Group 1

ID	Warning Letter or Non-Conformance Report detailed text	ALCOA+ categories not met
1.1	US Warning Letter 320-15-17: For your (b)(4) products returned due to the presence of extraneous threads, the investigator found many inconsistencies in your reprocessing batch records. Specifically, operators signed batch records for periods when they were not in your facility, indicating these activities were documented by personnel who did not perform them. During the inspection, and in your written responses, your managers admitted that the batch records were created after the manufacturing process.	**Contemporaneous** (records created after manufacturing) **Attributable** (signing for activities not done by them)
1.2	US Warning Letter 320-16-17: we reviewed the (b)(4) API 12-month (b)(4) Commercial Stability assay test for residual solvent by gas chromatography (GC). For batch #(b)(4) US-DMF ((b)(4)), you reported an (b)(4)% result for (b)(4) residual solvent (specification (b)(4)-(b)(4)%) obtained on July 18, 2013. We documented that the original peak had been integrated inconsistently. Standards and samples had been processed using different integration parameters with no documented reason; there were no controls in the software to prevent analysts from manipulating integration settings in order to obtain passing results that you relied on to evaluate the quality of this product. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, an out-of-specification (OOS) value of (b)(4)% was obtained.	**Accurate** (not using correct parameters) **Complete** (processing repeated with different parameters)
1.3	EU NCR IT/GMP/NCR/INT/1-2014: 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; 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. 2. 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;	**Attributable** (analysts using administrator privileges) **Contemporaneous** (change date and time to overwrite results) **Enduring** (results are overwritten) **Complete** (repeated testing, data has been deleted) **Consistent** (do not meet validation requirements)

European Non-Conformance Reports taken from:
http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do

US FDA Warning Letters taken from:
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

Group 2:

ID	Warning Letter or Non-Conformance Report detailed text	ALCOA+ categories not met
2.1	US Warning Letter 320-15-12: Our investigators found that some of your operators used "rough notes" (unbound, uncontrolled loose paper) to capture critical manufacturing data and then destroyed these original records after transcription into the batch production records. For example, the (b)(4) chemist recorded original manufacturing data as rough notes and left these rough notes for the (b)(4) chemist to transcribe into the batch production records. The next morning, the (b)(4) chemist signed the batch production records and destroyed the original rough notes. We interviewed employees during the inspection who confirmed your firm's practice of transcribing data to batch records and destroying original records.	**Original** (original data destroyed after transcription) **Contemporaneous** (data is later typed into the production records)
2.2	US Warning Letter 320-16-06: During the inspection, we reviewed the electronic log for high performance liquid chromatography (HPLC) system #36 and determined that the audit trail was disabled on February 6, 2014. One of your analysts executed 80 HPLC injections for assay and impurity tests of validation stability batches (b)(4) of (b)(4) API. Because the audit trail was disabled, neither your quality unit nor your laboratory staff could demonstrate that records for these batches included complete and unaltered data. All supporting raw data was discarded, including sample solution dilutions and balance weight printouts. Sample analyses were not recorded in the instrument use logbook. Test results were deleted from the hard drive and all supporting chromatograms were discarded. Audit trail functions were re-enabled on February 8, 2014, and the same analyses were repeated. You submitted the February 8th test results to the FDA in March 2014 in support of Drug Master File (DMF) (b)(4). During the inspection, we asked the analyst who generated the data submitted to the FDA whether audit trails could be disabled. The analyst stated that another employee, who was no longer with the company, had disabled the audit trails. Your firm could not explain why the audit trail was disabled or why the original data was deleted, nor could you demonstrate whether the original results were within specification.	**Complete** (no audit trail, raw data discarded) **Original** (no audit trail) **Enduring** (results deleted)
2.3	EU NCR INS16-001C: use in quality control a non-qualified chromatographic equipment, with operating faults and with an unvalidated computerized management system. As a result, the integrity, reliability, up-to-dateness, originality and authenticity of the data that are obtained cannot be guaranteed.	**Consistent** (un-qualified equipment, un-validated system)

Group 3:

