Samples: If we have an IMP manufactured and tested at a sister site in the US, this will be covered by a QP declaration of GMP equivalent to EU standards, which will be part of the CTA. Is the acceptance of the CTA then sufficient acceptance by "the Community" to enable the reference samples to be stored at the originator site or, in the absence of a Mutual Recognition Agreement with US, do we need to have reference samples stored in the EU (EEA)?	The existence of the QP declaration does not constitute 'appropriate arrangements ...made by the Community'. The arrangements referred to here relate to MRAs. In this case it would be expected that the reference samples are stored in the EU unless the dispensation of 'exceptional circumstances' applies.
	3.7	6	IMP	Please can you confirm that a single bulk reference sample of a batch of IMP may be stored in a representative primary container and that it is not necessary to have a reference sample in each of the different primary containers that may be used in subsequent packaging jobs.	The reference sample is maintained for the purposes of testing should the need arise. The need to store the sample in different primary containers would generally not be necessary (different size containers made of the same material) but there could be circumstances where it may be appropriate to hold more than one sample – particularly if the container is likely to have an impact on the quality of the product during its shelf life.

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	5.1	31	GMP	<p>During the consultation period there were many improvements suggested by industry for inclusion in the update to Annex 13 that were not incorporated.</p> <p>Is there any mechanism for industry to propose updates to the GMP guidelines and Annexes?</p>	<p>Dave Cockburn; It might be worth pointing out that the Commission is responsible for the GMP Guide and therefore European industry associations can/should approach it when they think the guidance needs to be changed.</p> <p>For background with regard to Annex 13, many comments were received that were outside the scope of the consultation but some were nevertheless taken on board as editorial improvements. The majority that were not taken on board were related to labelling and would have involved a substantial amount of work and would have needed the creation of a new revision process. Nevertheless a look at the labelling may yet be on the cards because the GCP IWG is raising many issues.</p> <p>The GMDP Inspectors Working Group (IWG) at the European Medicines Agency is the forum for review of EU GMP Parts I, II, III (currently at consultation) and the Annexes. The process within the IWG typically starts with a Problem Statement to describe an issue and a proposed remedy(ies). If, after discussion, it is accepted into the IWG's work programme, a Concept Paper is put forward by a rapporteur and drafting group which sets out the scope of the issue and general approaches to the remedy(ies). Although focus is placed on the specific problem area, the Commission is keen to avoid a 'piecemeal' approach to changes within Chapters and Annexes so other problem areas within the same Chapter or Annex may also be taken into account in the same piece of work. When the Concept Paper is accepted it is put out for a 3 month public consultation. The public comments are then taken into account by the drafting group who draw up new GMP/GDP text, when this is accepted by IWG it goes out for a further public consultation (currently 6 months but the Commission is considering reducing this to 3 months). Public comments are again taken into account in the drafting of the finalised GMP/GDP text, this has to be accepted by the IWG who then forward it to the Commission for adoption and publication on Eudralex Volume 4.</p> <p>Potential GMP and GDP issue therefore need to get to the IWG. For national organisations and associations this should be via the national Competent Authority, for European or international organisations and associations this can be done by direct approach to EMA.</p>

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	5.2	21	GMP	We are a small manufacturing operation with only one available Qualified Person. On occasion, the QP is off-site for professional development or annual leave. What provisions are acceptable for the deferred certification of product by the company during these short absences?	Each batch manufactured is required to be certified prior to release by a QP. Only in exceptional circumstances would retrospective certification be accepted. The circumstances described do not fit into this category as they are predictable and suitable back up arrangements can be put in place.
	5.3	36	GMP	My question is related to component batch number traceability. Specifically for Oral dry powder filling, is it essential to know the constituent batch numbers of the bottles and caps used to manufacture each batch of product?	It would be expected that records were maintained to provide traceability for primary product contact items such as bottles and caps.
	6.1	6	REGULATORY	Do MHRA know if there are plans to include within the European Pharmacopoeia the possibility of using Water Activity (Aw) for microbial quality attribute testing (as USP<1112>)? If so, what is the likely timeframe for this?	<p>A chapter entitled "(2.9.39.) Water-Solid Interactions: Determination of Sorption-Desorption Isotherms and of Water-Activity" (please find attached) is being presented for adoption this week at the European Pharmacopoeia Commission in Strasbourg.</p> <p>The text was prepared and signed off by the Pharmacopoeial Discussion Group (EP, USP & JP) in October 09. If adopted by the various delegations, I would expect this document to be published in the next edition of the European Pharmacopoeia (7.0) in about 6 months.</p> <p>The text does refer to microbial contamination in the introduction but in less detail than the current USP chapter <1112>.</p>

