

The United States Pharmacopeia (USP) has defined the limits of “allowable adjustments” in USP General Chapter <621>, where revalidation is required if adjustment limits are exceeded.

Even though this chapter might be taken as more “guidelines” than “rules”, it is best to heed the warning and take the precautions that have been set.

We are here to act as your unassigned tour guide as we take you through USP <621>.

Who is USP-NF?

The USP-NF is a book of public pharmacopeial standards for chemicals and biological drug substances, dosage forms, compound preparations, excipients, medical devices, and dietary supplements. See the USP official site for more information. USP-NF is also recognized by the U.S Federal Food, Drug and Cosmetics Act which designates them as the official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP-NF to avoid possible charges of adulteration and misbranding.



What does USP <621> Mean for You?

The latest revisions to USP <621> (which can be found [here](#)) provide a much clearer definition of what adjustments are allowed. It provides the following key points for allowable adjustments to chromatography systems in order to meet system suitability requirements.

The Key Points of Chapter <621> include:

- Defines chromatographic terms and procedures
- Allows for adjustments to methods
 - “in order to comply with system suitability”
 - when “it may be desirable to use a column with different dimensions”
 - “only when suitable standards (including Reference Standards) are available for all compounds used in the suitability test and the adjustments or column change yields a chromatogram that meets all the system suitability

requirements specified in the official procedure.”

- “are not to be made in order to compensate for column failure or system malfunction”

- Defines the maximum allowable adjustments
- Making adjustments may require additional verification
- Multiple adjustments should be considered carefully
- Address the continued trend toward < 3 particles, superficially porous particles (core-shell), and fast LC/UHPLC

Now we want to guide you through a breakdown of what Chapter <621> can mean for what you are doing in the lab. But first, here are a couple of the most frequently asked questions that USP receives.

Most Asked Questions the U.S. Pharmacopeial Convention Receives (Source)

1. To what degree can a chromatographic procedure be modified and still be in compliance? Can column length, internal diameter, mobile phase composition be modified?

- Chromatography General Chapter <621> contains a list of allowable adjustments to chromatographic systems. However, the user should verify the suitability of the method under the new conditions by assessing the relevant analytical performance characteristics potentially affected by the change

2. How much deviation is allowed from a relative retention time prescribed in a monograph?

- From <621>, the deviations of relative retention time values measured for the

test substance from the values obtained for the reference compound and mixture should not exceed the reliability estimates determined statistically from replicate assays of the reference compound. Also, relative retention times may be provided in monographs for informational purposes only, to aid in peak identification. There are no acceptance criteria applied to relative retention times.

Now into the quick breakdown.

How Adjustments Affect System Suitability

System suitability is an integral part of HPLC methods by verifying that the system is adequate for intended analysis. Each HPLC method in a monograph may have its own specific system suitability requirements, and this is important to note, because if the requirements are not successfully met, results for analysis of samples are invalid.

When it comes to allowable adjustments, and staying within the requirements for system suitability, you should be aware of USP <621> guidelines. Adjustments cannot be made where there is column failure or system malfunction. Adjustments may require verification, and consider carefully when making multiple adjustments as they can have a cumulative effect on system performance. However, validation is required when making changes to the stationary phase (e.g. L7 (C8) column in place of L1 (C18) column) because this is a modification.

USP <621> and Guard Columns

A guard column may be used with the following requirements, unless otherwise indicated in the individual monograph. All system suitability requirements specific in the official

procedure must be met with the guard column installed.

- The length of the guard column must be no more than 15% of the length of the analytical column,
- The inner diameter must be the same or smaller than that of the analytical column, and
- The packing material should be the same as the analytical column and contain the same bonded phase.

The benefits of using guard columns sufficiently outrank not using one. They protect valuable analytical columns by removing particulates and strongly retained sample components that may accumulate on the column. Using guard columns will help to maintain high column efficiencies, resolution, peak shape, as well as increase the lifetime of the analytical column and also be cost-effective.

Allowable Adjustments

Every year USP updates various monographs and general chapters. However, while the revisions from year-to-year may not be significant, if you are working with USP monograph methods, it is strongly recommended to pay attention to each new USP-NF.



For a full look at the allowable adjustments and how they affect mobile phase, column temperature, injection volume, flow rate, and more, check out this free webinar with

Phenomenex Senior Technical Manager, Philip J. Koerner, Ph.D. on “NEW Approaches for Improving HPLC and UHPLC Methodologies within Acceptable Pharmacopeia Guidelines”.

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