ID	Warning Letter or Non-Conformance Report detailed text	ALCOA+ categories not met
3.1	US Warning Letter 320-15-12: Additionally, our investigators found backdated batch production records dated February 10 to February 25, 2014, signed by your Production Manager and Technical Director in the "Batch Manufacturing Record Reviwed [sic] by" section. The Technical Director stated that he was not in the facility on these dates and was "countersigning" for another person who allegedly performed these review activities. However, these records did not contain signatures (contemporaneous or otherwise) of the alternate reviewer who purportedly conducted the review. Furthermore, the Technical Director backdated his own signature to the date the quality unit (QU) reviewed and released your drug product. His backdated signatures are on (b)(4) batch records for lots (b)(4); and (b)(4) batch records for lots (b)(4). You released these batches before the Technical Director returned to the facility and backdated his signatures. The batch records, therefore, do not demonstrate that you completed your required review before releasing your products.	**Contemporaneous** (backdating) **Attributable** (no signatures of alternate reviewer)
3.2	EU NCR UK GMP 89143 Insp GMP 8913/378537-0004-NCR: 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.	**Original** (evidence of data falsification and manipulation) **Complete** (unreported trial runs, deleted data)
3.3	US Warning Letter 320-15-10: While investigating these discrepancies, our investigator requested the original electronic raw data. Your quality unit, after consulting with the Information Technology (IT) department, stated they were unable to retrieve the original electronic raw data because back-up discs were unreadable. Your quality unit then stated that back-up disks have been unreadable since at least 2013. Your HPLC system is used to test (b)(4), API for batch release. However, without complete, accurate, reliable, or retrievable raw data about the HPLC system's qualification, you lacked complete assurance that the system was operating as intended.	**Complete** (raw data missing) **Available** (backup) **Consistent** (lack of qualification)

Group 4:

ID	Warning Letter or Non-Conformance Report detailed text	ALCOA+ categories not met
4.1	US Warning Letter 320-15-17: During the inspection, we noted that you had no unique usernames, passwords, or user access levels for analysts on multiple laboratory systems. All laboratory employees were granted full privileges to the computer systems. They could delete or alter chromatograms, methods, integration parameters, and data acquisition date and time stamps. You used data generated by these unprotected and uncontrolled systems to evaluate API quality.	**Attributable** (no unique logins or access levels, all had full privileges) **Complete** (data could be deleted) **Original** (data could be changed) **Contemporaneous** (time stamps could be changed)
4.2	US Warning Letter 320-15-10: Our inspection noted that your firm did not retain complete raw data from testing performed to assure the quality of (b)(4), API. Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms that form the basis of your product release decisions. Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system, which is intended to demonstrate correct operation of the HPLC. These discrepancies included injection sequences and values to calculate relative standard deviation (RSD).	**Complete** (raw data missing) **Available** (backup) **Consistent** (calculations not verified / validated)
4.3	EU NCR DE-NI-014-20141029: The company failed to establish a procedure to identify and validate GMP-relevant computerized systems in general. Two batch analysis reports for Colistin Sulfate proved to be manipulated. HPLC chromatograms had been copied from previous batches and renamed with different batch and file names. …Neither the individual workstation nor the central server had been adequately protected against uncontrolled deletion or change of data. The transfer of data between workstations and server showed to be incomplete. No audit trail and no consistency checks had been implemented to prevent misuse of data.	**Consistent** (no validation) **Enduring** (files had been copied and renamed) **Original** (record could have been changed) **Complete** (no audit trail, data could have been deleted, transfer of data incomplete)

Group 5:

ID	Warning Letter or Non-Conformance Report detailed text	ALCOA+ categories not met
5.1	US Warning Letter 320-15-17: We found that some analytical testing data was inadequately maintained and reviewed. i. Your HPLC 14 computer files included raw data for undocumented (b)(4) stability samples analyzed on December 30, 2013, but no indication of where these samples came from and why they were tested. ii. In a data file folder created on May 22, 2013, 23 chromatograms were identified as stability samples for (b)(4) lots (b)(4), and (b)(4). Results were not documented. More importantly, the acquisition date was July 7, 2013, more than six weeks after the samples were run. iii. (b)(4) lots (b)(4) and (b)(4) were not in your stability study records at the time of inspection. Additionally, there were no log notes of any samples from the three lots removed from the stability chamber	**Original** (no record of where the samples came from) **Contemporaneous** (acquisition date is 6 weeks after the sample run) **Complete** (no notes of the samples being removed from the stability chamber)
5.2	EU NCR 14MPPP078: 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); 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)	**Attributable** (no logins, access levels) **Enduring** (poor archiving) **Original** (data could have been changed, inadequate traceability) **Complete** (no audit trail, data could have been deleted)
5.3	US Warning Letter 320-16-17: We found documented instances of analytical test results without original data. For example, your raw data is incomplete for GC analysis performed during the (b)(4) method verification for (b)(4) USP (raw material) and (b)(4) (raw material).	**Complete** (raw data missing) **Consistent** (method verification data missing)