1 INTRODUCTION

1.1 This protocol establishes a standardized means for performing and documenting the quality control (QC) procedures used in the Toxicology Unit (TX). All members of the Unit have an obligation to ensure that proper QC procedures and documentation are being employed and are in place at all times.

1.2 All calibration records (pipettes, analytical balance, volumetric glassware and thermometers) are retained as specified in the Laboratory Quality Assurance Manual (GL-1).

1.3 A FSE2 or higher is responsible for monitoring and assigning QC tasks, as necessary, to ensure they are completed correctly and in a timely fashion.

1.4 The laboratory's Quality Manual supersedes anything in this document and is to be reviewed and followed by all members of the Toxicology Unit.

2 DOCUMENTATION

2.1 Every purchased reagent/solution, solvent and reference material received shall have a Certificate of Analysis (COA) stored electronically in the Unit. Any updated versions of a COA are saved alongside the previous version.

2.1.1 Whenever possible, reference materials should be acquired from approved vendors, which are listed in the QMS. If the vendor is not in the QMS, provide the vendor information to the unit manager to have them added/approved for use.

2.1.2 When possible, reference material will be purchased in solution rather than powder form.

2.2 The preparation of any solutions or reagents (non-single use) within the TX shall be documented on the reagent preparation and QC log.

2.3 All drug standards are stored according to the manufacturer's specifications (room temperature/refrigerator/freezer) until their expiration date.

2.4 Materials prepared in-house will be stored according to instructions within individual procedures. When uncertain how to store a material consult a FSE2 (or higher).

2.4.1 Expired materials will not be used within casework. Expiration dates with just a month and a year will be considered expired on the last day of that month.

2.4.2 Assigned expiration dates for in-house prepared materials will not extend past any expiration date for the materials that make up that material. For example, an in-

house prepared drug solution made on 05/01/2022 from a reference standard with an expiration date of 07/04/2022 and a solvent with an expiration date of 12/25/2022 can't have an expiration date greater than 07/04/2022.

2.5 Evidence should be kept in storage areas (e.g., refrigerators, freezers) separate from non-evidentiary materials (i.e., reference standards).

2.6 When reference standards are not stored in their original container, the new container must be labeled with the name of the standard, concentration, solvent, lot number and expiration date.

2.7 Calibrators and controls shall be made with reference standards from different manufacturers. If different manufacturers are not available, the calibrator and controls shall be prepared by separate analysts. Different lot numbers will be used, if available.

2.8 Documentation for purchased reagents, solutions and solvents (excluding reference materials)

2.8.1 The following information must be present on the containers of purchased reagents, solutions and solvents:

2.8.1.1 Name of Reagent, Solution or Solvent

2.8.1.2 Any serious health or safety hazards associated with reagent/solution or solvent (NFPA label), if practical. NFPA labels may be documented in a Chemical Hazard binder.

2.8.1.3 Lot Number

2.8.1.4 Date Received and the initials of the person who received the reagent/solution or solvent

2.8.1.5 Once a reagent/solution has been opened, the date opened and the initials of the person who opened the solution/reagent

2.8.1.6 Storage Conditions (i.e. room temperature)

2.8.1.7 Expiration date: The expiration date assigned shall be determined by the manufacturer. If the manufacturer only states the month and year of expiration, the expiration date shall be the last day of the specified month.

2.8.1.8 If no expiration date is provided by the manufacturer, the expiration date assigned shall be five years from the date the solution/reagent is received.

2.8.1.9 If there are different solution/reagent containers with the same lot number

but different receive dates, the expiration date may be set to the earliest date

2.9 Documentation for reference materials

2.9.1 The following information must be present on the container of reference materials:

2.9.1.1 The identity of the reference material as well as concentration

2.9.1.2 Special storage and handling requirements

2.9.1.3 Expiration date

2.9.1.4 The date on which it was received and the initials of the person who received it

2.9.1.5 Once opened, the date opened and the initials of the person who opened it

2.10 Documentation of prepared reagents, solutions and solvents (non-single use)

2.10.1 Solutions used in TX will be prepared according to the protocols set forth in each assay-specific protocol. Note: Different volumes of solutions may be prepared as long as the ratio or concentration is consistent.

2.10.2 Each prepared solution (non-single use) will be assigned a unique and traceable lot number, which follows a standard lot nomenclature.

