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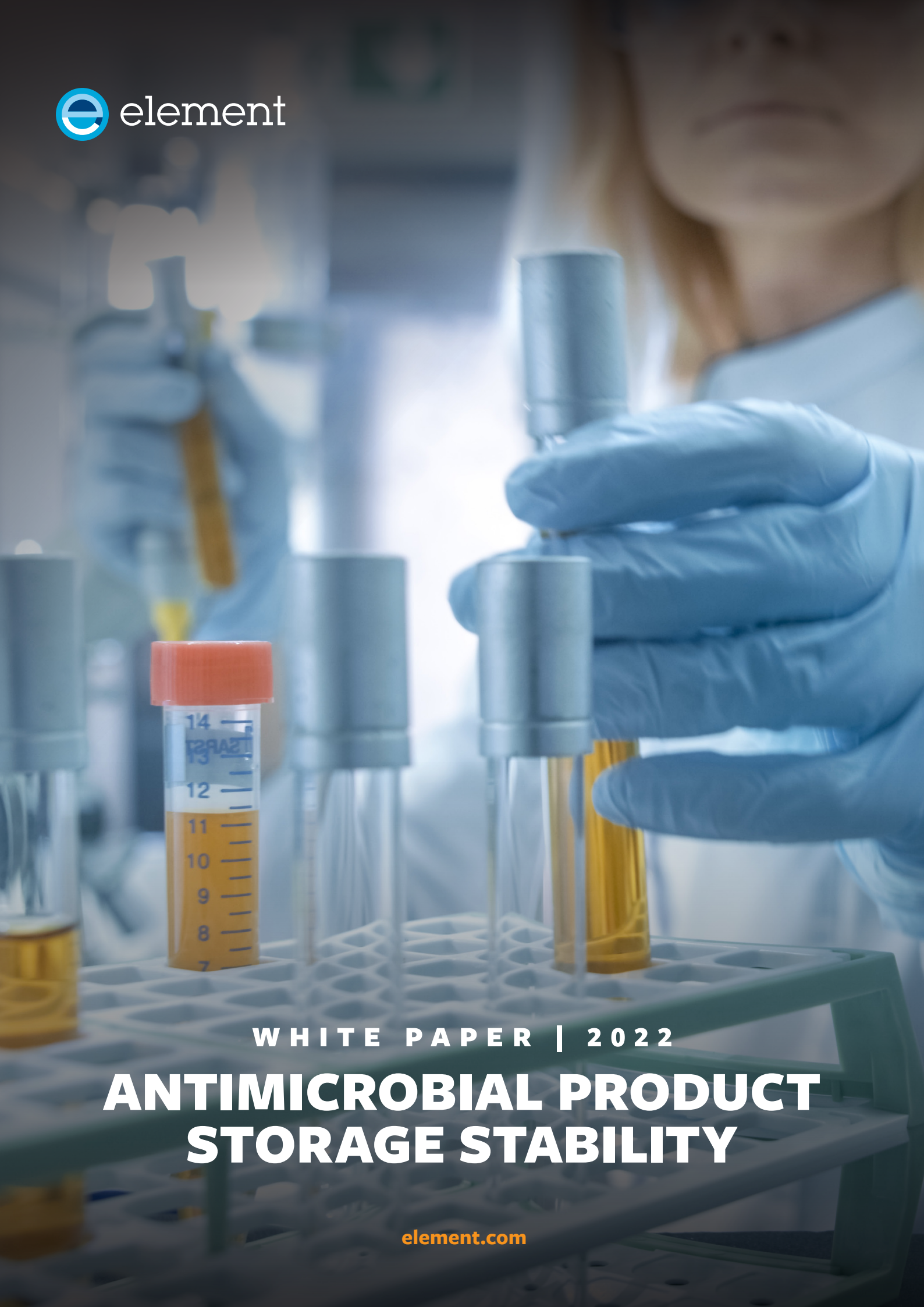

WHITE PAPER | 2022

ANTIMICROBIAL PRODUCT STORAGE STABILITY

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CONTENTS

INTRODUCTION

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INTRODUCTION

One of the major analytical tests required to register an antimicrobial product is stability testing. This article is designed to provide some background on the main considerations for product stability testing.

OVERVIEW & TESTING REQUIREMENTS

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OVERVIEW & TESTING REQUIREMENTS

Storage stability testing is designed to confirm the product's ability to maintain integrity throughout the intended shelf life, and to identify any storage limitations your product might have. The ultimate end-goal of this testing is to determine the appropriate expiration date for the product.

