

determined. Therefore, an accurate quantitation of an unknown peak is not possible.

- Comparison of an unknown peak to the RAL determines if an investigation is initiated. There are multiple Safety Factors typically applied in the RAL calculations. Therefore, the risk of having an unknown peak present that is significant to toxicity or dose limits is relatively low considering the conservative approach chosen to calculate the RAL.
 - It is very unlikely that there is an additive or cumulative pharmacological effect of the individual peaks. The primary residue being removed during cleaning is that for which we may expect potential pharmacological impact, and upon which the RAL is based.
 - The investigation of the sum of unknown peaks is technically challenging and impractical in many cases. It would require an evaluation of all peaks that make-up the sum, regardless of their relative size. Alternatively, the largest peaks that make up the sum could be investigated, but this becomes the same approach as investigation of each peak that exceeds the RAL. Such an effort to sum all peaks and investigate each provides little value considering the Safety Factors already built into the RAL.
 - This approach of not summing peaks has been based on common benchmarking within many API site.
- **Confirmation of Results**

Investigative evaluation of the equipment and unknown contaminant prior to re-clean should first include confirmation of the analytical result. If the analytical result is confirmed, the investigation should then include a review of cleaning procedures, visual inspection of the equipment and reporting of the failure and trending of past results. Once the initial investigative evaluation has been conducted the equipment is typically released back to production by the site quality team, upon successful completion of the equipment re-cleaning. This may be done prior to the completion (e.g. approval) of the formal investigation report.
 - **Limits**

For worst-case limits calculations, the unknown peak investigation should initially be based upon 100% of the worst-case (e.g. lowest) RAL of the target residue. If the limits are then subsequently recalculated based on the specific product A to product B changeover (vs. worst-case limit), the new limit could release the equipment for subsequent use to produce product B. This approach is based on risk and the multiple safety factors already included within the calculated matrix.