

# The price of not using USP Reference Standards

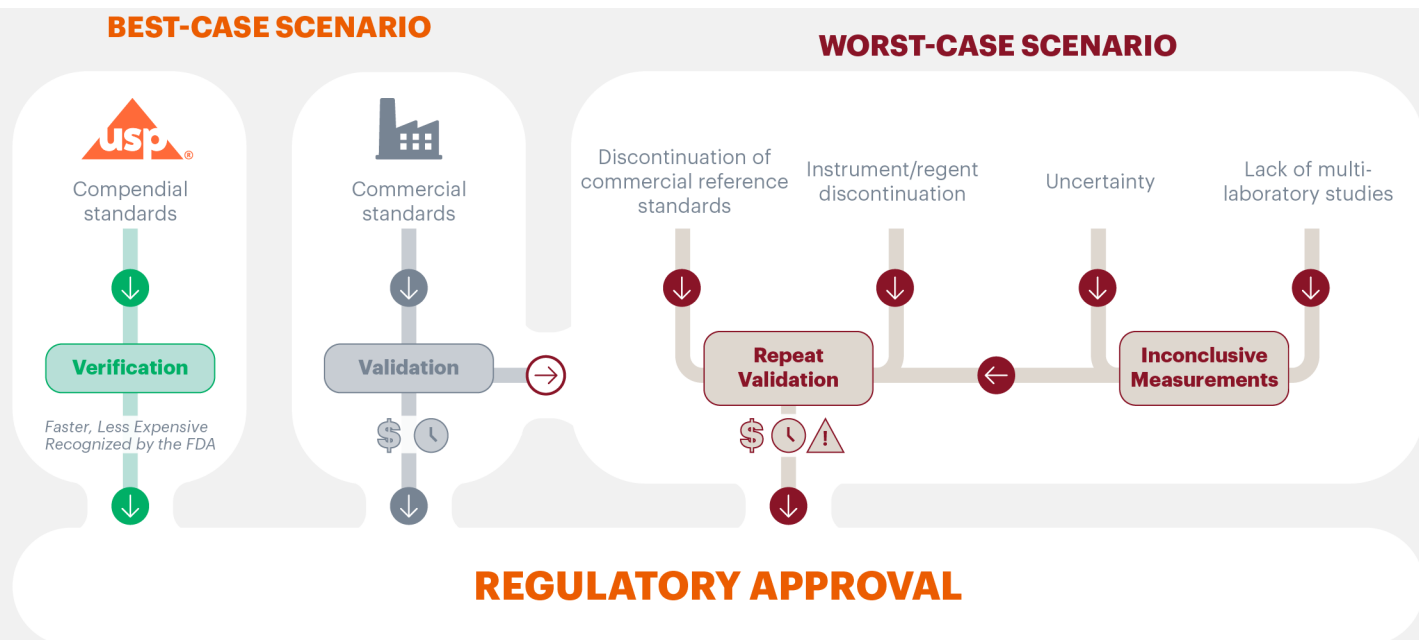
## The risks of replacing compendial solutions with secondary and other commercial standards



The U.S. Pharmacopeia (USP) offers reference standards to support assays and tests specified in the official USP compendia and beyond. When cited in the *USP-NF*, USP Reference Standards are part of the compendial standard(s) which offer great value to the pharmaceutical industry by supporting the quality of medicines, accelerating drug development, and facilitating interactions with the Food and Drug Administration (FDA)<sup>1,2,3</sup>. However, many non-compendial commercial reference standards are being produced for use with the tests and assays required by the USP monographs and general chapters. These reference standards often claim to meet the guidelines for pharmacopeial analysis, raising

the question of whether USP Reference Standards offer advantages over these commercial reference standards.

**Figure 1** describes two different scenarios regarding the use of compendial and commercial standards. The “best-case scenario” ignores risk and assumes that everything will go smoothly during drug development and release testing and the “worst-case scenario” assumes unexpected problems that might arise when using commercial reference standards.



**Figure 1.** Analytical development of medicines using USP compendial standards (incl. USP Reference Standards) or commercial standards. Compendial standards provide a faster, less expensive, and FDA-recognized route toward regulatory approval. The use of commercial standards can introduce risk to the development timelines with one example being the required analytical validation.

\*For reference, the term “compendial standards” refers to a USP compendial method (documentary standard) associated with its respective compendial reference standard. The term “commercial standards” refers to a commercial reference standard associated with any method.

