Guidance Number 37:

APPENDIX A: SAMPLING OF NON-STERILE LIQUID AND SEMI-SOLID DOSAGE FORMS

The following sampling plan examples may be used as a guide for sampling liquid dosage forms (solutions and suspensions) and semi-solid dosage forms (lotions, creams, ointments, pastes and gels) but should be evaluated on a case-by-case basis. Each sample should be evaluated individually and samples should not be composited. Where appropriate, a risk based approach may be applied to further define the validation sampling plan (e.g. a reduced sampling plan)) based upon historical data or manufacturing experience according to a defined rationale.

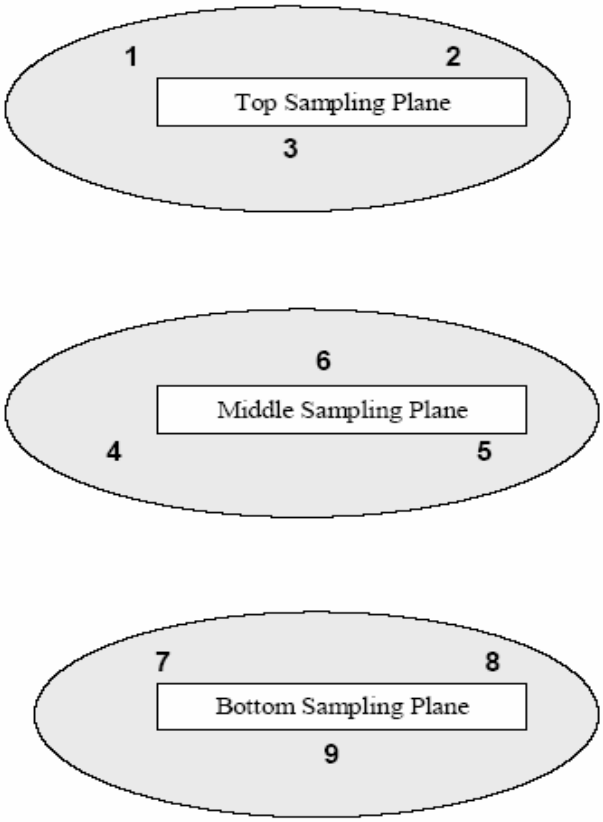
I. Dosage Form: SOLUTIONS

<table>
<tr><th>Manufacturing Stage</th><th>Process Validation Sampling Guideline</th></tr>
<tr><td>Mixing</td><td>Verify that the drug substance and preservatives are dissolved. Samples are taken from the manufacturing vessel from the top, middle and bottom of the container and tested for potency and preservative content (if applicable) to show even distribution of the API and preservative (if applicable). The number of samples to be taken will depend on the vessel geometry. If satisfactory data are available on similar formulations, using the same/equivalent equipment and mixing process, less than nine samples can be justified (e.g. one sample from top, middle and bottom of the mixer).

Manufacturing Vessel Samples:
Samples should be taken from the manufacturing vessel after the completion of the final mix step. Samples are taken to prove product uniformity of API and preservatives at the end of bulk manufacture. A possible sampling scheme would be as follows:

<table>
<tr><th>Sample Location</th></tr>
<tr><td>1. Top-Left Side</td></tr>
<tr><td>2. Top-Right Side</td></tr>
<tr><td>3. Top-Middle</td></tr>
<tr><td>4. Left 3-6” below surface (Middle)</td></tr>
<tr><td>5. Right 3-6” below surface -Middle</td></tr>
<tr><td>6. Middle-Middle</td></tr>
<tr><td>7. Left - Bottom</td></tr>
<tr><td>8. Right - Bottom</td></tr>
<tr><td>9. Middle- Bottom</td></tr>
</table>
Note 1: Sufficient sample volume should be taken from each sampling location to allow for the defined testing, together with investigation of any Out of Specification (OOS) or unexpected results.
Note 2: For solutions, it may be necessary to take pre- and post- filtration samples to prove adequate dissolution of actives and preservatives at the end of manufacturing.</td></tr>
</table>

TYPICAL SAMPLING LOCATIONS AT THE DIFFERENT SAMPLING PLANES FOR SOLUTIONS



APPENDIX A: SAMPLING OF NON-STERILE LIQUID AND SEMI-SOLID

I. Dosage Form: SOLUTIONS (cont.)

Manufacturing Stage	Process Validation Sampling Guideline
Holding	Refer to Holding time sampling guidance
Filling/Packaging	Take 3 samples at 10 sampling points distributed throughout the packaging process. Samples are taken and tested for potency and preservative content (if applicable) to prove product uniformity for API and preservatives (if applicable). Also refer to the Semisolids Filling section (below).

