Eudra GMDP and WHO Notice of Concern Letter
Associated with Data Integrity / Data Management
January 2016

Sixteen (16) reports of GMP non-compliance were issued in 2015 and published by European Authorities on the *EudraGMDP web site.* Inspections may have been conducted months earlier. Within that group, eleven (11), 69%, cited deficiencies in the category of data management / data integrity. This may be an incomplete listing because the competent authorities are not *required* to post the summary reports for non-compliant inspection outcomes. These reports are summaries, rather than copies of the reports, and thus are more limited in detail than a US form 483 or warning letter. The reports may be found at the Eudra GMDP link above.

If you are interested in data integrity deficiencies across the entire collection of non-compliant summary reports, not just 2015, posted on the EudraGMDP sites, please contact Barbara Unger, bwunger123@gmail.com

The table below identifies the company name, date of the report, inspecting authority and location of the site in question. France and Italy were particularly active in this area in 2015 with four (4) summaries reports each followed by one each for the UK, Slovenia and Sweden. Five of the sites in question are in China, four sites in India and one each in France and Italy. None of the firms identified were the subject of FDA warning letters issued in 2015 although Wockhardt received two warning letters in 2013 *HERE* and *HERE* .

Company Name	Country Location	Inspecting Authority	Date of Report Issuance
Wockhardt Limited	India	UK	January 16, 2015
North China Pharmaceutical Group Semisyntech Co., Ltd	China	France	January 22, 2015
Huzhou Sunflower Pharmaceutical Co., Ltd	China	France	March 25, 2015
Polydrug Laboratories PVT. Ltd	India	Slovenia	June 12, 2015
Wuxi Jida Pharmaceutical Co., Ltd	China	Italy	July 28, 2015
Parabolic Drugs Limited	India	Italy	July 28, 2015
Jinan Jinda Pharmaceutical Chemistry Co., Ltd	China	Italy	July 28, 2015
Cargill France	France	France	October 30, 2015
Iason Utakua Srl	Italy	Italy	December 1, 2015
AstraZeneca Pharma	India	Sweden	December 11, 2015
Minshing Group Shaoxing Pharmaceutical Co. Ltd.	China	France	December 28, 2015

WHO has also been active in this area and issued two Notice of Concern Letters in 2015, both for the areas of GLP and GCP. Micro Labs Limited, mentioned in the Quest Life Sciences Private Limited letter below, also received a *Notice of Concern* letter in May 2014 for deficiencies in GMP, a *warning letter* from FDA in January, 2015, and became subject of a FDA import alert in September, 2014. In general, when enforcement actions are taken against GCP firms, it impacts multiple products and calls into question the data associated with multiple products.

COMPANY	DATE	COUNTRY
Quest Life Sciences Private Limited Deficiencies in GCP and GLP studies conducted for products from Micro Labs Limited.	June 30, 2015	India
Svizera Labs Private Limited Deficiencies in GCP and GLP studies.	September 2, 2015	India

Company and Date of Issue	Country	Inspection Authority	Non-Compliant Operations	Nature of Non Compliance
Wockhardt Limited (Jan 16, 2015)	India	UK	Other products or manufacturing activity	A critical deficiency was cited with regards to data integrity of GMP records, entries were seen to be made when personnel were not present on site, documentation was seen that was not completed contemporaneously despite appearing to be completed in this manner. 2. A second critical deficiency was cited regarding potential product contamination, this included the use of inappropriate materials close to product e.g. asbestos coated PTFE seals for centrifuge manways. 3. A major deficiency was cited with regards to equipment and facility, maintenance, design and qualification. Examples included, inappropriate pressure differentials that were not in line with the original design but had not been changed using change control, cleaning validation that was not sufficiently robust to confirm cleaning practices and maintenance issues, such as the failure to spark test glass lined reactor vessels for integrity especially following maintenance.
North China Pharmaceutical Group Semisyntech Co., Ltd (Jan 22, 2015)	China	France	Manufacture of Active Substance by Chemical Synthesis, Manufacture of sterile Active Substance, General Finishing Steps and Quality Control Testing	Overall, 17 deficiencies were observed during the inspection, including 2 Critical and 4 Major deficiencies: [Critical 1] Manipulation and falsification of GMP documents (rewriting of records with change of content, an inconsistency of signatures and date in many records, etc.) were observed in different department; [Critical 2] Lack of data integrity in the QC laboratory (No access control, inadequate traceability and archiving practices, no audit trail, no restriction on the deleting of data, etc.) and falsification of the analytical results for residual solvents; [Major 1] Risk of contamination in grade B area; [Major 2] The change control related to (i)- the change of the identification number of some manufacturing equipment and (ii)- the merger project of NCPC semisynthec and Hebei Huari was found deficient; [Major 3] Lack of documentation management, control, and retention of superseded or obsolete version; [Major 4] The company personnel was not adequately trained in GMPs as evidenced by the critical and major deficiencies identified during this inspection.

