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Compilation of EDQM Non-Compliance Report Observations (2012-2015)

Concerns related to data integrity

- 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. (HUZHOU SUNFLOWER PHARMACEUTICAL CO., LTD, China)

- 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. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- 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. (WOCKHARDT LIMITED, India)

- Data falsification in relation to training records which were rewritten without authorization. (WOCKHARDT LIMITED, India)

- The control of visual inspection activities for sterile products was not robust. Following the inspection, it has also come to light that senior QA personnel mentioned in the organisational charts are not resident on site but are based at other Wockhardt site around 30km away in Aurangabad. Senior QA oversight on site was therefore poor. (WOCKHARDT LIMITED, India)

- Data falsification. (MEDREICH LIMITED – UNIT V, India)

- 4 were related to documentation (documentation management and data integrity with difficulty to demonstrate that the actions recorded were genuine). (MEDREICH LIMITED – UNIT V, India)

- The inspection team tried to verify some regulatory information requested during the assessment of the dossier and reached the conclusion that fundamental GMP and regulatory requirements such as loss of data integrity, combined with insufficient management of data, change control system, supplier qualification, laboratory controls as well as the accuracy of data submitted, were not adequately implemented/considered because of a weakness of the QA system and regulatory affairs department. (Fujian South Pharmaceutical, China)

- Refers to the production of Glutathione sodium sterile (GSS) The documentation review pointed out that I.C.I. INTERNATIONAL CHEMICAL INDUSTRY carried out “a shadow” production unauthorized and with lack of traceability; this production was defined by the company as “unofficial” and was carried out between 2009-2013 June. The unofficial batches were put on the market but there was no evidence of batch release by the qualified person. The Company was authorized to manufacture GSS starting from 28 December 2010, but GSS batches were released for the market before granting the authorization in the period 21st January 2009 – 28th December 2010. Rapid alert IT/II/11/01 was issued on 18 July 2014 related to the production of GSS unofficial batches, recommending withdrawal of the GSS concerned batches. In addition, the inspection of the manufacturing area “Sterile 1”, where GSS was manufactured, arose deficiencies on hygiene conditions, HVAC and equipment maintenance which require adequate corrective actions. In this area other APIs were manufactured (sterile Ademetionine 1,4 butanedisulfonate, sterile Fructose 1,6 diphosphate trisodium salt, ferric gluconate and iron sucrose oral grade); a list of questions has been submitted to the Company in order to finalize the risk assessment and to make a decision on the products on the market. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- One critical deficiency dealing with the documentation management system and the quality management system has been raised during the inspection performed by ANSM, leading inspectorate and MPA, supporting inspectorate. Indeed the documents provided by the site have been found by the inspectors unreliable and evidences of manipulation of data have been found. As an illustration: - In an "In Process Control" room, located in plant A (Cephalosporine products manufacturing) – non sterile manufacturing area, the following items have been found (among others): • Parts of original batch record (from recent and non recent batches). • Copies of batch records of products not manufactured on site such as Turbuhaler product (Budesonide). • Blank batch records forms. • Original analytical data (from recent and non recent batches). • Reprocessing protocols. - Moreover, in a another room which is an office located in plant A, the batch record of Tabiclor MR 3BF168 has been found. According to this batch record, the batch has been entirely packed (97330 tablets) on 26th September 2013 and transferred in the Finished Goods Warehouse the same day. However, this batch has been found in the Work In Progress area, as unpacked bulk tablets, in drums. (TABUK PHARMACEUTICAL MANUFACTURING CO . – TABUK, Saudi Arabia)

- Manipulation and falsification of documents and data were observed in different departments . (Smruthi Organics Limited, India)

- Denial of access to information relating to the above two major deficiencies and request from the firm to terminate the inspection at the beginning of the second day of the inspection. As a consequence, it was not possible to further investigate these 2 major deficiencies. The verification of data integrity and material traceability could not be performed. (WUXI KAILI Pharmaceuticals Co., Ltd, China)

- Quality Management: Critical regarding falsification of documentation and deliberately hiding the use of an unapproved critical starting material. (Bajaj Healthcare PVT Ltd, India)

- Written production and process control procedures are not documented at the time of performance. Specifically, Too Numerous to Count (TNTC) torn and discarded controlled manufacturing batch records for a variety of different products issued by the Quality Unit were found during a walk-through inspection of the facility. Five batch records were compared with the archived manufacturing one and it was ascertained that no records had been made for duplicate issuance of these five batches chosen for review, as required per SOP QA/SOP/DOC/001. Notably, after subsequent investigation it was found that the Master Batch Record (version 0) had been back-dated by the most responsible persons within your firm's Quality and Manufacturing departments, which was confirmed by these persons during our inspection. (SRI KRISHNA Pharmaceuticals Ltd., India)

- This is the first time this site has been inspected by EEA- inspectorate; it was inspected in relation to a marketing authorization application currently under assessment by HPRA (Ireland). Batch release site for the EU is located in Spain. Several critical and major deficiencies to EU Good Manufacturing Practice Guide (Part I) were observed. Most serious deficiencies are summarized below: • Defective performance of cleaning, lack of effective supervision of cleaning and housekeeping. • Inappropriate validation of cleaning procedures. • Failures in line clearance • Record integrity and veracity: some records were made up or altered. • Defects on deviation recording and investigation. • Lack of mechanisms to ensure integrity of analytical data. (RENOWN PHARMACEUTICALS PVT. LTD., India)