2.10.3 Generally, the lot nomenclature consists of preparing analyst's initials and the date of preparation (e.g. JLG01312020 or 01312020JLG).

2.10.4 Additionally, when multiple bottles of a solution are prepared on a given day, an integer (i.e 1, 2, 3) will be added to the end of the lot number to further differentiate each bottle creating a unique lot number (e.g. JLG01312020-1).

2.10.5 If the same solution was made using different reagents or at different times during the same day, lot numbers can be differentiated using hyphenated letters (e.g., JLG07042016-a, JLG07042016-b). (Example: THC Stock Calibrator and THC Working Calibrator).

2.10.6 The following information will be on each prepared solution: Name of Solution, Lot Number and Expiration Date.

2.10.7 Any serious health or safety hazards associated with reagent/solution or solvent (NFPA label), if practical. NFPA labels may be documented in a Chemical Hazard binder.

2.10.8 The reagent preparation and QC log is filled out documenting the preparation.

2.11 Single use reagents must be labeled with the name of Reagent and the expiration date.

2.11.1 A reagent preparation and QC log does not need to be maintained if identity of the chemicals used, lot number and expiration date of all chemicals used to make the reagent are included in the TOX reagent report.

3 QC REAGENTS, SOLUTIONS AND SOLVENTS

3.1 Only one lot number of internal standard, calibrator solution, control solution, solid phase extraction columns or prepared reagents/buffers shall be used within one analytical run when being used to analyze casework. Multiple lot numbers are acceptable when validating new solutions.

3.2 Before a new batch (or lot) of a solvent, reagent, reference material, or similar material is used for analyzing casework it will be appropriately validated using established methods/procedures. 'Appropriately validated' means that the solvent/reagent/reference material will be analyzed contemporaneously with previously validated materials and is shown to be appropriate for use with casework. Blanks/negative controls are acceptable when they are shown to not contain analytes of interest (nor contaminants that would have interfered with the overall findings). Positive controls are acceptable when the expected data is produced (e.g. comparable to the lot in use). Documentation for the acceptability will be appropriately retained (e.g., within batch documentation, logbook, electronically).

3.3 Solutions will be marked with a colored sticker (e.g., green) to indicate that a solution/material has been validated for use, the method the solution is verified for (if applicable) and the date it was validated., and the analyst's initials who ensured that the validation was complete. If there is not enough room on a solution /material's container to record all information then such information can be located within a logbook or electronically within LIMS.

3.4 The procedures used to ensure solutions/materials were validated for use shall be such that if the results demonstrate acceptability within comparable methods then those validated materials can be considered acceptable for use across such procedures. For example, if a new batch of methanol was validated to be acceptable for use using full screening procedures, it is deemed acceptable for use within quantitative method.

3.5 Materials for Qualitative Analyses

3.5.1 Positive control solutions must be validated using a previously validated solution as a comparison. This can be done by analyzing the un-validated solution within a validated batch and comparing resulting data, (chromatographic and mass spectral evaluations will follow the same decision processes as for reporting unknown analytes). Alternate ways to validate such solutions may be acceptable upon approval of a FSE2 (or higher).

3.5.2 A preparation worksheet (or equivalent) must be completed that documents lot numbers, expiration dates, pipettes used during the preparation, and any relevant information (e.g., deviations) that may be necessary for quality purposes. Any deviations must be approved prior to being implemented.

3.6 Materials for Quantitative Analyses

3.6.1 An in-house prepared calibrator solution must be validated using a previously validated control solution. This will be done by creating calibrator solutions and analyzing them alongside a validated batch or alongside validated control solutions separately (chromatographic and mass spectral evaluations will follow the same decision processes as for reporting unknown analytes). Alternate ways to validate calibrator solutions may be acceptable upon approval of a FSE2 (or higher).

3.6.2 An in-house prepared positive control solution must be validated using a previously validated calibrator solutions. This will be done by creating a control solution and analyzing it alongside a validated batch or alongside validated calibrator solutions separately. Alternate ways to validate calibrator solutions may be acceptable upon approval of a FSE2 (or higher).

3.6.3 A preparation worksheet (or equivalent) must be completed that documents lot numbers, expiration dates, pipettes used during the preparation, and any relevant information (e.g., deviations) that may be necessary for quality purposes. Any deviations must be approved prior to being implemented.

3.6.4 Each new positive control or calibrator solution must be within +/-15% of its expected value. If an analyte is outside of the +/-15% expected range, then consult with a FSE2 (or higher) for resolution.