Huzhou Sunflower Pharmaceutical Co., Ltd (March 25, 2015)	China	France	Manufacture of Active Substance by Chemical Synthesis, General Finishing Steps and Quality Control Testing	Overall, 27 deficiencies were observed, including 1 critical deficiency and 4 major deficiencies: [Critical 1] The controlled area and the equipment that were used for the final synthesis step in the manufacture of Povidone Iodinated, namely the complexation reaction of Iodine with Povidone K30, presented a risk to the patients due to contamination issues with particles and degradation products ; [Major 1] Materials and quality documents were found at a scrap yard outside the main building of the company as well as inside the neighbouring company's building without any written justification ; [Major 2] The purified water production and distribution systems were deficient (presence of a dead-leg, replacement of conductivity controllers without formal change control, mistakes in calibration documentation, etc.) ; [Major 3] Issuance of 2 different Certificate of Analysis in a Batch Record of Povidone K30 without an appropriate deviation management ; [Major 4] Deficient IR spectrophotometer management (no user requirements prior to acquisition of the equipment, no evidence that the instrument was suitable with its intended use, no evidence that the instrument was belonging to the inspected site).
Polydrug Laboratories PVT. Ltd (June 12, 2015)	India	Slovenia	Manufacture of Active Substance by Chemical Synthesis, General Finishing Steps and Quality Control Testing	Overall, 17 deficiencies were found, of which 5 Major consisting in: - Customer complaints deliberately unregistered in the official logbook - Storage of quality documents in an uncontrolled location, involving staff from QC, QA, maintenance and production - Deficient management of paper documents - Deficient management of the computerised system - Failure to address risks of cross contamination for APIs sent out to micronisation subcontractor. The combination of these major deficiencies represents a critical deficiency leading to a potential risk for the patient.
Wuxi Jida Pharmaceutical Co., Ltd (July 28, 2015)	China	Italy	Manufacture of Active Substance by Chemical Synthesis, Manufacture of sterile Active Substance, General Finishing Steps and Quality Control Testing	The inspection was performed by GMP inspectors in relation to the manufacture of sterile glutathione sodium lyophilised object of a variation. The inspection was focused on site 1 and production workshop number 3. During the inspection 28 deficiencies were found, 15 of which were rated as major deficiencies. Major Deficiencies: In many production steps deviations were found regarding the sterility assurance and a risk of contamination of the product: a) Sampling room (deviations 14-15-16): the changing room was not designed in a suitable way to minimize the risk of contamination; the differential pressure between the areas maintained at different cleanliness grade was not monitored; the garments procedure was not in accordance to the principle of classified areas; b) Production areas (deviations 19-20-21-24): the pressure differential between adjacent areas at different cleanliness grade was not in compliance with the guidance value of the European good manufacturing practices; the maintenance and cleaning conditions of some production rooms

