INTRODUCTION
Regulatory Agencies have clearly established the need to identify and control harmful chemicals which may leach from container closure systems into the final packaged drug product. While inorganic metal additives are necessary components in the manufacture of the glass, polymers, and elastomers, these same compounds may be considered adulterants in the final drug product. Total potentiality of some metals at extremely low levels is well established.

While United States Pharmacopoeia methods <381>, <661> and <662> detail colorimetric methods for screening heavy metal catalysts from elastomers, glass and polymers, these methods are inadequate to identify and quantify these contaminants. We explore the impact of various extraction and detection methods on metal detection and quantification.

1. OBJECTIVES
To assess the impact of the following experimental variables on elemental extractable levels:
- Extraction technique
- Solution pH
- Detection method

2. METHODS

2.1 SAMPLES
Two components and two closures tested by the extraction from each testable are as follows: (a) a bottle containing Compound 1, which was expected to present only the closed end (not used in a pharmaceutical industry).

2.2 EXTRACTION TECHNIQUES:
- 1) Heat at 70°C for 24 hours.
- 2) Autoclaved at 121°C for 1 hour.
- 3) Soxhlet extraction with acid, base, and oxidative solvents.
- 4) 1.0% H2O2 (Loreo Lot 091409, exp. 09/24/15).
- 5) 0.1 N HCl.
- 6) 0.1 N NaOH.
- 7) Water.

2.3 ANALYTICAL TECHNIQUES:
- ICP OES
- ICP MS

TABLE 1:
Extractants were screened for the following metals:
- Class 1: Arsenic
- Class 2: Elemental Impurities

3. RESULTS

3.1 Zn Concentration in Elastomeric Stoppers in Various Solvents

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>USP &lt;661&gt;</th>
<th>WFI</th>
<th>AA</th>
<th>ICP OES</th>
<th>ICP MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.117</td>
<td>0.204</td>
</tr>
<tr>
<td>Water</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.117</td>
<td>0.204</td>
</tr>
</tbody>
</table>

3.2 Zn Concentration in Glass Vials

<table>
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4. CONCLUSION

For data references:
- 1. There is a high degree of variability in metal levels from container closure systems depending upon the method of extraction and detection.
- 2. USP, ICP OES, and ICP MS methods yield significantly more extractable metal than USP U.S.P. Colorimetric method.
- 3. ICP OES is the most sensitive and reliable detection technique.
- 4. Atomic Absorption Apparatus. A standard curve was developed with reference standards.
- 5. Elemental Analysis Focus: This is a variance of 350%.
- 6. Extraction of elastomeric closure in a basic solution covered with Soxhlet extraction with acid, base, and oxidative solvents.
- 7. Zinc:

[Table of results and additional details for each metal concentration]