## Best-case scenario: USP makes drug development faster and less expensive

If nothing goes wrong, it is still worth using USP compendial standards. Other options may or may not be less expensive, but they require a lot more work for the laboratory, increasing the time and costs associated with their use. (Figure 1, left side). The use of non-compendial standards requires the validation of the analytical methods. This is an extensive and costly process described in the *USP General Chapter <1225> Validation of Compendial Procedures*. Validation requires multiple experiments to demonstrate that the method consistently delivers reproducible, precise, and accurate results. Experimental evidence needs to address the following parameters: specificity, linearity, robustness, range, detection limit, quantitation limit, ruggedness, selectivity, and sustainability<sup>4</sup>. One should expect to allocate a significant budget, time, equipment, and highly trained staff to accomplish this goal.

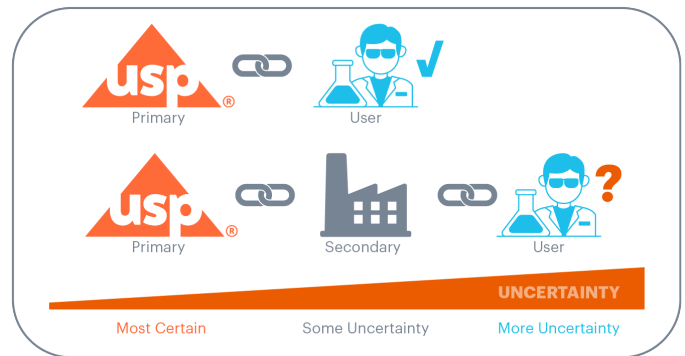
The good news: users can skip the validation process when using USP compendial standards. Compendial standards are backed up by methods rigorously characterized and validated. Therefore, developers are only required to perform verification. This is a shorter and faster process described in the *USP General Chapter <1226> Verification of Compendial Procedures* where the suitability of the analytical procedure is verified under actual conditions of use. The FDA Guidance For *Industry-Analytical Procedures And Methods Validation For Drugs And Biologics* mentions USP-NF as an “FDA recognized source” and clarifies that analytical procedures must originate from the *USP-NF* or from “a validated procedure you submitted that was determined to be acceptable by FDA”<sup>5</sup>. According to 21 CFR 211.194(a)(2), it is necessary to demonstrate that “the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested” but the regulation states that “If the method employed is in the current revision of the *United States Pharmacopeia, National Formulary*, AOAC INTERNATIONAL, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice”<sup>6</sup>. Therefore, the use of compendial standards saves time and money by allowing users to skip the validation procedure.

Ideally, a laboratory will experience the best-case scenario, validate their method or use USP Documentary and Reference Standards, and obtain regulatory approval. This optimistic scenario is illustrated in **Figure 1** (left side) and does not consider all the things that could not go as expected when using other options (**Figure 1, right side**). Some of these issues will be discussed in the next section.

## Worst-case scenario: Compendial reference standards mitigate risk

### The uncertainty of secondary standards

After multiple, interlaboratory collaborative studies and intensive discussions between stakeholders, a USP Reference Standard is approved by the appropriate USP Expert Committee (EC). With few exceptions (e.g., when World Health Organization (WHO) international reference standards exist), USP Reference Standards are primary reference standards. It is a common practice that commercial companies develop products designed to support the same tests supported by USP Reference Standards. These products, known as secondary standards, have values comparable to the primary standard and need to ensure this traceability. These secondary standards can also be referred to as certified reference materials, reference materials, or analytical standards.



**Figure 2.** As consecutive measurements are undertaken during the development and final use of reference standards, the uncertainty associated with the result inevitably increases. The first row indicates that there is some uncertainty for users using USP primary standards and the second row indicates that secondary standards add “extra links to this chain” increasing the uncertainty associated with this scenario.

One issue of “creating a standard out of a standard” is that the uncertainty associated with each measurement result increases during this process. If an experiment was performed today and then repeated tomorrow with the same sample, instrument, and laboratory analyst, would the results be exactly the same? What if there was a change to one of these variables, would the result be the same? These results may not be the same because there is variability associated with these measurements. The uncertainty in the development of USP primary Reference Standards is minimal but present, calculated, and addressed in the specification of a USP monograph. The variability associated with the

development of a secondary standard will introduce more uncertainty when compared to the primary standard and the uncertainty in test results increases as one “adds links in this chain” (**Figure 2**). Secondary standards inevitably increase the uncertainty associated with your final measurements<sup>7,8</sup>. Therefore, acceptance zones (i.e., specifications) in USP compendial standards do not apply when using secondary standards. Unless the acceptance zones are modified, there is a double-edged risk: users might underestimate uncertainty and release a product out of specification, or overestimate uncertainty and wastefully reject a product that is within specification limits.