- The company declared that the manufacturing operations of Cinnarizine were stopped in blocks A and B at the end of September. However, there was no documented evidence that this stop was effective at this date. (Fleming Laboratories Limited, India)

- One individual training file of an employee has been observed to be recently re-rewritten. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- The sample retention log-book for Trimethoprim had falsified entries. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- Lack of data in laboratories. (GUERBET PRODUTOS RADIOLOGICOS LTDA, Brazil)

- The scope of this inspection was related CEP dossier: CEP 2001-409: Norfloxacin. However, the deficiencies found give evidence of the severe nature of GMP violations such as: lack of implementation of a consistent and reliable Quality Management System. Documentation of produced batches was found out of the control of Quality Assurance, therefore out of a GMP environment. Approach to hide non-conformities with respect to specifications. Manufacturing of some of the production steps in building Unit I which does not operate under a Quality Assurance System based on EU GMP Part II. Inconsistent coding system for batches of norfloxacin, which leads to a lack of traceability of the batches manufactured. Deficient, incorrect or ambiguous records in batch records and analytical reports. Inconsistent vendors qualification procedure, in which a part of the responsibility is under R&D Department, therefore out of the Quality Assurance System. According to these findings it is considered that the products pose a significant risk to patient health and safety. (Smruthi Organics Limited, India)

- There was evidence of data integrity issues within GMP documents, buildings were also falsified to mislead the inspectors. Evidence of a number sterility assurance and cross contamination issues were identified including facility maintenance, processes, environmental monitoring and validation sterilisation practices. (MICRO LABS LIMITED, India)
- An acceptable QA system was not implemented since a broad range of GMPdocumentaion had been systematically falsified, rewritten or inapproprietally destroyed. (RUSAN PHARMA LTD., India)

- 1. Documented evidence of false and misleading records was established within environmental data log sheets. 2. A lack of controls to minimise cross contamination, significantly the lack of appropriate cleaning validation. 3. There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP 4. Inadequate control of starting materials - raw materials were observed to be stored at temperatures and relative humidity's significantly outside of their stated requirements 5. Supplier Assurance processes were significantly lacking including compliance with the TSE regulations 6. Non compliance with commitments made at the previous inspection. (SOFTGEL HEALTHCARE PRIVATE LIMITED, India)

- Falsification of GMP documents; design and maintenance of equipment; design and maintenance of premises; potential for product contamination; quality system - change management, quality risk management; qualification of processes and equipment; control of starting materials - supplier evaluation, warehouse controls; training of personnel;

provision of misleading information in the dossier. (BAJAJ HEALTHCARE LTD – GUJARAT, India)

- On the basis of the inspection findings, National Competent Authorities are recommended to consider recall of product in their territory due to the risk of cross-contamination and falsification of records, which do not provide assurance of product quality. National supply situations and clinical requirements should be taken into account when making this decision. (SHARON BIO-MEDICINE LIMITED, India)

Deficiencies in the Quality Control Laboratory

- 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. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)
- Consideration of a supply prohibition should be given due to the lack of data integrity in the QC laboratory, falsification of the analytical results and manipulation of GMP documents. Using QRM principles, National supply situations and clinical requirements should be taken into account when making this decision. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- Critical: Laboratory Controls. This repacker does not have laboratory facilities. It is not possible to ensure that APIs are in compliance to established standards of quality and purity. No tests to verify the identity of a batch of material are conducted and original manufacturers have not been evaluated and approved. Major deficiencies (8). Weakness in the QA system and a significant risk of repackaging operations summarize these deficiencies. This repacker has not established, documented and implemented an effective system of managing quality to ensure confidence that the API will meet its intended specifications for quality and purity. Subdividing operations are not conducted under appropriate environmental conditions to avoid contamination and cross-contamination. Repackaging operations are conducted in a manner that will not prevent contamination between APIs. Utensils are not cleaned and stored to prevent contamination. There are not an adequate number of personnel qualified by appropriate education, training and experience to perform and supervise the manipulation of APIs. Buildings used in the manipulation of APIs are not properly maintained, repaired and kept in a clean condition. HVAC systems are not qualified, appropriately monitored and actions are not taken when limits are exceeded. Materials are not handled and stored in a manner to prevent degradation, contamination, and cross-contamination. Deviations are not sufficiently investigated, documented and explained. (Ranbaxy Laboratories Limited, India)

- Laboratory Controls. This repacker does not have laboratory facilities. It is not possible to ensure that APIs are in compliance to established standards of quality and purity. No tests to verify the identity of a batch of material are conducted and original manufacturers have not been evaluated and approved. (MANUEL RIESGO S.A., Spain)

- The critical deficiency was found during inspection of the quality control laboratories. The company failed to establish a procedure to identify and valdate GMP-relevant computerized system in general. (Zhejiang Apeloa Kangyu Bio-Pharmaceutical Co. Ltd., China)

- Issues were identified which compromised the integrity of analytical data produced by the QC department. Evidence was seen of data falsification. A significant number of product stability data results reported in the Product Quality Reviews had been fabricated. Neither hard copy nor electronic records were available. In addition issues were seen with HPLC electronic data indicating unauthorised manipulation of data and incidents of unreported trial runs prior to reported analytical runs. (WOCKHARDT LIMITED, India)

- There was no raw data available in the Quality Control laboratory for the verification of compendial analytical methods. (Smruthi Organics Limited, India)

- The critical deficiency concerns systematic rewriting/manipulation of documents, including QC raw data. The company has not been able to provide acceptable investigations and explanations to the differences seen in official and non-official versions of the same documents. (Seikagaku Corporation, Japan)