				were poor and not adequately handled; the particle counters in B class grade (i.e. freeze-dryers and capping room) were unsuitable located for the intended use; the API transfer from the mixer to aluminum tin did not exclude a risk of API contamination. c) Validation (deviation 7 from letter a to j): the validation approach for different activities was not correctly performed according to the GMP requirements and validation reports were not detailed (warehouse temperature mapping; holding time for sterilization of tools; stay-time in UV-pass box; maximum number of filters sterlisation (20) validation for the moist heat sterilizer used for the rubber stopper sterilization; validation for the dry heat steriliser used for the aluminium tin sterilisation; validation for LAF in weighing room; validation for the HVAC of the sampling room; validation for front-freezing room classification; validation report for the process simulation namely maximum filling time of loading the bulk product in freeze-dryers and maximum time of transferring API from mixer to aluminum tins and capping. d) Packaging and labeling (deviations 5-10-11-13): the management for the container closure system for sterile glutathione sodium freeze-dried was found lacking in some tests to guarantee the sterility assurance of the product; a "wrong"and not-updated label was used as a standard to verify the shipping labels of API; in the API warehouse, the aluminum tins of sterile API were not sealed; the aluminum caps were not identified with a batch number loosing traceability. e) Laboratory testing (deviation 28): some deviations were found for the IR instrument, in particular the IR software had not a controlled access via ID and password and it was not forbidden to copy and rename a file. f) Personnel behavior (deviations 2-7i(ii)-18-19): during the inspection, the inspectors' team received inconsistent and conflicting answers on the same topic from both personnel and management; sometimes the answers seemed to be modified according to the inspectors' requests. The documentation was showed in an ambiguous way as the examples: some layouts were replaced; some documentation was unrelated to the topic. Finally management did not comply with the clothing procedure during the inspection tour.

Parabolic Drugs Limited (July 28, 2015)	India	Italy	Manufacture of Active Substance by Chemical Synthesis, General Finishing Steps and Quality Control Testing	The quality management system was found to be seriously uncontrolled and deficient in all "Principles" (except principle 2.13 and 2.14) reported in the EU-GMP requirements as evidenced by critical and major deviations found in the following areas: inadequate storage and control of documents and samples and material, falsification of documents and data, integrity and security of data in the QC laboratory, Change Control, Deviations management and Risk management. In total 27 deficiencies were found: 3 classified as Critical were found in the area of Documentation management system, Falsification and Security and integrity data; 7 classified as Major deficiencies were found in the area of QC, Personnel, Documentation and Change Control.
Jinan Jinda Pharmaceutical Chemistry Co., Ltd (July 28, 2015)	China	Italy	Manufacture of Active Substance by Chemical Synthesis, General Finishing Steps and Quality Control Testing	In total 18 deficiencies were identified by the inspection team, one of them was classified as critical and six as major. The critical observation was related to an unofficial and non-controlled storage area containing mainly raw materials and finished products which had been made inaccessible to inspectors as the door had been removed and replaced with a panel fixed with screws to the wall, which during the inspection the Company was requested to remove. The material stored in this area was to be managed outside of the Quality Assurance system and the investigation carried out by the inspection team concluded there was a serious risk of data falsification. One of the six major deficiencies was related to a very similar issue, as access to a locked garage was given to the inspection team only hours after requesting it. In both cases the explanations provided were not sound and different versions were given during the inspection. The remaining five major deficiencies were related to specific aspects of the Quality Assurance System with regards to training, cleaning validation, breaches of data integrity in the context of HPLC analysis, microbiological laboratory, qualification of contract manufacturer of a key intermediate of Nitrofurantoin production.
Cargill France (Oct. 30, 2015)	France	France	1.2 Non-sterile products 3.2 Extraction of Active Substance from Natural Sources 3.5 General Finishing Steps	Overall, 14 observations were made, including 1 critical deficiency and 4 major deficiencies: [Critical] The management of semi-finished batches and of the mixing operations was deficient and conformity of the final batches to specifications, notably Ph.Eur. specifications, could not be guaranteed. [Major 1] The site had been manufacturing an active substance without ANSM authorisation. [Major 2] The change control related to the suppression of one filtration step in the active substance manufacturing process was deficient. [Major 3] The manufacturing of the active substance had not been made using master production instructions and no batch production records had been

