TABLE 2 Example PHA for Materials Vs. Hazards for Potential Leachables

Potential for leachables	Investigate hazard	*S*	*F*	Imp $S \times F$
Component	Significant contact area	5	3	15
	Long duration	5	3	15
Primary material	Solubility in media	5	3	15
	Exposure to high temperatures	5	3	15
	Sublimation of chemical constituents	5	3	15
	Conditions above T_g	5	3	15
	Previous data unknown	5	3	15
	Known constituents of concern	5	3	15

Abbreviations: PHA, preliminary hazard analysis; S, severity; F, frequency.
(3) ICH Q9 Quality Risk Management

ranking. A standard method for identification of hazards or rating of those hazards does not exist for CCS materials used with pharmaceutical products as it depends on the particular system being analyzed and the target profile. Material rankings are defined relative to the individual system and are subjective; typically a conservative approach is taken without prior experience or regulatory direction. The PHA of the existing system will enable proper components to be selected and prioritized for further studies early in the development process when little information on the materials of construction is known.

QUALIFICATION AND CONTROL OF CCS

The studies required to qualify as CCS are extensive, incorporating both chemical and toxicological evaluations. The testing strategy can build depending on the pharmaceutical phase of development. Initially, CCS features such as performance attributes, compendial tests, and Food and Drug Administration (FDA) sanctioned (GRAS, generally recognized as safe) materials and/or designated as medical grade should be verified. Further testing can be planned in advance of the next stage to allow for appropriate protocols and sampling plans to be established. The work can be initiated relative to risk-benefit factors. Advanced planning for CCS studies can be guided by the pharmaceutical development phases; Figure 4 illustrates activities to be considered.

The depth of data to acquire becomes increasingly important as phase 2 approaches. Knowledge drawn from initial studies will facilitate a proper experimental design. During the preclinical phase, critical CCS components used for manufacturing, storage, and administration should be investigated so that in phase 1 the material selection can be narrowed down. Compatibility studies should be planned for the following indications:

- Loss of active/denaturing/binding
- Detection of interaction and degradation products
- Migration of CCS chemical constituents
- Formation of precipitates
- Detection of particles
- Discoloration of product/package
- Drug product pH change
- Brittleness of package component
- Change in CCS physical properties
- Inadequate CCS protection/performance