3.6.5 In the event that no validated solutions exist for either an in-house prepared calibrator solution or an in-house prepared control solution, un-validated solutions of both can be compared to one another provided that different analysts have

prepared each type of solution (i.e., one Analyst prepared the positive control solution and another Analyst prepared the calibration direct dilution solutions). Calculated concentration values will be within ±15% of expected values. This situation should typically only be seen when a new assay is developed or if previously verified solutions were inadvertently consumed or destroyed.

3.7 Internal Standard Solutions

3.7.1 Newly prepared internal standard (IS) solutions (i.e., deuterated reference materials) can be validated by qualitatively analyzing them against previously validated IS solutions. The comparison between newly prepared and validated IS solutions can be either in the form of extracted or un-extracted samples. Resulting data will not contain non-deuterated analytes (if applicable) nor extraneous peaks which would cause issues with using for casework.

3.7.2 Internal standard solutions containing different lot numbers will not be used within a single batch.

3.8 In-house Prepared Reagents/Buffers and Mobile Phases

3.8.1 Non-validated reagents can be validated by utilizing them as would be done for casework along with validated controls (i.e., positive, negative) using appropriate procedures. The analytical results from the control solution samples must demonstrate acceptable results (i.e., positive control gives a positive result, negative control gives a negative result)

3.8.2 Non-validated mobile phases can be validated together (e.g., Mobile Phases A and B) by utilizing them within the instrument performance check and analyzing a validated performance solution along with a validated solvent blank. The analytical results from the performance solution sample must demonstrate acceptable results (i.e., all analytes detected at appropriate chromatographic peak area counts and producing appropriate mass spectra).

3.9 Solid Phase Extraction (SPE) Columns/Cartridges

3.9.1 Non-validated SPE columns can be validated by utilizing them as would be done for casework along with validated controls (i.e., positive, negative) using appropriate procedures. The analytical results from the control solution samples must demonstrate acceptable results (i.e., positive control gives a positive result; negative control gives a negative result).

3.9.2 If multiple expiration dates of a newly purchased lot/batch of columns is received, a column from each expiration date lot must be verified independently.

3.9.3 If no expiration date is provided by the manufacturer, the expiration date assigned shall be five years from the date the columns are received.

3.9.4 At least one (1) column from each lot/batch needs be validated per extraction type (e.g., Cannabinoids or Screening method). Use at least one (1) validated column with the same samples that are to be used for the non-validated columns. Perform extractions per appropriate procedures and analyze sample extracts on multiple instruments to ensure validation data is evaluated appropriately (i.e., same extracts analyzed on low resolution and high-resolution mass spectrometers).

3.9.5 If no previously validated columns are available for comparison then notify a FSE2 (or higher). Either acceptance will be granted based on the fact that validated control samples are to be used or the use of a full set of calibration samples may be warranted for the column validation.

3.10 Validation Data Storage and Retention

3.10.1 The data supporting validations is stored in designated locations (e.g., a Quality Control (QC) filing cabinet or electronically).

3.10.2 The data may be archived once a given lot is removed from service.

3.11 Negative Control/Blank Matrices

3.11.1 A new lot/batch of negative control matrix must be appropriately validated prior to use with casework samples. Aliquoted samples from a matrix lot/batch will be analyzed along with a validated positive control according to appropriate procedures (e.g., General Screen, Cannabinoid) and shown to be analyte-free and appropriate for use as a negative control. The new lot of blank matrix should be run along with the old lot of blank matrix. Analyte-free refers to analytes of interest and such materials may contain analytes that would not diminish quality from its use (e.g., containing nicotine, caffeine).

3.11.2 If a matrix is negative for all relevant analytes then its information is documented in the appropriate log and marked accordingly on its container as being acceptable for routine use.

3.11.3 If a matrix is positive (greater than cutoff or LOD for given assay) for a reportable drug (e.g., diphenhydramine) then it must be documented in the appropriate log and marked accordingly as such (i.e., “Contains diphenhydramine”). This matrix may not be used for assays targeting the analytes that it contains.

3.12.3.1 If a reportable drug is present at a concentration less than the cutoff or LOD for the desired assay, consult with a FSE2 (or higher).

4 REFRIGERATORS/FREEZERS

4.1 Refrigerators and freezers are used to store some standards, reagents, and biological evidence. The temperatures are monitored to ensure that there is not a gradual temperature drift, which may indicate refrigerator/freezer failure.