				established. [Major 4] No review of batch production records of critical process steps had been done before release of the active substance for distribution. 7 observations are related to lack of traceability, risks of contamination induced by the absence of cleanliness in the production environment, very bad condition of the production equipment and insufficient equipment cleaning procedures. The inspection's observations also apply to the manufacture of pharmaceutical excipients and starting materials that are intended to be used as ingredients in cosmetics and medical devices, which are manufactured under the same conditions as the active substance.
Iason Utakua Srl (Dec 1, 2015)	Italy	Italy	1.1 Sterile products 1.5 Packaging 1.6 Quality control testing	During the inspection 19 deficiencies were identified, 3 of them were rated as critical deficiencies and 11 as major deficiencies. The main deficiencies were related to the Quality Management and the Quality Assurance Systems also in terms of sterility assurance and risk of contamination/defects of the final product. One critical deficiency was related to failure to fully investigate and document out-of-specification results for microbiological environmental monitoring in class A isolator and class B/C surrounding areas, in manufacture of radiopharmaceuticals aseptically prepared. The company didn't carry out an appropriate and full-scale investigation to determine what caused the OOSs. An appropriate level of corrective action analysis was not applied during the investigation and the true root cause(s) were not determined. Failure to address the root cause due to ineffective CAPA revealed a lack of the quality assurance framework system. Another critical deficiency was reported with regards to production processes which were considered not satisfactory controlled: it was found that for the manufacture of some batches of the radiopharmaceutical Pcolina (Iasocholine) a non suitable reagent was used (expired dibromomethane). Moreover, for some batches of released RPs master batch documents were incomplete. No adequate review by QA or QP. Furthermore, preparation of the starting material set for radiopharmaceuticals was performed in condition not appropriate to guarantee an adequate level of chemical and microbiological containment. The inspection's team has rated also as critical the observation related to the number of personnel in force to the manufacturing site, which were considered not appropriate to conduct all the activities in accordance with the GMP and to maintain the quality management system and its effectiveness. The remaining major deficiencies were related to specific aspects of the Quality Assurance System with regards to PQR assessment, revalidation and recalibration of critical equipment, data integrity in the context of HPLC management, storage of materials and documentation system.

AstraZeneca Pharma (Dec 11, 2015)	India	Sweden	1.4 Other products or manufacturing activity 3.1 Manufacture of Active Substance by Chemical Synthesis 3.5 General Finishing Steps 3.6 Quality Control Testing	The API manufacturing process was not acceptably validated and was not under control after the validation. The concerned batches have been sent to the EEA (Sweden) and to a third country (China). During the inspection, 24 deficiencies were found. None of the deficiencies was critical but 4 were major. The 4 major deficiencies were found in the areas of documentation routines and data integrity (2), design and maintenance (1), validation (1). After three CAPA responses from the company the major deficiency regarding validation still remains.
Minshing Group Shaoxing Pharmaceutical Co. Ltd. (Dec 28, 2015)	China	France	Non-sterile products, Active Substances	Nature of non-compliance : Overall, 18 deficiencies were observed during the inspection, including 2 Critical and 4 Major deficiencies: [Critical 1] Falsification of source of API (Thiamphenicol): Repackaging, relabeling and selling of purchased API from a non-GMP company (Zhejiang Runkang Pharmaceutical Co.Ltd.) as if manufactured in-house; [Critical 2] Praziquantel manufactured according to CP process/grade was released as USP process/grade without a full traceability of the testing activities ; [Major 1] The maintenance and the cleaning operations of the manufacturing line used for the production of Praziquantel (API) were found deficient; [Major 2] The pipes design of some equipment used for the manufacturing of Praziquantel, the handling of change related to these equipment and the instruction used for the transfer of the intermediate solution using nitrogen were found deficient ; [Major 3] The hoses used for unloading of solvent were not identified, had no cleaning status and were stored on a dirty floor of an area not mentioned in the general layout of the site; [Major 4] There was no procedure in place for audit trail and there was no effective audit trail in place to determine any change or deletion of the chromatographic raw data. The audit trial function including the administrator profiles was enabled for all the QC staff. The inspection was performed in the framework of WHO prequalification of medicines programme for the manufacture of Praziquantel API.