With the implementation of the OPPTS 830.6317 guideline in June 2002, the EPA established the framework of how storage stability testing should be conducted for products registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This guideline requires that all products demonstrate package integrity, that all products maintain their active ingredient levels within the nominal range (see below) and that all products be free from significant physical changes that may occur throughout the product lifetime. To confirm these requirements, stability testing is performed. According to the guideline, products are to be tested within the intended commercial packaging (or representative packaging of the same construction and material) and evaluated for active ingredient changes over time. The framework of a stability study should be set up according to one of the following strategies:

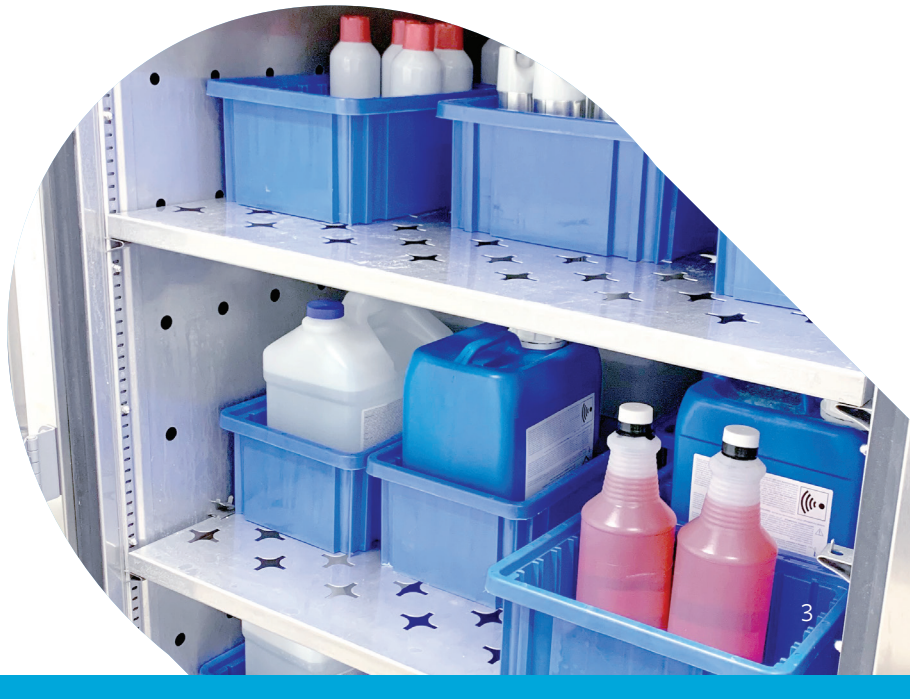
TABLE 1: STABILITY STUDY FRAMEWORK

Stability Study Conditions	Temperature	Storage Intervals
Shelf Conditions	20 or 25°C[1]	3, 6, 9, & 12 months
Accelerated Conditions[2]	40-54°C	30 days
Accelerated Conditions[3]	54±2°C	14 days

[1]A 50% relative humidity specification applies if packing is permeable.

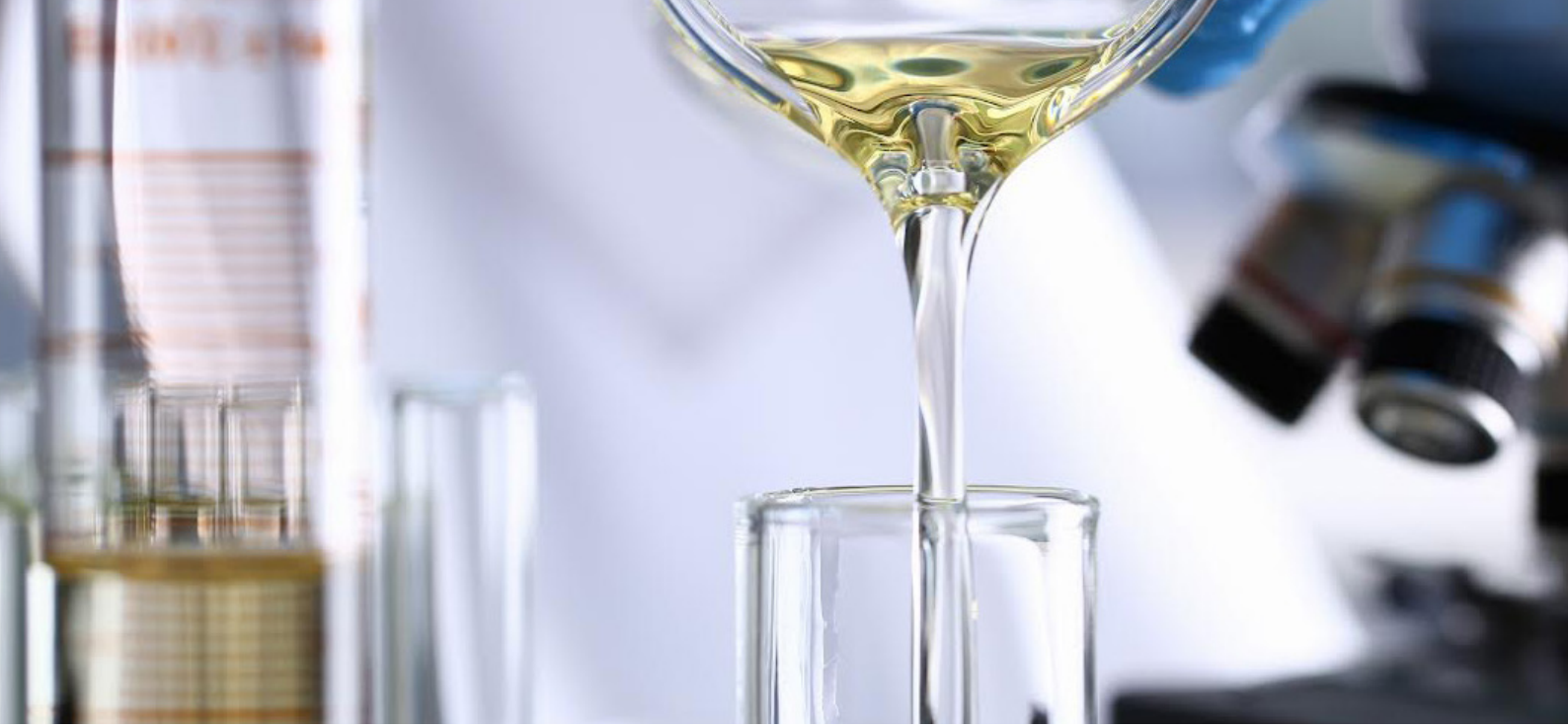
[2]Intended to be evaluated in conjunction with a shelf conditions study to provide adequte preliminary data for conditional registrations.