- Data recording and integrity in the QC laboratory. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)

- Although data manipulation was actually observed only in 2 (out of a total of 29) reviewed batch analysis records from one operator and affected Colistin Sulfate batches only the extent of the violation cannot be delimited precisely. The company performed ad hoc investigation and risk assessment on the issue and came to the conclusion that no evidence for further affected batches could be found. The overall quality risk was rated to be low by the company. Parts of the reserve samples of the two batches with the manipulated batch anlaysis records were taken during the inspection and analysed by the InphA GmbH Bremen (OMCL of Lower Saxony). The results of the HPLC testing on composition and related substances met the specification. (Zhejiang Apeloa Kangyu Bio-Pharmaceutical Co. Ltd., China)

- Insufficient securisation of the electronic raw data in the Quality Control laboratory (No limitation of access levels, no restriction on the deleting of data, no audit trail, inadequate traceability and archiving practises). (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)

- Drug products failing to meet established quality control criteria are not rejected. In particular: a) analysts routinely use the PC administrator privileges to set the controlling time and date settings back to over-write previously collected failing and/or undesirable sample results. This practice is performed until passing and/or desirable results are achieved; b) Analysts routinely perform "trial" injections of sample aliquots prior to performing the official/reported analysis. There are no documented sample preparation details for these trial analyses. The results of these trial injections are not reported, and were found to differ significantly from the subsequent reported results; c) Analysts routinely perform "trial" injections of sample aliquots prior to performing the official/reported analysis. The resulting raw data chromatogram files were often found to have been deleted and unavailable for review; d) Analysts delete undesirable and/or failing results (entire sample sequences) and retest samples until desirable results are achieved. (SRI KRISHNA Pharmaceuticals Ltd., India)

- 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. (HUZHOU SUNFLOWER PHARMACEUTICAL CO., LTD, China)

- Established laboratory control mechanisms are not followed. Electronic records are used, but they do not meet systems validation requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records. (SRI KRISHNA Pharmaceuticals Ltd., India)

Cross-Contamination/Equipment Concerns

- 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. (HUZHOU SUNFLOWER PHARMACEUTICAL CO., LTD, China)

- Design and operation of the cleanrooms. (Ranbaxy Laboratories Limited, India)

- Potential chemical contamination, it was found that the company were manufacturing a potent cytotoxic (Amsacrine) product in the non-potent suite. Processes intended to contain the product had failed and cleaning process and verification were weak with contamination of general manufacturing areas seen. (SCM PHARMA LIMITED, United Kingdom)

- Serious deficiencies related to sterility assurance, sterilisation processes and the Pharmaceutical Quality System have been identified at Moorfields Pharmaceuticals.

Concerns implicate all aspects of aseptically prepared and terminally sterilised products. Failures and non-compliances were identified with the approach to qualification and the routine controls of sterilisation. Poor aseptic practices were noted with manufacturing processes. Grade A HEPA filter integrity failures have been noted for some areas. Microbiological environmental monitoring and media simulation programmes were deficient. Media simulation failures have been identified. Serious deficiencies were noted with the Pharmaceutical Quality System. Company Corrective and Preventative actions and remediation, to date, have failed to adequately address all deficiencies and non-compliances. There is currently no evidence of non-sterile product on the market. Most unauthorised medicinal products are small volume short shelf life, and not subject to sterility testing. A supervisory risk assessment has been circulated via rapid alert. (MOORFIELDS PHARMACEUTICALS, United Kingdom)

- The management and redistribution (reselling) of batches contaminated with over sulphated chondroitin sulphate (OSCS) and, separately, with ruminant DNA. (Chongqing Imperial Bio-chem. Co., Ltd., China)

- Serious equipment qualification and process validation. (INVENTIA HEALTHCARE PRIVATE LIMITED, India)

- 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. (WOCKHARDT LIMITED, India)

- Controls for preparation (including sterilization) of components and equipment. (Ranbaxy Laboratories Limited, India)

- Refers to the freeze drying production area, used for oral drug substances and oral bulk mixture “Piroxicam β-ciclodestrine” (called Workshop 3). The documentation review pointed out that I.C.I. INTERNATIONAL CHEMICAL INDUSTRY manufactured batches of “collagene”, “CDX017- enzyme” and “Omogeneizzato liofilizzato” (consisting of lactobacillus lyophilized) on the same production line of piroxicam β-ciclodestrine and not according to the GMP quality system. The products collagene, CDX017- enzyme and Omogeneizzato liofilizzato were manufactured for not pharmaceutical use but as medical devices and nutraceuticals; the relevant Italian competent authorities were informed. After the inspection AIFA addressed the safety issues related to biological origin of the substances manufactured in the same equipment used for the product Piroxicam β-ciclodestrine and according to the current information collected recall of Piroxicam β-ciclodestrine is not considered necessary. Since additional requests were submitted to the Company, any change of the assessment done by AIFA will be promptly communicated. Summary of the Major deviations: The other deviations, classified all as “Major”, showed: - Several batches of GSS and Piroxicam β-ciclodestrine were stored in

non GMP areas (R&D and “technical area”); the Company submitted evidences that all batches were destroyed after the inspection; - The HVAC for the preliminary treatment of the Sterile 1 was not subjected to preventative maintenance; - Lack of maintenance in the oral lyophilisation department; - Poor cleaning condition in the dispensing area; poor maintenance in the dissolution room; lack of hygiene and organization in warehouses, archives and offices close to the production area; - Pressure and temperature out of specifications values of were observed in Sterile 2 workshop; - The warehouse computerized system is not validated; The Company submitted a corrective action plan which encompasses revamping of the sterile 1 manufacturing area; AIFA suspended the manufacture authorization which can be restored only after an inspection aimed to verify compliance with GMP and legal requirements. After the assessment of the available information a recall was recommended only for the unofficial/unauthorized GSS, as per Rapid alert IT/II/11/01. Further investigations are ongoing. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- Potential microbial contamination. There were contaminated process media simulations that were not adequately investigated and root cause explained and mitigated. VHP sanitisation of the filling isolator inadequately controlled and validated and weaknesses in the environmental monitoring program. (SCM PHARMA LIMITED, United Kingdom)