4.2 Temperatures of refrigerators/freezers will be monitored at least weekly and will be recorded on an appropriate form. Temperature logs are reviewed by a FSE2 (or higher) on a monthly basis.

4.3 At the end of each calendar year logbooks (or records) will be filed appropriately and a new logbook (or records) will be established for the next calendar year. Logbook may be kept hardcopy or electronic.

5 PIPETTES

5.1 New pipettes will be purchased with a NIST traceable calibration certificate. The traceable certificate acts as a demonstration that the device meets the needs of the toxicology unit.

5.2 All pipettes used for casework will be calibrated annually by an approved vendor. The calibration certificate will be maintained electronically.

5.3 Any pipettes that are found to be in non-working order, dropped or damaged are to be taken out of service and a FSE2 (or higher) notified. Upon repair and calibration by an approved vendor, pipettes can be returned to use.

5.4 For performance check of pipettes in-house (performed as needed) refer to GL-21 for guidance.

6 BALANCES

6.1 Prior to daily use, each balance shall be checked to make sure it is level and free of debris.

6.2 Mass reference standards used to check the performance of any analytical balances must be NIST traceable or equivalent.

6.3 For proper handling and protection, all mass reference standards used for performance checks must be stored in protective cases when not in use.

6.4 Plastic tweezers and/or protective cloth gloves must be used when handling mass reference standards.

6.5 Balance Verification

6.5.1 Balances are calibrated annually by an approved vendor. Calibration certificates will be maintained electronically.

6.5.2 Balances used on any given day for casework that involve critical measurements (e.g., those measurements that would significantly affect the outcome of a result of an examination) should be checked for accuracy using at least one (1) NIST–traceable weight.

6.5.3 The weight of the mass reference standard shall be recorded on the analytical balance check sheet, which can be kept hardcopy or electronic.

6.5.4 The serial number of the mass reference standards utilized shall be recorded on the analytical balance check sheet for traceability.

6.5.5 Each analytical balance shall be verified using at least one external mass reference standard.

6.5.6 Any mass reference standard that is dropped or damaged shall be taken out of service and evaluated for use by an approved vendor prior to use.

6.5.7 The weight that is used to check the balance must give a weight that is ±5% of its true value. The analyst should select a mass/weight that is appropriate to the material that is to be weighed.

6.5.8 If the measurement is outside the acceptable ±5% limit, then the balance should not be used until either a FSE2 (or higher) is notified and the issue is resolved.

7 VOLUMETRIC GLASSWARE

7.1 Initial calibration by an approved vendor is acceptable for volumetric glassware (pipettes, volumetric flasks) upon receipt to the laboratory.

7.2 Volumetric glassware will be visually inspected for damage before use. Any volumetric glassware that is accidentally dropped or damaged shall be labeled “Out of Service” and a FSE2 (or higher) shall be notified.

7.3 Volumetric glassware (pipettes, volumetric flasks) are calibrated every ten years by an outside contractor. Calibration certificates will be maintained electronically.

7.4 Volumetric glassware (pipettes, volumetric flasks) shall be used for the in-house preparation of reagents/solutions used for quantitative measurements, if

applicable.

8 CENTRIFUGES

8.1 Centrifuges are not calibrated, as specific RPM is not required for analysis.

8.2 For routine maintenance, reference the appropriate centrifuge user manual.

8.3 Routine maintenance may include the following:

8.3.1 Greasing of arms (metal points where cups sit)

8.3.2 Lubrication of pistols

9 ANALYTICAL INSTRUMENTATION

9.1 It is the responsibility of the analyst to ensure appropriate QC and/or performance checks are conducted prior to using an instrument for casework.

9.2 Any QC or maintenance performed is to be recorded in the instrument logbook stored next to the instrument or electronically. This logbook may be archived as needed, to reduce the amount of paperwork near the instrument. However, enough recent data should be available to allow an analyst to estimate current instrument performance.

9.3 If an instrument shuts down during an analytical run (i.e instrument status becomes standby) or if an analyst aborts the run, a calibrator or control must be injected to show that the instrument is performing in the same manner as before the shutdown.

9.4 If there are any recurring problems with an instrument system, these problems shall be brought to the attention of a FSE2 (or higher). If necessary, a service call should be placed with the appropriate vendor and any documentation placed in the instrument binder and the analyst shall mark the instrument as “out of service”.

