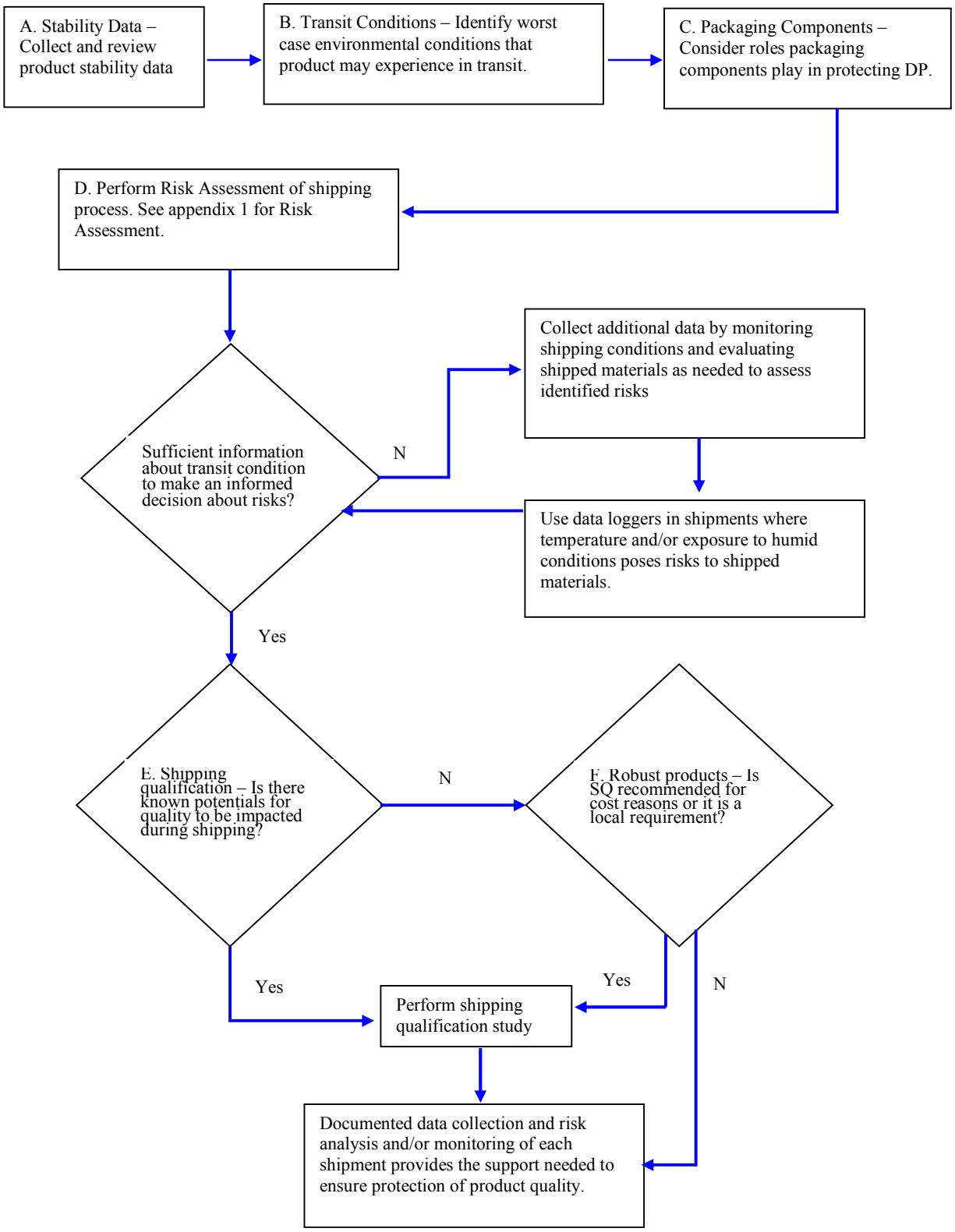
Guidance Number: 121

Figure 1: Workflow and Decision Tree for Assessing Shipping Processes



Appendix 1: Basis for a Risk Assessment on Determining the need for a Shipping Qualification

1. INTRODUCTION AND OBJECTIVE

This appendix is aimed at providing risk-based guidance on when shipping qualification should be applied. A completed, product specific risk assessment can also be employed as part of the supporting documentation package to justify the choice of shipping process and that receipt testing is not value adding (if appropriate).