- Repeated critical deficiency related to the cross-contamination of the facility with beta-lactam. (North China Pharmaceutical Co., Ltd, China)

- The purification of the sub-batches of crude Ciclosporine was found to be not in compliance with the basic principles of GMP. It could not be excluded that manufactured batches could harm human or veterinary patients evidenced by the following observations: a. There was neither a test nor a specification in place for the second crop product (NB: There was a specification for the mother liquor of the second crop to be reintroduced into the purification steps). This observation had also been noted in the previous EDQM inspection. b. The second crop was merged with the product from the first crystallisation. c. The second crop process was not subjected to process validation. d. The resulting individual batch was not considered as such and consequently the following observations were made: The specification of the so-called ‘semi-product’ was only related to the level of loss of drying (NMT 1.8%) and blended with another batch of purified Ciclosporine without further testing. e. The recovery of material from the crystallization mother liquor (second crop) was not described in the certification dossier. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)

- Controls concerning aseptic filling. (Ranbaxy Laboratories Limited, India)

- Maintenance and cleaning of process equipment. (Suzhou No. 4 Pharmaceutical Factory, China)

- The lack of quality assurance in the supply chain in place at the Chongqing Huhao workshop where Raw Heparin Sodium is manufactured. Eleven Major Deficiencies were identified during the course of the inspection; these related to a number of areas within the quality system. (Chongqing Imperial Bio-chem. Co., Ltd., China)

- Risk of contamination in grade B area. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- In workshop B-03 the room used to perform the first purification of Docetaxel anhydrous by liquid chromatography was found not suitable for its intended use, as there was a potential risk of contamination. (Fujian South Pharmaceutical, China)

- Several batches of GSS and Piroxicam β-ciclodestrine were stored in non GMP areas (R&D and "technical area"). (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- Inadequate cleaning and maintenance of the production equipment. (North China Pharmaceutical Co., Ltd, China)

- Building and facilities. (Suzhou No. 4 Pharmaceutical Factory, China)

- Handling of the HVAC systems. (GUERBET PRODUTOS RADIOLOGICOS LTDA, Brazil)

- Process Equipment. (SHANGYU JINGXIN PHARMACEUTICAL CO., LTD, China)

- Several manufacturing areas were seen insufficiently protecting the product from outside contamination. (Aarti Drugs Limited, India)

- Doesn't have premises for production, control and storage complying with Good Manufacturing Practice requirements. (ET "DIKRASIN - DIMITAR KRASTEV", Bulgaria)

- Production and In-Process Controls. (MEHTA API PVT. LTD., India)

- Subdividing operations are not conducted under appropriate environmental conditions to avoid contamination and cross-contamination. Repacking opertaions are conducted in a manner that will not prevent comtamination between APIs. (MANUEL RIESGO S.A., Spain)

- A second major deficiency regarding maintenance of equipment and facilities with poor controls witnessed. (SCM PHARMA LIMITED, United Kingdom)

- The tank used for the storage of crude Trimethoprim was found to be in an unacceptable condition. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- Buildings and Facilities. (Suzhou No. 4 Pharmaceutical Factory, China)

- Inadequate storage conditions and labeling of 2 commercial drums (one labelled as "Cimetidine HCl" and one unlabelled) and 5 retention samples of Cimetidine CEP grade. (WUXI KAILI Pharmaceuticals Co., Ltd, China)

- The removal of particles and endotoxins in vials. (GUERBET PRODUTOS RADIOLOGICOS LTDA, Brazil)

- Production equipment still showed risks of contamination (a similar deficiency was raised during the previous inspection). (Albert David Ltd, India)

- Equipment. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)

- Several clean areas were seen in a dilapidated state of cleanliness and maintenance. (Aarti Drugs Limited, India)

- Cleaning of Equipment. (VITAL HEALTH CARE PVT LTD, India)

- Facilities. (AANJANEYA LIFECARE LIMITED, India)

- 5 were related to the maintenance of equipment (depyrogenisation tunnel and RABS used for the filling operation, LAF used for the sampling of sterile starting materials ...). (MEDREICH LIMITED – UNIT V, India)

- Utensils are not cleaned and stored to prevent contamination. (MANUEL RIESGO S.A., Spain)

- The Company's manufacturing process C for Docetaxel anhydrous requires the blending of individual batches. The insufficient equipment capacity requires the material previously obtained to be split into two single batches. The manufacturing operations to be conducted in the final purification step are four crystallisations followed by drying. No testing of the individual batches was required prior to the blending operation. This approach could lead to masking of Out-of-Specification results in the individual batches. The remaining 22 deficiencies identified some additional issues in the field of Quality Management, Buildings and Facilities, Process Equipment, Documentation and Records, Laboratory Controls, Validation, Rejection and Re-use of Materials. (Fujian South Pharmaceutical, China)