### Multi-laboratory studies

Not all standards are created equal. USP relies on state-of-the-art laboratories and experts to test our reference standards, but would the results be the same if another lab performs these same tests? One factor that makes USP Reference Standards unique is the collaborative nature of our testing. USP Biologics sends reference standard candidate materials to multiple laboratories for testing and analyzes the results obtained from these external and accredited laboratories. Therefore, the measurements associated with our reference standards account for inter-laboratory variation and ensure the quality of our results. For example, ultra-violet (UV) spectroscopy was used to determine the protein concentration of our monoclonal antibody (mAbs) Reference Standards. These standards were tested by three different laboratories before a concentration value was assigned. Another example is the testing of our CHO genomic DNA Reference Standard where four laboratories performed a standard curve run by real-time PCR (qPCR). It is important to note that these collaborative studies are performed not only for our first lots. Every new replacement lot is submitted for collaborative testing. It is also important to note that the development of USP Reference Standards is approved by our Expert Committees (ECs) which include key opinion leaders from industry and are observed by representatives from the FDA.

This rigorous and collaborative testing of USP Reference Standards brings confidence to the measurements and acceptance criteria associated with USP compendial standards. Are the same multi-laboratory tests performed by manufacturers of secondary reference standards? Do these

reference standard manufacturers use the same rigid quality control? Are the acceptance criteria for product release adjusted for the use of secondary reference standards? The answers to these questions and the risks associated with them must be considered. For instance, if any problems did arise with a drug during FDA's quality surveillance program, their laboratories will have detected these issues by testing the drug to the standards set by USP, using both USP Documentary and Reference Standards<sup>9</sup>. According to USP General Notices 5.80, results obtained by compendial methods will only be conclusive upon the usage of its respective compendial reference standards. Therefore, by not using USP Reference Standards, users face a real risk of regulators requesting to repeat their validation procedures resulting in additional time and resources towards regulatory approval.

### Avoiding discontinuation of reference standards

The discontinuation of a reference standard is an issue of concern for drug manufacturers. Commercial reference standards are risky because, as the demand for such a product decreases, many commercial companies will discontinue it due to the profit-driven nature of their business. This is problematic for manufacturers that trained their personnel and adjusted their laboratories to suit the tests related to a specific reference standard. Avoiding discontinuation is an important reason why the pharmaceutical industry prefers to trust USP Reference Standards over commercial reference standards.

The discontinuation of a compendial Reference Standard is a rare occasion that requires a monograph or general chapter to be proposed for omission by the appropriate EC. The ECs are comprised of external volunteer members who are key opinion leaders in the field and will provide a science-based decision regarding the suitability of the reference standard and its respective compendial use. Upon EC approval, the omission suggestion is posted for public comment in the Pharmacopeial Forum (PF). If no major concerns are raised, the documentary standard omission is officially published and the Reference Standard may be withdrawn. This process provides ample time for industry to replace that material if necessary.

## Avoiding discontinuation of instruments and reagents

Another risk of using commercial reference standards is brand-related discontinuation. Companies supplying reference standards often provide them to be used with their own instruments and reagents. These non-compendial alternatives will claim to be a “one-stop shop” but this convenience becomes a problem when these brands decide to discontinue instruments, upgrade instruments, or modify reagent formulation, thereby forcing manufacturers to repeat the analytical validation. USP compendial methods are “brand-agnostic” and give users the freedom to decide between different brands, instruments and reagents.

One example is the use of qPCR for detection of residual DNA, a common impurity test for any recombinant protein product. Some vendors offer their own workflow with their own reference standard, qPCR instrument, proprietary reagents, and primers. Information such as the formulation of the reagents and the primers’ sequences are usually not disclosed to customers. Drug developers following

this commercial workflow are committing themselves to a complicated dynamic where the commercial brand can, at any time, decide to modify or upgrade any of these components. USP compendial methods are different. In residual DNA detection, for example, the USP general chapter <509> *Residual DNA Testing* discloses the sequence of the primers required for the method, provides instructions for the preparation of reagents, and is built upon a reliable reference standard. Our general chapter gives manufacturers control over their workflow, and flexibility to use different vendors.

In summary, the use of USP Reference Standards is a safe choice for regulatory approval and will avoid the high costs and complexity associated with the analytical validation. Drug developers willing to validate their methods should still take into consideration the risks associated with commercial standards such as uncertainty, lack of multi-laboratory studies, and discontinuation.

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