

	<b>ORA LABORATORY PROCEDURE</b> Food and Drug Administration	Document No.:	Version No.: 1.6
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Title: <b>ATTACHMENT A – MODIFICATION CRITERIA</b>		Effective Date: 10-01-03 Revised: 01-25-12	

If adjustments to operating conditions are needed, each of the following is the maximum specification (USP General Chapter <621> Chromatography) that can be considered. All adjustments falling outside the maximum specifications will be considered as method modifications and will be subject to the method modification protocol.

**pH of Mobile Phase (HPLC):** The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within  $\pm 0.2$  pH units of the value or range specified.

**Concentration of Salts in Buffer (HPLC):** The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within  $\pm 10\%$ , provided the permitted pH variation is met.

**Ratio of Components in Mobile Phase (HPLC):** The following adjustment limits apply to minor components of the mobile phase (specified at 50% or less). The amount(s) of these component(s) can be adjusted by  $\pm 30\%$  or  $\pm 2\%$  absolute (i.e., in relation to the total mobile phase), whichever is larger. However, the change in any component cannot exceed  $\pm 10\%$  absolute, nor can the final concentration of any component be reduced to zero. Examples of adjustments for binary and ternary mixtures are given below.

Binary Mixtures: Specified Ratio of 50:50 – Thirty percent of 50 is 15% absolute, but this exceeds the maximum permitted change of  $\pm 10\%$  absolute in either component. Therefore the mobile phase ratio may be adjusted only within the range of 40:60 to 60:40. Specified Ratio of 95:5 – Thirty percent of 5 is 1.5% absolute. However, because adjustments up to  $\pm 2\%$  absolute are allowed, the ratio may be adjusted within the range of 93:7 to 97:3. Specified Ratio of 2:98 – Thirty percent of 2 is 0.6% absolute. In this case an absolute adjustment of  $-2\%$  is not allowed because it would reduce the amount of the first component to zero. Therefore, the maximum allowed adjustment is within the range of 1.4:98.6 to 2.6:97.4.

Ternary Mixtures: Specified Ratio of 60:35:5 – For the second component, thirty percent of 35 is 10.5% absolute, which exceeds the maximum permitted change of  $\pm 10\%$  absolute in any component. Therefore, the second component may be adjusted only within the range of 25 to 45% absolute. For the third component, thirty percent of 5 is 1.5% absolute. Since  $\pm 2\%$  absolute is permitted and provides more flexibility, the third component may be adjusted within the range of 3 to 7% absolute. In all cases, a sufficient quantity of the first component is used to give a total of 100%.

**Wavelength of UV-Visible Detector (HPLC):** Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most,  $\pm 3$  nm.

**Column Length (GC, HPLC):** May be adjusted by as much as  $\pm 70\%$ .

**Column Inner Diameter (GC, HPLC):** may be adjusted by as much as  $\pm 25\%$  for HPLC and  $\pm 50\%$  for GC.

**Flow Rate (GC, HPLC):** May be adjusted by as much as  $\pm 50\%$ .

**Injection Volume (GC, HPLC):** May be reduced as far as is consistent with accepted precision and detection limits. It may be increased to as much as twice the volume specified, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity and retention times.

**Particle Size (HPLC):** May be reduced by as much as 50%.

**Column Temperature (HPLC):** May be adjusted by as much as  $\pm 10^\circ$ .

Oven Temperature (GC): May be adjusted by as much as  $\pm 10\%$ .

**Film Thickness (Capillary GC):** May be adjusted by as much as  $-50$  to  $+100\%$ .

**Column Temperature (GC):** May be adjusted by as much as  $\pm 2\%$ , in terms of absolute temperature.

**Oven Temperature Program (GC):** Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be held or for the temperature to be changed from one to another, an adjustment of up to  $\pm 20\%$  is permitted.