- The HVAC for the preliminary treatment of the Sterile 1 was not subjected to preventative maintenance. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- Buildings and Facilities. (CHANGSHU HUAGANG PHARMACEUTICAL Co., Ltd., China)
- Building and Facilities. (Suzhou No. 4 Pharmaceutical Factory, China)
- Equipment. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China
- Several occurrences of unhygienic particles or inadequate implementation of cleaning procedures of equipment. (Aarti Drugs Limited, India)
- Doesn't have equipment for quality control and production equipment complying with Good Manufacturing Practice requirements. (ET "DIKRASIN - DIMITAR KRASTEV", Bulgaria)
- Facilities. (AANJANEYA LIFECARE LIMITED, India)
- Multiple risks of contamination identified in the production areas of Ciclosporin (e.g. no protection of clean equipment outlets, equipment under status "to be used for production" stored dirty for several months, open parts of the final steps exposed in dirty surroundings). (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)
- Lack of maintenance in the oral lyophilisation department. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)
- Risk of contamination in the production area. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)
- The sampling and dispensing room used for solid raw materials was considered unsuitable for its intended use. (Fleming Laboratories Limited, India)
- Risk of contamination by reusable plastic containers of raw materials. (North China Pharmaceutical Co., Ltd, China)
- There was a significant risk of contamination within the oral solids manufacturing block. The risk arose from ingress of flies, poor facility maintenance and dust collection from vacuum dust collector outlets which were in close proximity to HVAC inlets. (WOCKHARDT LIMITED, India)
- Premises and Equipment. (MEDREICH LIMITED – UNIT V, India)

- Process Equipment. (CHANGSHU HUAGANG PHARMACEUTICAL Co., Ltd.,China)
- Building and facilities. (Suzhou No. 4 Pharmaceutical Factory, China)
- Equipment. (AANJANEYA LIFECARE LIMITED, India)
- Buildings used in the manipulation of APIs are not properly maintained, repaired and kept in a clean condition. (MANUEL RIESGO S.A., spain)
- Poor cleaning condition in the dispensing area; poor maintenance in the dissolution room. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)
- Risk of contamination and cross-contamination of testing samples. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)
- The design and the usage of the different storage facilities lead to risks for the quality of the materials stored. (Fleming Laboratories Limited, India)
- Cross contamination issues between Phenoxymethylpenicillin potassium and Penicillin G Potassium. (North China Pharmaceutical Co., Ltd, China)
- Process Equipment. (Suzhou No. 4 Pharmaceutical Factory, China)
- HVAC systems are not qualified, appropriately monitored and actions are not taken when limits are exceeded. (MANUEL RIESGO S.A., Italy)
- Inappropriate equipment and area qualification (e.g. no qualification for the automatic temperature controllers at the fermentation warehouse, the strain centre for Ciclosporin and the cool storage area for Ciclosporin). (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD., China)
- Lack of hygiene and organization in warehouses, archives and offices close to the production area. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)
- The storage of raw materials, intermediates and finished products was considered not to be compliant with GMP requirements (e.g., materials segragation, housekeeping, etc.). (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)
- Repeated major deficiency related to the cleaning and maintenance of the utensils used for the solvents. (North China Pharmaceutical Co., Ltd, China)

- Deficiencies were related to the premises which were poorly maintained associated with a deficient pest control. Different areas, where products and cleaned equipment were exposed, were not supplied by filtered air. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- Premises and Equipment. (MEDREICH LIMITED – UNIT V, India)

- Pressure and temperature out of specifications values of were observed in Sterile 2 workshop. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- Risk of contamination in the filtration and washing area for inadequate cleaning of the production equipment and tools. (North China Pharmaceutical Co., Ltd, China)

- Risk of microbial, particle and chemical contamination of starting materials. (North China Pharmaceutical Co., Ltd, China)

- Deficiency related to equipment. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- Deficiencies were related to production with a poor cleaning of production areas/equipment, an unsatisfactory handling of cleaned/ uncleaned status resulting in a risk of cross contamination or mix-up. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- Production. (AANJANEYA LIFECARE LIMITED, India)

- Sanitation. (MEDREICH LIMITED – UNIT V, India)

- This inspection was performed in the frame of the EDQM inspection programme (Inspection number INSP 2007-020 P03). The scope of this inspection was the manufacturing of Phenoxymethylpenicillin Potassium. The site was already GMP non compliant following the previous EDQM inspection conducted on 14-16 October 2010 and the proposed actions were described in the NCS # Insp GMP 36204/1375445-0001. - This site is not suitable for supply of any other materials for EU products due to the risk of contamination with Phenoxymethylpenicillin Potassium. (North China Pharmaceutical Co., Ltd, China)

- There is a public health concern with regards to the potential cross-contamination of non-antibiotic products with beta lactams given that the suite is not maintained, operated or monitored to acceptable standards. Hypersensitivity reactions to beta lactams is commonly experienced, and this may include life-threatening anaphylactic reactions. There is therefore a risk that such patients when exposed to contaminated

non-antibiotic products may inadvertently suffer a hypersensitivity reaction related to the beta lactam contamination. This constitutes an immediate risk to public health. Medical advice is that a safe level of Penicillin contamination cannot be determined for adjacent production areas in this facility. (NESTOR (UK) LIMITED, United Kingdom)

