Bethesda Towers
4350 East West Highway, Ste. 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

**OFFICERS**
Chair
**Rebecca Devine, PhD**
Regulatory Consultant

Chair-Elect
**Jette Christensen**
Novo Nordisk A/S

Secretary
**Steven Lynn**
Consultant

Treasurer
**Michael Sadowski**
Baxter Healthcare

Immediate Past Chair
**Martin VanTrieste**

President & CEO
**Richard M. Johnson**

**DIRECTORS**
**Masahiro Akimoto**
Otsuka Pharmaceutical Factory, Inc.

**Barbara Allen, PhD**
Eli Lilly and Company

**Joyce Bloomfield**

**Véronique Davoust**
Pfizer

**Ghada Haddad**
Merck & Co./Merck Sharp & Dohme

**Kerry Ingalls**
Amgen

**Mary Oates, PhD**
Pfizer

**Emma Ramnarine**
Roche Pharma

**Stephan Rönninger**
Amgen

**Anil Sawant, PhD**
Merck & Co./Merck Sharp & Dohme

**Susan Schniepp**
Regulatory Compliance Associates

**Melissa Seymour**
Biogen

2 May 2018

Keith Pugh                                   Brendan Cuddy
Chair Quality Working Party    Chair GMDP Inspectors Working Group

European Medicines Agency,
30 Churchill Place
Canary Wharf, London E14 5EU, United Kingdom
QPdeclaration@ema.europe.eu.

**Reference:** Letter and questionnaire from the Quality Working Party and the GMDP Inspectors Working Group

Dear Dr. Pugh and Mr. Cuddy:

PDA appreciates being included with the industry stakeholder groups consulted by the EMA on the series of questions relating to QP and API Site Audits. Please see our detailed responses in the attachment.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. PDA has a public ID number in the EU Transparency Register of 894106921549-04. Our comments are based on a member survey and prepared by a committee of experts in regulatory affairs including members of the PDA Board of Directors and the Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me via email at johnson@pda.org .

Sincerely,

Richard Johnson
President, PDA

Cc: Kiera Heffernan, EMA, Denyse Baker, PDA, Falk Klar, PDA

| | QUESTION | PDA RESPONSE |
|---|---|---|
| 1. | Do you think that there should be any restrictions on to whom the MIAH can outsource the audits of active substance manufacturers?<br><br>If so, please elaborate on the criteria that should be used in deciding the suitability of an auditor. | Yes<br>The following consensus on restrictions/ suitability of an auditor was provided to this response.<br>All auditors should<br>- Have API manufacturing expertise<br>- Knowledge and understanding of EU GMPs /API guidelines/regional regulations & QP role and responsibilities (Annex 16). |
| 2. | What kind of restrictions are being imposed on auditors by API manufacturers (e.g access to facilities, documents/personnel/audit fees)? | - Numbers of auditors<br>- Frequency/scheduling of audits - i.e. days allowed to audit<br>- Inability for guest auditors to attend e.g. QP<br>- Lack of access to trained personnel/manufacturing facilities/support areas on days of audit<br>- Lack of access to documents or lack of access to confidential elements of documents e.g. partial DMF<br>- Lack of access to subcontractor information<br>- Fees |
| 3. | What kind of practical strategies can an auditing body employ to overcome these restrictions? | - Technical/Quality Agreement clearly outlining roles and responsibilities in relation to types of audits, frequency of audits, auditor numbers, access to personnel, facilities and documents. Inclusion of mediation processes where required etc<br>- Clear audit scope/agenda submitted pre-audit (focus on areas of criticality)<br>- Use of independent qualified third-party auditor<br>- Development of good collaboration |
| 4. | What else could be done to make audits more effective? | - Clear audit plan/agenda/timeline (experienced auditors, language fluency/translators where required)<br>- Request documentation in advance<br>- Employ joint audit program (where feasible)<br>- Good collaboration<br>- Employ mediation processes where necessary |
| 5. | What kinds of information does a QP typically have when signing a QP declaration? | - Most recent audit report (observation/responses)<br>- EU GMP cert<br>- MIA/FEI<br>- Audit history<br>- Quality/technical agreement<br>- Quality plan (list of changes/deviations/audit responses etc)<br>- Good knowledge of Quality Systems in place by API manufacturer<br>- API manufacturer's audit reports on intermediate API manufacturer (if different) can be accessible to QP/drug product manufacturer |
| 6. | Are there potential gaps in the information that is available to the QP? | - Audit report not detailed enough<br>- Auditor knowledge of API manufacturing limited |
| 7. | What could be done to address these gaps? | - Provide guidance to auditor on requirements to support a written QP declaration |

| | | |
|---|---|---|
| | | - Audit plan/report development with QP review/input<br>- QP attendance of audits as guest/formal auditor<br>- Use qualified 3<sup>rd</sup> party auditors |
| 8. | Based on your experience as MAH holder/QP, can you estimate within your organization or among your clients, how many API sites have either been withdrawn from MAs or never been used in the first place due to the outcome of an audit?<br>1 or 2 sites<br>3 to 5 sites<br>More than 5 sites<br>Additional comments | Based on knowledge set/population of people whom responded to this question; it was estimated that 1-2 sites have been have either been withdrawn from MAs or never been used in the first place due to the outcome of an audit.<br><br>Note: There may be other reasons also for non-employment of a particular site. |
| 9. | Should information about negative audits be made more transparent?<br>If yes, how could this be achieved? | The collective response based on population for data surveyed was; Yes.<br>PDA recommends a publicly available webpage through the Eudra GMDP portal similar to how MHRA shares inspection findings or the US FDA posts 483 warning letters. |
| 10. | Do you have any opinions on why auditors find that a site complies with GMP when subsequent EU inspections find the site non-compliant? | - An audit conducted is a point in time assessment of compliance.<br>- An audit is scope, time and expertise dependent.<br>- EU regulatory inspections outcomes can have a more impactful impact.<br>- EU regulatory inspections have unlimited access to documents, personnel, facilities<br>- There may be a difference in interpretation of GMP requirements between different auditors, different inspectors or between an auditor and inspector.<br>- There have also been occasions where EU inspectors find the site compliant with GMP, where industry auditors did not which still results in corrective actions. |