

# PostScript

## Challenges Facing an Analytical Laboratory

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The importance of quality control (QC) testing by an analytical laboratory cannot be overstated, as it serves as one of the “checks and balances” between the pharmacy and the consumer. We are all aware that a quality preparation is vital, and the QC laboratory should play an integral part in establishing the safety and accuracy of pharmacy preparations.<sup>1</sup> As the compounding practice continues to evolve, the QC laboratory by necessity has to evolve as well. With the advent of new, more sensitive technologies, new drugs, and improved formulations, the challenges that potentially face the QC laboratory are threefold – analysis, microbiological control, and communication. Each of these challenges presents its own unique difficulties and associated solutions.

### Analytical Challenges

Analytical challenges can cover a multitude of areas ranging from lack of an appropriate reference standard for comparative analysis to complication quantitative analysis by a complex sample matrix. Tacrolimus, methylcobalamin, and levalbuterol are examples of drugs in which an appropriate reference standard is not readily available for comparative analysis. This creates complications for the laboratory, since qualitative and quantitative results are based on analysis of a suitable reference standard, often forcing the pharmacy to send bulk chemicals for analyses prior to initiating QC testing. Biopolymer products such as mucopolysaccharides (glycosaminoglycans) present their own set of analytical problems arising from their inherent structure and high molecular weights. Heparin is an example of a drug whose varied molecular weight range makes selection of the standard difficult if the exact molecular weight limit utilized by the compounding pharmacist is unknown.

Solubility is a challenge with some drugs because of the physiochemical properties of the drug or characteristics of the specific formulation. Deslorelin, for example, presents challenges to solvent selection, requiring a multisolvent system to solubilize the drug for quantitation. It is important to know all of the contents in the formula. This is due to potential interference of the active ingredient by the excipients during analysis. The matrix or excipients of a sample itself can also present problems. For example, slow-release formulations with potent drugs, such as triiodothyronine ( $T_3$ ) or thyroxine ( $T_4$ ), carry their own specific problem, such as releasing the drug from the binders into solution for quantitation when the drug is designed to slowly release for absorption into the blood stream. Overcoming this challenge entails utilization of suitable solvents with homogenization to maximize drug solubility. Complex formulations such as total parenteral nutrition solution, which contain upwards of 50 ingredients, complicate isolation and quantitation of individual

constituents. Instrument sensitivity can also present potential problems. Potent drugs such as oxytocin may be below the limit of quantitation or limit of detection of some instruments, which necessitates a thorough understanding of the laboratory’s capabilities.

### Microbiology Challenges

Delivering a safe and reliable compounded parenteral preparation in most cases requires that the preparations be tested to ensure that it is sterile and does not contain harmful endotoxin levels. While process validation, personnel training, and environmental controls are essential to this testing and should be in place, finished preparation release checks are still required according to *United States Pharmacopeia (USP)* Chapter <797>.<sup>2</sup> The QC laboratory facilitates these release checks by utilizing its staff’s thorough understanding of the regulatory requirements and employing analytical techniques that ensure preparation safety. Even with this knowledge, challenges arise in the microbiological testing of some preparations. The key challenges are the development of new and more sensitive methods and the interpretation of some results. In sterility testing, for instance, the addition of an antimicrobial agent to a drug formulation may require a number of modifications to permit accurate analysis, such as addition of a neutralizer to the medium or use of a more concentrated culture medium to compensate for subsequent dilutions. Another approach that is applicable in certain situations is to add the medium directly to the container. Subtle changes introduced by the antimicrobial agent’s may affect the drug’s filterability, potentially requiring that additional amounts of the preparation be requested for validation or that sterility be tested by direct inoculation. Each of these modifications or revisions is approved by *USP* as long as it is validated by bacteriostasis/fungistasis testing.

Endotoxin testing presents many of the same challenges, yet troubleshooting is generally more effective because of the information generated from each test.<sup>2,3</sup> It is still critical that the laboratory staff know the drug concentration, excipients, final pH, and maximum human dose per hour, and whether the preparation contains a suspending agent such as sodium carboxymethylcellulose. This knowledge equips the laboratory staff to determine whether dilution is needed to further overcome inhibitors (e.g., trivalent cations) or promoters (certain glucans). Portions of this information are necessary in performing calculations to find the maximum valid dilution or minimum valid concentration, and in determining the endotoxin limit (EL) when not published. The maximum human dose is especially important in establishing an EL for combination drugs such as multivitamins. On the basis of this information, the laboratory can test the preparation and obtain accurate endotoxin data. These data are reported to the pharmacist and may be useful when discussing with a prescriber whether the endotoxin value is within the allowable limit—that is, whether the preparation is safe. By incorporating the patient’s body weight (EU/kg) into a suitable equation, the allowable EL can be calculated for the preparation class (e.g., intrathecal,

subcutaneously, or radioactive). An excellent model for calculations related to typical prescriber questions that are typically received is presented in detail in a back issue of the *International Journal of Pharmaceutical Compounding*.<sup>4</sup> It should be emphasized that even minor formulation changes can present challenges to endotoxin testing.

### Communication Challenges

Sir Frances Bacon, a renowned scientist who was ahead of his time, once said, "Knowledge is power," a statement that continues to hold true today. QC laboratories are on the front line of testing compounded preparations, improved formulations, and new drugs as they become available. QC laboratories also provide assistance in troubleshooting problems encountered by compounding pharmacies or research/development facilities. This requires communication. One of the roles of a QC laboratory is equipping compounding pharmacists and specialists with the information and results (knowledge) they need. To ensure the accuracy and quality information, the laboratory must have as much information as possible regarding the specific drug and/or formulation. This in turn gives the compounding pharmacist confidence in the pharmacy's materials and procedures.

While the challenges encountered by the QC laboratory are at times arduous, the reward comes in playing a role in getting the consumer a safe and reliable preparation.

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