- Based on 1) the risk assessment related to the medicinal products on the market provided to AFSSAPS by MA holders using this supplier of molsidomine and 2) the analytical results from the AFSSAPS Laboratories on the samples collected on site concluding to the compliance to the specifications and to the absence of selected potential contaminants (other APIs manufactured in the same workshop), no further action on the medicinal products on the market is required. (Changzhou Longcheng Pharmaceutical Co., Ltd., China)

- At the time of the inspection the site was found to have serious GMP deficiencies in the following areas: Quality management systems, purified water system, facility and equipment maintenance, potential for contamination of product, quality control systems, control of the manufacturing process for Isoniazid, personnel, material control and document management. (AMSAL CHEM PRIVATE LIMITED, India)

- Risk of cross-contamination of the Cyclizine Base API with agrochemical/pesticides manufactured in adjacent fume hoods in a shared laboratory area. Significant gaps in the quality management system. Material status and temperature control deficiencies. (Edinburgh Pharmaceutical Processes Limited, United Kingdom)

- 1.Doesn’t have premises for production, control and storage complying with Good Manufacturing Practice requirements 2.Doesn’t have quality control manager and a qualified person 3.Doesn’t have equipment for quality control and production equipment complying with Good Manufacturing Practice requirements. (ET "DIKRASIN - DIMITAR KRASTEV", Bulgaria)

- 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. (WOCKHARDT LIMITED, India)

- 9 were related to production (sterile and non-sterile products) including risk of cross contamination, poor visual inspection process handling, poor in-process control handling (weight of vials, weight of tablets and hard capsules), poor handling of broken vials issues. (MEDREICH LIMITED – UNIT V, India)

- An out-of-specification result obtained for an In-Process Control, performed by TLC, was considered as compliant by the analys. (Smruthi Organics Limited, India)

Incomplete Deviation Investigations

- Some Corrective and Preventive Actions, related to deficiencies raised during the previous inspection were not satisfactorily addressed . (Smruthi Organics Limited, India)

- The management and investigation of the OSCS and ruminant contamination incidents. (Chongqing Imperial Bio-chem. Co., Ltd., China)

- 5 were related to poor level of quality management (inadequate deviations management system with no exhaustive record, no classification and no thorough investigation). (MEDREICH LIMITED – UNIT V, India)

- A major deficiency regarding the change control program (not all changes were controlled appropriately) and investigations, which were poor in quality with regards to root cause analysis and corrective and preventative actions and were not performed in a timely manner. (SCM PHARMA LIMITED, United Kingdom)

- Despite its commitment following the last inspection (June 2010) to replace 4 pieces of manufacturing equipment, the company has only decided to replace 2 of them and repair the 2 others, without carrying any risk assessment or providing documented justification for this CAPA modification . (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- The out-of-specification results were not systematically investigated. (Fleming Laboratories Limited, India)

- A failure to effectively address the deficiencies cited at the previous inspection. (WOCKHARDT LIMITED, India)

- Manufacturing operations and handling of deviations. (Linaria Chemicals (Thailand) Ltd., Thialand)

- Inability of the Quality Control unit to conduct and manage HPLC tests appropriately (e.g. no documentation and justification of deviations from analytical procedures, no detection of analysts errors). (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD., China)

- The non-conformance/deviation management system was weak and unplanned deviations were not routinely recorded. (WOCKHARDT LIMITED, India)

- Corrective actions were announced but not implemented yet. (GUERBET PRODUTOS RADIOLOGICOS LTDA, Brazil)

- Deviations are not sufficiently investigated, documented and explained. (MANUEL RIESGO S.A., Spain)

- Complaints: deficient investigation of a complaint regarding Mefenamic Acid. (Ningbo Smart Pharmaceutical Co. Ltd, China)

- The site has failed to implement an acceptable CAPA plan and can not commit to re-inspection within required timescales. Statement of non-compliance issued on this basis. (SOFTGEL HEALTHCARE PRIVATE LIMITED, India)

- Deficiencies were related to the quality management system: poor supervision of activities including recording, investigation and implementation of CAPA; documents not correctly distributed and maintained; self-inspection not addressing adequately the situation (no comment on the excessive degradation of premises and equipment in the last reports). (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

Lack of Personnel and/or Training

- Quality Management: due to a global lack of understanding of Good Manufacturing Practice, underlined by the combination of major deficiencies. (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Poor training of operators. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- 3 were related to personnel (no formal policy on temporary workers specially for quality critical activities such as visual inspection). (MEDREICH LIMITED – UNIT V, India)

- Training of personne. (Linaria Chemicals (Thailand) Ltd., Thialand)

- Doesn’t have quality control manager and a qualified person. (ET "DIKRASIN - DIMITAR KRASTEV", Bulgaria)

- Personnel training was deficient for induction training and for any further training needs. (Fleming Laboratories Limited, India)

- Poor training of operators. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- The company personnel was not adequately trained in GMPs as evidenced by the critical and major deficiencies identified during this inspection. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- There are not an adequate number of personnel qualified by appropriate education, training and experience to perform and supervise the manipulation of APIs. (MANUEL RIESGO S.A., Spain)

- Training of personnel. (VITAL HEALTH CARE PVT LTD, India)

Water System Concerns

- Purified Water System. (MEHTA API PVT. LTD., India)

- 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.). (HUZHOU SUNFLOWER PHARMACEUTICAL CO., LTD, China)

Other Concerns

- Issuance of 2 different Certificate of Analysis in a Batch Record of Povidone K30 without an appropriate deviation management. (HUZHOU SUNFLOWER PHARMACEUTICAL CO., LTD, China)