9.5 After an instrument is determined to be no longer “out of service”, it must be noted in the maintenance log that the instrument is “back in service”. Any maintenance performed as part of troubleshooting or repair shall be documented on the maintenance form.

10 LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY/MASS SPECTROMETRY (LC-MS/MS)

10.1 A checklist is utilized to indicate that specific items are performed each day of use prior to the instrument being marked as acceptable for use.

10.1.1 Checklist items include but not limited to:

10.1.1.1 Checking and recording nitrogen generator output

10.1.1.2 Checking mobile phase levels and/or preparing fresh mobile phase

10.1.1.3 Checking seal wash and needle rinse levels, if applicable

10.1.1.4 Checking and recording pressure of LC pump

10.1.1.5 Checking pump ripple; if applicable

10.1.1.6 Emptying drain water from nitrogen generator

10.1.1.7 Ballasting rough pump, if applicable

10.2 For Agilent LC-MS/MS, the following shall be performed as stated below:

10.2.1 Weekly

10.2.1.1 Perform a checktune

10.2.1.2 Save checktune file in designated location

10.2.1.3 Evaluate all results on the output and determine if all results are reported as “PASS”. If results are not “PASS”, perform an autotune.

10.2.2 Every 3 months or after MS maintenance

10.2.2.1 Perform an autotune

10.2.2.2 Save autotune file in designated location

10.2.2.3 Evaluate all results on the output and determine if all results are reported as “PASS”. If results are not “PASS”, notify a FSE2 (or higher).

10.3 For Thermo Q Exactive:

10.3.1 Weekly/As needed:

10.3.1.1 Perform positive mode mass calibration

10.3.1.2 Perform negative mode mass calibration

10.3.1.3 To ensure mass accuracy is < 5 ppm, mass calibration shall be performed prior to the start of any casework batch.

10.3.1.4 If mass calibration is not successful, notify a FSE2 (or higher)

10.3.2 Monthly/As needed:

10.3.2.1 Perform positive mode full calibration

10.3.2.1.1 Includes "Basics – Positive Ion" and "Isolation Mass and Resolution", followed by a mass calibration

10.3.2.2 Perform negative mode full calibration

10.3.2.2.1 Includes "Basics – Negative Ion" and "Isolation Mass and Resolution", followed by a mass calibration

10.3.2.3 If any portion of a full calibration is not successful, notify a FSE2 (or higher).

10.3.2.4 A full calibration can be performed more frequently than monthly if after mass calibration is performed, the mass accuracy is still high. It may also need to be performed after maintenance.

10.4 For all LC-MS/MS instruments, the following are examples of maintenance performed as needed:

10.4.1 Replacing the guard column (~ once a month)

10.4.2 Cleaning the column: (~ after every batch)

10.4.3 Replacing the column: (~ every 3 months)

10.4.4 Replacing tubing pre-column or post-column to source

10.4.5 Replacing or cleaning any LC or MS/MS parts

10.4.5.1 Parts include but are not limited to curtain plate, nebulizer, sweep cone, ion transfer tube, etc.

10.4.6 Isopropanol system flush

10.4.7 Service by an outside vendor

10.5 Performance Check

10.5.1 Performance checks shall be performed before an instrument is used for

casework. Instruments must be fully equilibrated (column at temperature, stable pressure, and MS ready) for at least 30 minutes prior to running a performance check.

10.5.2 For the performance check on the Agilent LC/MS/MS, one level from the calibration curve shall be run.

10.5.3 For the performance check on other LC/MS/MS instruments, the following solution shall be run:

10.5.3.1 Combine 20 µL each of the 1 mg/mL purchased reference standard solutions of Amphetamine, Codeine, Hydrocodone and Diazepam into a 100 mL volumetric flask and diluting to volume with MeOH. Stable for 1 year from date of preparation.

10.5.3.2 Place the printout of the performance mix in the instrument logbook or store electronically.

10.5.4 Performance check should meet the following criteria:

10.5.4.1 Analyte peaks are present

10.5.4.2 No unexpected analyte peaks

10.5.4.3 Chromatography must be acceptable

10.5.4.4 Retention time and peak area meet criteria for peak identification within software.

10.5.5 If performance check does not meet acceptable criteria, address appropriately (i.e. maintenance) or consult a FSE2 (or higher).

