Leachables from the backing, release liner and storage pouch of transdermal patches present a potential risk to patient safety if these leachables enter the patient during the administration of the transdermal patch. Since these leachables have the potential to be a threat to patient health, evaluation of leachables from transdermal patches is likely to be requested from the FDA.

The first step toward evaluating the risk of leachables is to identify the potential leachables from the components of the transdermal patch and its pouch. This is done by performing an extraction study under exaggerated conditions with the goal of identifying the observed extractables. Extractables are the compounds that can be extracted from the patch and pouch that might become leachables. For transdermal patches and pouches, an extraction study will typically be done by extracting the components in two solvents for a predetermined time and temperature. The solvents should be selected based upon the drug product but will usually be water and 50% isopropanol in water. The extractables in the sample extracts are identified by GC-MS, LC-MS and ICP-MS.

At the completion of the extraction studies, a list of extractables is generated. The challenge at this point is to select which extractables present a toxicological risk and thus should be monitored as leachables. To evaluate the toxicity of each observed extractable, the safety concern threshold (SCT) is used. The SCT is the absolute highest acceptable exposure of a patient to a leachable in drug product and is usually expressed in terms of µg of leachable per day. If an SCT is not known (which is typically the case), the recommended SCT for a transdermal patch is 1.5 µg of each individual leachable per day.

The analytical evaluation threshold (AET) is calculated from the safety concern threshold (SCT) of 1.5 µg/day, the number of doses per day, the number of doses contained in the patch (typically 1 dose/patch), and the weight of the transdermal system.

$$AET = \frac{1.5\ (\frac{ug}{day})}{\#\ of\ doses/day} \times \frac{dose/patch}{weight\ of\ component(g)}$$

The AET will have units of µg/g (surface area instead of the weight may be applicable in some situations resulting in units of µg/cm2).

From the observed extractables, target leachables are selected from the extractables above the AET and analytical methods are developed for these compounds in the extraction solvent to be used during the leachables evaluation. In most cases, the solvent for the leachables evaluation will be an aqueous buffer intended to mimic human perspiration and the analytical methods will be GC-MS, LC-MS and ICP-MS. Patches that had been aged in pouches for various times including the target shelf life are extracted with the leachables solvent and then analyzed using the developed analytical methods.

The observed levels of leachables are evaluated against the analytical evaluation threshold. If all leachables remain below the AET for the entire shelf life, there is no risk to patient safety. If

an individual leachable is observed above the AET, a toxicological assessment is required on the specific leachable to determine the risk to patient safety.