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	6.2	6	REGULATORY	<p>1. Is MHRA aware of Industry's concerns about the cost and availability of the instrumentation (ICP or ICP/MS) that will be required if USP implements its proposed change from Heavy Metals <231> to Elemental Impurities <232>?</p> <p>2. Is it anticipated that the proposed USP monograph will become an harmonised monograph?</p> <p>3. Is there any evidence that the lack of specificity and accuracy of the current testing has actually led to patient safety issues, i.e. are such changes warranted on a risk-based approach?</p>	<p>1. This is a USP revision, USP are aware of concerns (see attached Comment/Response document). Adrian Evans is the UK representative on the EPC HM WP and would welcome any comments regarding the USP proposals being sent directly to his mailbox (adrian.evans@mhra.gsi.gov.uk).</p> <p>The questions from PQA regarding industry concerns over the cost and availability of the proposed instrumentation and the rationale for the proposal is covered in the published USP article and in particular the published Q&As regarding the proposal, all are available on the USP website. I have included a link to the relevant webpage below and PDF's of the original article and the Q&A article: http://www.usp.org/hottopics/metals.html</p> <p>2. Possibly. The EPC HM WP is reviewing the approach in the Ph. Eur, as well as this USP are the lead Pharmacopoeia in PDG for 'Heavy Metals' and this harmonisation is at the 'Concept Paper' stage. The ICH Steering Committee have also endorsed this approach with the decision to create a new guideline: ICH Q3D Metal Impurities. As above please let the PQG members aware that they can send comments/concerns directly to Adrian.</p> <p>3. The risk based approach taken by the USP will be discussed by the EPC HM WP at future meetings to be held in 2010.</p> <p>With regards to the EPC review, this was initiated based on the drafting of the EMA Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents by the Safety Working Party in 1998/2000, which came into effect in September 2008.</p>

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	7.1	29	RISK	ICH Q9. What level of evidence will the MHRA be looking for regarding Risk Management, for example will they want to review the risk register or mitigation plans?	<p>MHRA will expect to see that companies have a policy and system for Quality Risk Management that complies with Chapter 1 and Annex 20. MHRA inspectors will be taking a holistic view of how a company manages risk and uses the principles of QRM. The principles of QRM will be expected to pervade everything a company does but of course the extent and formality of the QRM processes would be expected to be proportionate to the problem/issue at hand. In practice most companies will be actively using QRM principles in their routine work but in some cases documented evidence that this is the case will be lacking. Inspectors will expect to see participation in the risk management and specific risk assessment by staff with appropriate knowledge and experience. Inspectors may request to see specific risk assessments to confirm that these have been applied in an appropriate manner and that conclusions are supported by evidence and sound science.</p> <p>MHRA is an active member of the PICs expert circle on QRM which is expected to soon publish an aide Memoire to Members which describes the sort of questions that an inspector might usually make in their inspections and the areas which an inspector might reasonably be able to demonstrate proactive and reactive use of QRM principles. This Aide-Memoire is one of a number of training materials being presented at a PICs training meeting in Poland in April 2010.</p> <p>A company would normally be expected to hold a risk register should be held and this should be available on request by the inspector. The company should be prepared to openly share and discuss GMP aspects of that register that with an inspector however because the risk register will almost certainly contain commercially sensitive material the inspector it unlikely that an Inspector would routinely request a retention copy of the register. However like any other GMP related document the Inspector does have the legal right to examine and request copies.</p>