APPENDIX A: SAMPLING OF NON-STERILE LIQUID AND SEMI-SOLID

II. Dosage Form: SUSPENSIONS

<table>
<tr><th>Manufacturing Stage</th><th>Process Validation Sampling Guideline</th></tr>
<tr><td>Mixing</td><td>Manufacturing Vessel Samples:
Samples should be taken from the manufacturing vessel after the completion of the final mix step. Samples are taken and tested for potency and preservative content (if applicable) to prove product uniformity of API and preservatives (if applicable) at the end of bulk manufacture.

A possible sampling scheme would be as follows:

<table>
<tr><th>Sample Location</th></tr>
<tr><td>1. Top-Left Side</td></tr>
<tr><td>2. Top-Right Side</td></tr>
<tr><td>3. Top-Middle</td></tr>
<tr><td>4. Left 3-6" below surface (Middle)</td></tr>
<tr><td>5. Right 3-6" below surface -Middle</td></tr>
<tr><td>6. Middle-Middle</td></tr>
<tr><td>7. Left - Bottom</td></tr>
<tr><td>8. Right - Bottom</td></tr>
<tr><td>9. Middle- Bottom</td></tr>
<tr><td>10. Bottom (from drain if possible)</td></tr>
</table>

Note 1: Sufficient sample volume should be taken from each sampling location to allow for the defined testing, together with investigation of any OOS or unexpected results.

Note 2: Take samples from Top, Middle and Bottom of the tank for viscosity testing.</td></tr>
<tr><td>Holding</td><td>If packaging of the lot is delayed and the suspension is transferred to a Holding Storage Tank, Refer to Holding time sampling guidance</td></tr>
<tr><td>Filling/Packaging</td><td>Take 3 samples at 10 sampling points (including the end of the batch/lot) distributed throughout the packaging process. Samples are taken to prove product uniformity of API and preservatives (if applicable).
Also refer to the Semisolids Filling section (below).</td></tr>
</table>

APPENDIX A: SAMPLING OF NON-STERILE LIQUID AND SEMI-SOLID

III. Dosage Form: SEMISOLIDS

<table>
<tr><th>Manufacturing Stage</th><th>Process Validation Sampling Guideline</th></tr>
<tr><td>Mixing</td><td>Sample from the manufacturing vessel from the top, middle and bottom of the container for homogeneity of the API by testing the samples for potency. The number of samples to be taken will depend on the vessel geometry. If satisfactory data are available on similar formulations, using the same/equivalent equipment and mixing process, less than nine samples can be justified (e.g. one sample from top, middle and bottom of the mixer).

Mixing vessel
<table><tr><th>Sample Location</th></tr><tr><td>1. Top-Left Side</td></tr><tr><td>2. Top-Right Side</td></tr><tr><td>3. Top-Middle</td></tr><tr><td>4. Left 3-6” below surface (Middle)</td></tr><tr><td>5. Right 3-6” below surface -Middle</td></tr><tr><td>6. Middle-Middle</td></tr><tr><td>7. Left - Bottom</td></tr><tr><td>8. Right - Bottom</td></tr><tr><td>9. Middle- Bottom</td></tr></table>Note 1: Sufficient sample volume should be taken from each sampling location to allow for the defined testing, together with investigation of any OOS or unexpected results.</td></tr>
<tr><td>Holding</td><td>Refer to Holding time sampling guidance</td></tr>
</table>

APPENDIX A: SAMPLING OF NON-STERILE LIQUID AND SEMI-SOLID

III. Dosage Form: SEMISOLIDS (cont.)

<table>
<tr><th>Manufacturing Stage</th><th>Process Validation Sampling Guideline</th></tr>
<tr><td>Filling/Packaging</td><td>
Samples should be taken from throughout the filling operation. Matrixing and bracketing can be applied and the worst-case package size validated. This would typically be the largest surface to volume ratio, which is usually the smallest package size, and would also represent the longest filling time. These samples should be taken and tested for potency and preservative content (if applicable) to prove product uniformity (of the API and preservatives) is maintained throughout the filling operation, and also that the filling operation does not have an adverse affect on the overall quality of the finished product. A suggested sampling scheme would be as follows:
<table>
<tr><th>Sample Location</th><th>Number of samples</th></tr>
<tr><td>Beginning of Filling (ideally first 10 packages kept as product for sale)</td><td>10</td></tr>
<tr><td>Middle (taken from throughout the middle of the filling operation)</td><td>10</td></tr>
<tr><td>End (ideally the very last containers packaged that would be kept as product for sale)</td><td>10</td></tr>
</table>
Also consider the following:

If there are critical occurrences during the packaging run which may affect the product (e.g. line break downs), then samples should also be collected at start-up immediately following such an event. The rationale behind collection and/or testing of these samples should be outlined in the protocol.
In addition, samples should be taken at pre-determined intervals from the filler hopper to validate product and preservative uniformity if there is a need to evaluate holding time.
Depending on the length of the run and product microbial risk, it may be prudent to take samples for micro count and pathogen testing.

</td></tr>
</table>