11 DECISION CRITERIA FOR LC/MS/MS BATCHES

11.1 The information below will replace guidance listed in individual assay procedures. Information will be removed from individual procedures with next revision.

11.2 The following criteria are used as guidelines in determining the acceptability of the data produced in this assay. Retention time (chromatographic characteristic), fragmentation pattern and qualified ion ratios (mass spectrometric characteristics), and other characteristics are used as the basis for detection and identification. In most cases, all of the criteria below should be met in order to identify the appropriate drugs within biological specimens.

11.3 If a solvent blank was injected, it must be reviewed for possible carryover.

11.3.1 The solvent blank shall not contain any analyte measured by the assay, at a response greater than 10% of the lowest calibrator or cutoff, which meets reporting criteria (retention time and peak shape). If an analyte is present in the solvent blank and the following injection, the analyte may not be reported in that injection. Upon re-injection of the solvent blank and the corresponding sample, if the solvent blank acceptance criteria are met, proceed with analysis.

11.3.2 If a case specimen exceeds the upper limit of quantitation (or limit specifically listed in an assay procedure) and a solvent blank was not run immediately after it, repeat or reinject (with a solvent blank prior) the next case specimen if that specimen is positive for the analyte that exceeded the upper limit of quantitation.

11.4 Chromatography

11.4.1 All chromatographic peaks for the analytes of interest should show good chromatographic characteristics, with reasonable peak shape, width, and resolution. For low concentrations of an analyte (e.g., ≤5 ng/mL), there may be transitions that are not optimal. In order to be determined as acceptable, a chromatographic peak in a sample should compare favorably to the same analytes chromatographic peak in a known sample, which has been analyzed on the same system and in the same, or subsequent, analytical timeframe.

11.5 Retention Time (RT)

11.5.1 The retention time of a peak of interest should be within 0.1 minute of the retention time of a reference standard (i.e., calibrator or positive control).

11.6 Mass Spectrometry

11.6.1 Ion ratios within case samples should compare favorably to ion ratios of an extracted calibrator or positive control at a comparable concentration (e.g., positive control). Generally, ion ratios are within the limits as specified within the Section procedure related to mass spectral comparisons.

11.6.2 With the exception of the internal standard, it is recognized that some ion ratios are concentration dependent; thus, concentrations at the ends of the calibration curve may not be within the updated ratios and may be acceptable.

11.7 Batch Acceptance:

11.7.1 In order for a batch to be acceptable:

11.7.1.1 No analytes of interest will be detected in the Negative Control.

Analytes of interest are considered those compounds that are being reported.

11.7.1.2 Significant carry-over will be brought to the attention of a FSE2 (or higher) to determine if evidentiary samples have been negatively impacted. If so, re-analyses will occur and sample re-extraction may be necessary. Appropriate case documentation will accompany these instances within affected case files to record events.

11.7.1.3 Quantitative values greater than the upper limit of quantitation can be reported as "greater than" and no uncertainty value will be associated with that result.

11.7.1.4 All applicable analytes of interest within Positive Controls, as well as internal standards, will be identified.

11.7.1.5 Quantitative results of positive controls must fall within ±20% of the analytes target concentration. If one drug does not demonstrate acceptable quantitative results, all other drugs that are acceptable may be reported. This is not applicable for qualitative analyses.

11.7.1.6 Statistical data of positive controls used for quantitative analysis should be recorded and evaluated within appropriate charts.

11.8 Calibration

11.8.1 Calculations are performed by the applicable instrument software.

11.8.2 A correlation coefficient should be ≥ 0.990 when using deuterated internal standards. If the correlation coefficient is lower than 0.990 then approval from a FSE2 (or higher) must occur and, if deemed acceptable, justification must accompany the applicable data. For analytes where a corresponding deuterated internal standard is not used, a correlation coefficient ≥ 0.98 is acceptable. Following a weighted linear or quadratic regression, reprocessed calibrators shall be within 20% of their target value. Calibrators shall not be removed from calibration curves without approval from a FSE2 or higher. Such removal of calibration points will be appropriately documented within batches and within each case file (e.g., case notes, summary sheets). Calibration data are used for the analysis of each batch and are done independently.

11.8.3 Such instances may involve reporting results as 'greater than the highest calibrator' may be acceptable and would avoid dilution and re-analysis. The lower limit of quantitation (LLOQ) is the concentration of the lowest

calibrator. The upper limit of quantitation (ULOQ) is the concentration of the highest calibrator.