- 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. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- Lack of documentation management, control, and retention of superseded or obsolete version. (North China Pharmaceutical Group Semisyntech Co., Ltd, China)

- One manufacturing process has not been revalidated after severe process changes (frequent quality defects of this product have been reported to the inspectorate). The company failed to prove that all relevant analytical methods used have been validated

by the QC department. (AGEPHA, Anstalt zur gewerblichen Produktion von Heilmitteln und Arzneiwaren GmbH, Slovakia)

- Inappropriate reference material has been used – the company could not deliver proof that the current reference material is suitable for the intended use. (AGEPHA, Anstalt zur gewerblichen Produktion von Heilmitteln und Arzneiwaren GmbH, Slovakia)

- Missing or poor quality agreement. (SRI KRISHNA Pharmaceuticals Ltd., India)

- Weakness in the QA system and a significant risk of repackaging operations summarize these deficiencies. This repacker has not established, documented and implemented an effective system of managing quality to ensure confidence that the API will meet its intended specifications for quality and purity. (MANUEL RIESGO S.A., Spain)

- Materials are not handled and stored in a manner to prevent degradation, contamination, and cross-contamination. (MANUEL RIESGO S.A., Spain)

- Numerous weaknesses in the quality management system (review of process validation data, documentation, product quality review). (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD., China)

- Blending of Ciclosporin batch tails without adequate traceability and validation combined with unsuitable sample representativity and traceability. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD., China)

- The issuance of quality related documentation was found inadequately controlled/secured by QA. (Fujian South Pharmaceutical, China)

- The product stability monitoring programme had not been maintained to cover products currently on the market. (WOCKHARDT LIMITED, India)

- Deficiencies in material cold storage arrangements. The site was re-inspected on [28 April to 1 May 2014]. The company's remediation plan remains in progress, and compliance has not yet reached a satisfactory level. No change in product risk was identified as a result of the re-inspection, and no changes to existing regulatory action are proposed. The company remains under close regulatory supervision. (WOCKHARDT LIMITED, India)

- The Company submitted evidences that all batches were destroyed after the inspection. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- The warehouse computerized system is not validated. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- The Company submitted a corrective action plan which encompasses revamping of the sterile 1 manufacturing area. (I.C.I. INTERNATIONAL CHEMICAL INDUSTRY S.P.A., Italy)

- Weak and not fully implemented Quality Assurance system. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)

- Documentation management. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)

- Material management and qualification of the approved supplier. (HEBEI DONGFENG PHARMACEUTICAL Co., Ltd, China)

- The Batch Manufacturing record was lacking details with regards to manufacturing steps and in-process controls. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- The company did not establish different product codes for the different Trimethoprim processes. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- The Validation Master Plan did not contain any clear description of the policy, intentions and approach to validation. (PUNJAB CHEMICALS AND CROP CORPORATION LIMITED, India)

- The documentation practices for process validation were found unacceptable. (Smruthi Organics Limited, India)

- The company's approach and understanding of the GMP requirements for the re-qualification of the equipment was found to be unsufficient. (Smruthi Organics Limited, India)

- The critical deficiencies were found in the areas of: Quality Management. (Suzhou No. 4 Pharmaceutical Factory, China)

- The major deficiencies were found in the areas of: Quality Management. (Suzhou No. 4 Pharmaceutical Factory, China)

- Laboratory Control. (Suzhou No. 4 Pharmaceutical Factory, China)

- Change Control. (Suzhou No. 4 Pharmaceutical Factory, China)

- Based on the combination of the critical and major deficiencies it cannot be excluded that there would be a significant risk that APIs manufactured on-site could harm human or veterinary patients. (Suzhou No. 4 Pharmaceutical Factory, China)

- An out-of-specification result obtained for an In-Process Control, performed by TLC, was considered as compliant by the analyst. (Fleming Laboratories Limited, India)

- The company's Validation Master Plan did not follow GMPs basic rule. (Fleming Laboratories Limited, India)

- Implementation of the CAPA related to Deficiency D28(c) of the previous inspection, related to the execution of the cleaning validation, was found insufficient. (Fleming Laboratories Limited, India)

- The change control related to the shifting of the Cinnarizine production from production Block B to Block E was found deficient. (Fleming Laboratories Limited, India)

- The lack of quality assurance oversight for the entire supply chain, from abattoirs to the mixing plant. (Chongqing Imperial Bio-chem. Co., Ltd., China)

- Inadequate control and storage of quality documents such as certificates of analysis of various grades of Cimetidine, analytical raw data, etc. (WUXI KAILI Pharmaceuticals Co., Ltd, China)

- 4 deficiencies (out of them 2 critical) related to the previous inspections not satisfactory corrected. (North China Pharmaceutical Co., Ltd, China)

- Incomplete Annual Product Quality Reviews. (North China Pharmaceutical Co., Ltd, China)

- Inadequate control and storage of quality documents. (North China Pharmaceutical Co., Ltd, China)

- Major regarding release routines. (Bajaj Healthcare PVT Ltd, India)

- Laboratory controls. (Bajaj Healthcare PVT Ltd, India)

- Contract Manufacturing. (Bajaj Healthcare PVT Ltd, India)

- Deficiency was related to the insufficient microbiological monitoring of the production areas. (LABORATOIRES OPODEX INDUSTRIE - VILLENEUVE LA GARENNE, France)

- Quality Management. (MEDREICH LIMITED – UNIT V, India)
- Documentation. (MEDREICH LIMITED – UNIT V, India)