The risk question for this exercise is – "Which product-specific Critical Quality Attributes are at risk of adverse impact under conditions proposed for the intended shipping method and that without SQ would justify product re-testing upon receipt/importation?"

The critical quality attributes of some products (APIs and DPs) are sensitive to impairment during shipping. The physical form of the product is a key factor, but of greater significance is how well controlled the transportation and intermediate storage conditions are during the shipping process. Impairment can come in the form of degradation, microbiological proliferation, moisture absorption, particle size stratification and dosage form breakage to name but a few. The integrity of packaging may also be compromised in some instances.

The maintenance of product quality during shipment can be assured by a number of mitigating factors – including, but not limited to:

- Product design (e.g., inherent stability or dosage form robustness)
- Packaging design/qualification (e.g. light, oxygen and/or moisture excluding, shock absorbing, tamper evident etc)
- Labeling
- Partnering and contractual arrangements
- Supplier (shipper) audit and/or qualification
- Cold chain transport and storage
- Data logging during transport
- Limited duration transport or special transportation arrangements
- Enhanced short-term stability study
- Receipt testing
- Shipping qualification

In addition to this, should a problem be found upon receipt of goods, then quality systems such as 'notification of damaged goods' will be used to prompt an

investigation and resultant corrective and preventative actions – which could include shipping qualification.

2. ASSESSMENT TEAM

The review team for this risk assessment comprised:

- Name Title
- Name Title
- Name Title

3. RISK ASSESSMENT METHODOLOGY

3.1 Approach

- Identify and analyze potential risks
- Evaluate the severity of each for potential impact
- Assess probability
- Evaluate mitigating factors and recommend additional controls and/or qualification for identified risks if appropriate

3.2 Severity Ranking Matrix

Severity Level	Conditions
3	High. Major impact on DP quality as a result of the shipping process. Could lead to adverse reaction in patient, stock out because product is unfit for use, or the product is outside the marketing authorization specification/requirements.
2	Medium. Minor impact on DP quality during the shipping process. Possible patient perception of safety issue, minor disruption in supply, but otherwise remains within the marketing authorization specification/requirements.
1	Low. Insignificant impact on DP/API quality as a result of the shipping process. No impact on patient and complies with marketing authorization specification/requirements..