- Production. (MEDREICH LIMITED – UNIT V, India)
- Quality Control. (MEDREICH LIMITED – UNIT V, India)
- Contract Manufacture and Analysis. (MEDREICH LIMITED – UNIT V, India)
- Raw Materials. (MICRO LABS LIMITED, India)
- Blending of batches. (MICRO LABS LIMITED, India)
- Quality management. (CHANGSHU HUAGANG PHARMACEUTICAL Co., Ltd., China)
- Materials management. (CHANGSHU HUAGANG PHARMACEUTICAL Co., Ltd., China)
- Laboratory controls.(CHANGSHU HUAGANG PHARMACEUTICAL Co., Ltd., China)
- Operating instructions. (Linaria Chemicals (Thailand) Ltd, Thialand)
- Qualification and validation systems. (Linaria Chemicals (Thailand) Ltd, Thialand)
- Contract management. (Linaria Chemicals (Thailand) Ltd, Thialand)
- Documentation and records. (Suzhou No. 4 Pharmaceutical Factory, China)
- Materials management. (Suzhou No. 4 Pharmaceutical Factory, China)
- Laboratory controls. (Suzhou No. 4 Pharmaceutical Factory, China)
- Validation. (Suzhou No. 4 Pharmaceutical Factory, China)
- Materials Management. (SHANGYU JINGXIN PHARMACEUTICAL CO., LTD, China)
- Production and In-Process Controls. (SHANGYU JINGXIN PHARMACEUTICAL CO., LTD, China)

- Quality Management: deficient management of the Annual Product Quality Reviews. (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Documentation and Records: deficient management of the batch manufacturing report (BMR) of Mefenamic Acid (e.g. numerous mistakes, insufficiently detailed production instructions, lack of indication of the production equipment. (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Materials Management:deficient approach for the qualification of a supplier of crude Mefenamic Acid API (e.g. no GMP requirement, no quality agreement, no follow-up on the implementation of the supplier CAPA action plan). (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Laboratory Control: lack of management of the reference standards (e.g. recommended storage conditions not followed, use of a chemical grade substance as working standard for impurity A). (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Validation: lack of understanding of the validation process management and deficient review of the Mefenamic Acid validation protocol/report by the quality unit. (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Qualification: deficient management for the qualification of the controlled area for Mefenamic Acid production (e.g. DQ performed after the purchase of equipment, IQ/OQ/PQ protocols not provided, IQ/OQ/PQ reports not signed). (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Change: deficient management of the change control procedure (e.g. CC initiated after completion of the DQ, implementation of a new analytical method for Mefenamic Acid without a CC). (Ningbo Smart Pharmaceutical Co. Ltd, China)

- Quality Assurance: lack of rigour in preparing and reviewing documents. (Albert David Ltd, India)

- Major risk of loss of traceability due to the incorporation of tailing material from previous batches and lack of assurances for the homogeneity of the blends. (Albert David Ltd, India)

- Major risk of loss of traceability for raw materials. (Albert David Ltd, India)
- Quality Assurance. (Smruthi Organics Limited, India)
- Documentation/Records. (Smruthi Organics Limited, India)
- Quality Management and Production. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)

- Quality Management. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)
- Documentation and Records. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)
- Quality Control. (TAISHAN CITY CHEMICAL PHARMACEUTICAL CO. LTD, China)
- Several anomalies regarding starting material batch traceability. (Aarti Drugs Limited, India)
- Quality Management. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)
- Compliance with the ASMF 98-080 for molsidomine. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)

- Material Management. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)
- Documentation and Records. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)
- Validation. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)
- Change Control. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)
- Labelling. (Changzhou Longcheng Pharmaceutical Co., Ltd, China)

- Quality Management System. (CSPC INNOVATION PHARMACEUTICAL CO., LTD, China)
- Quality Management System. (Henan Dongtai Pharmaceutical Co. Ltd., China)
- Quality Assurance. (VITAL HEALTH CARE PVT LTD, India)
- Documentation. (VITAL HEALTH CARE PVT LTD, India)
- Labelling and storage. (VITAL HEALTH CARE PVT LTD, India)
- Qualification. (VITAL HEALTH CARE PVT LTD, India)
- Archiving Practices. (VITAL HEALTH CARE PVT LTD, India)
- Change control. (VITAL HEALTH CARE PVT LTD, India)
- Product Quality Reviews. (VITAL HEALTH CARE PVT LTD, India)
- Quality Assurance. (VITAL HEALTH CARE PVT LTD, India)
- Documentation. (VITAL HEALTH CARE PVT LTD, India)
- Labelling and storage. (VITAL HEALTH CARE PVT LTD, India)

- Overall Lack of Quality oversight and systems to ensure compliance with EU GMP. (MonoSol Rx, United states)

- Quality Assurance. (MEHTA API PVT. LTD., India)
- Validation. (MEHTA API PVT. LTD., India)
- Change Control. (MEHTA API PVT. LTD., India)
- Contract Manufacturing. (MEHTA API PVT. LTD., India)
- Compliance with the CEP dossiers. (AANJANEYA LIFECARE LIMITED, India)
- Documentation. (AANJANEYA LIFECARE LIMITED, India)
- Materials Management. (AANJANEYA LIFECARE LIMITED, India)
- Storage. (AANJANEYA LIFECARE LIMITED, India)
- Laboratory. (AANJANEYA LIFECARE LIMITED, India)
- Change Control. (AANJANEYA LIFECARE LIMITED, India)
- Validation. (AANJANEYA LIFECARE LIMITED, India)