3.3 Probability Ranking Matrix

Probability Level	Conditions
1	Highly unlikely

2	Plausible
3	Highly likely

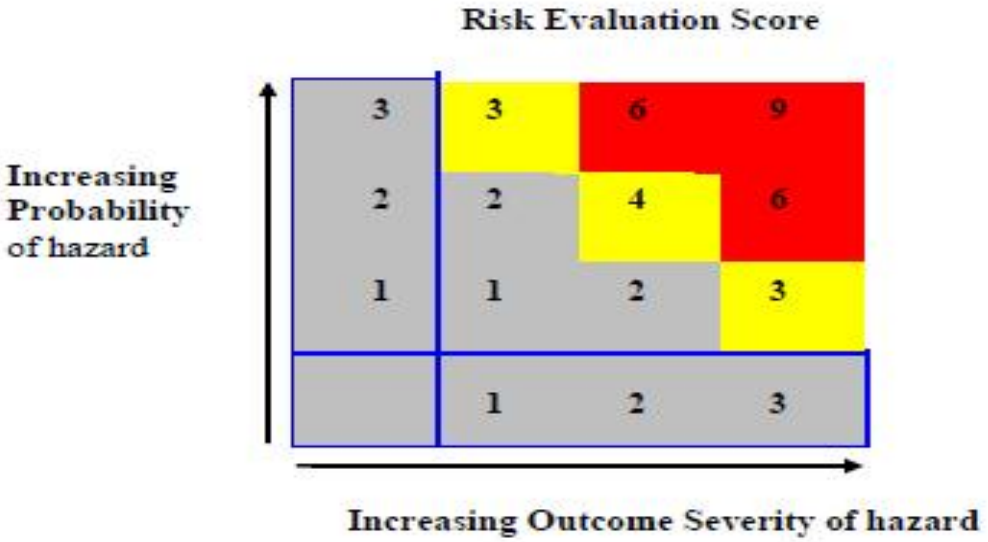
3.4 Detectability Rating

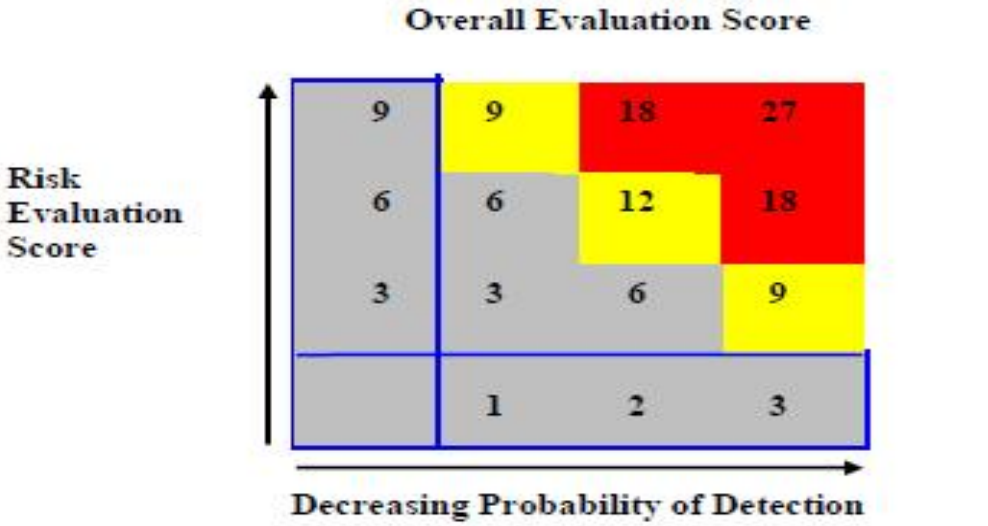
Detectability Rating	Conditions
3	**Undetected**. Visually impossible to detect issues before administration. Loss of product activity due to degradation or adulteration (e.g. via pathogen proliferation or build up of harmful impurities)
2	**Possibly detected**. Discoloration of liquids/solids due to degradation or microbiological proliferation, damage to secondary or tertiary packaging. May be obvious if routinely used, but not readily apparent if rarely administered.
1	**Readily detected**. E.g. breakage of vials or syringes, disintegration of tablets and damaged/ruptured primary packaging that is immediately obvious by visual observation during dispensing or at time of use

3.5 Outcome

Score	Interpretation
1-6	A minimal impact on product quality and therefore patient and/or business risk. No shipping qualification required.
9-12	A level of product quality and/or business risk that is generally acceptable without further mitigation in the short to medium term, but consideration must be given to how quality can be further safe guarded. Some level of shipping verification or evaluation is therefore recommended.
18-27	A high potential for product quality deterioration and/or a level of patient and/or business risk that is unacceptable. Shipping qualification is recommended.

3.6 Risk Ranking Matrix





3.7 Risk Ranking and Filtering

Potential Risks		Risk Analysis			Overall Score
		Probability	Severity	Detection	
1	What is the risk of significantly reducing product potency due to temperature, humidity, light or pressure variations during the shipping process?				
Comments					
2	What is risk of generating significant degradation related impurities due to temperature, humidity, light or pressure variations during the shipping process?				
Comments					
3	What is the risk of microbiological proliferation within the product as a result of the shipping process?				
Comments					
4	What is the risk of particle size stratification within bulk product due to agitation during the shipping process?				
Comments					
5	What is the risk of powder separation within bulk product due to vibration during the shipping process?				
Comments					
6	What is the risk of dosage form damage/breakage due to vibration or shock effects during the shipping process?				
Comments					
7	What is the risk of being out of compliance with Regulations or market authorizations associated with the receiving site/country should shipping qualification not be conducted?				
Comments					

4. RISK ASSESSMENT SUMMARY AND OUTCOME

5. ACTIONS SUMMARY AND COMMUNICATION

Implementation & Evaluation

Action Required	Responsibility	Target Date	Date Competed	Evaluation or further Recommend action if needed

6. REVISION HISTORY

Version	Reason for Revision	Supersedes Document Dated
1.0	This is the original.	N/A