[3]A supplemental memorandum, issued by the U.S. EPA on November 16, 2012, indicated that acceptable stability data generated after 14 days of storage at 54±2oC satisfies all stability testing requirements.



NOMINAL RANGE & STABILITY TESTING

For more information, please visit **element.com**



NOMINAL RANGE & STABILITY TESTING

The nominal range of an active ingredient is determined by a table provided in guideline OPPTS 830.1750 - Certified limits - published in August 1996. Unless a registrant proposes different limits, the table in OPPTS 830.1750 provides specific upper and lower certified limits based on the nominal concentration of the active ingredient stated on the product label.

TABLE 2: STANDARD CERTIFIED LIMITS

If the nominal concentration (N) for the active ingredient is:	The certified limits for that ingredient will be as follows:	
	Upper Limit (UCL)	Upper Limit (UCL)
N ≤ 1.0%	N + 10% N	N + 10% N
1.0% < N ≤ 20.0%	1.0% < N ≤ 20.0%	N - 5% N
20.0% ≤ N ≤ 100.0%	N + 3% N	N - 3% N

For example, a 10% Hydrogen Peroxide solution would have an upper limit of 10.5% and a lower limit of 9.5%, and thus a nominal range of 9.5-10.5% Hydrogen Peroxide. This nominal range must be understood when interpreting stability data because the range defines the acceptable stability limits for the active ingredient being tested. For a product to pass stability testing, it must be tested within the nominal range at the initial time point, and shown to remain in range after each time point throughout the duration of the stability study. If the active ingredient levels of the product are unable to remain within the certified limits, the product may require special storage labeling, shorter shelf life expiration dates or may be denied approval by the EPA.

STABILITY STUDY FRAMEWORK

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STABILITY STUDY FRAMEWORK

Most active ingredients desinged for EPA product registration under FIFRA fall under one of the following categories:

- Quaternary Ammonium Compounds (QACs)
- Alcohols (ethanol and isopropyl alcohol)
- Halogen Releasing Compounds (for example: bleach)
- Peroxygen-based Compounds (hydrogen peroxide or peroxyacetic acid)
- Acids (citric acid, hydrochloric acid)
- Aldehydes (formaldehyde, glutaraldehyde)

The remainder of products can usually be classified into a category such as phenols (halogenated or not), alkalis (such as sodium hydroxide) and metal ions (such as silver or copper). This section will focus on the six categories that are listed above. If your product falls into one of the additional categories, or you are unsure of what type of active you are working with, consult your testing lab or regulatory consultant.

Below is a chart that can be used to get you started in understanding which stability study framework should be pursued for the active ingredient in your product.

TABLE 3: ACTIVE INGREDIENT STABILITY CONSIDERATIONS

Active Ingredient Category	Suggested Stability Study	Common Failure Risk
Quaternary Ammonium Compounds (QACs)	54oC - Accelerated	Stability studies often fail to stay within the upper certified limit potentially due to loss of solvents often used in these products. (See Packaging Considerations)
Alcohols	54°C - Accelerated	Stability studies often fail to stay within the lower certified limit potentially due to evaporation of product, becuase of poor packaging/sealing of product. (See Packaging Considerations)
Halogen Releasing Compounds	Shelf Conditions	Stability studies often fail to stay within the lower certified limit due to active ingredient breakdown/consumption. Bleach-based products and other chlorine-based products break down at higher temperatures. Shelf stability is almost always required.
Peroxygen-based Compounds	Variable - Consult with Element about your active ingredient	Stability studies often fail to stay within the lower certified limit due to active ingredient breakdown/consumption. Some hydrogen peroxide materials will successfully pass accelerated stability while many others often fail. Due to the reactive nature of these active ingredients, care must be taken when considering the inert ingredients in the formulation (e.g. stabilizers, detergents and other co-active ingredients) to ensure stability of the active can be maintained.
Acids	Variable - Consult with Element about your active ingredient	Due to the variety of acids, potential outcomes can vary wildly. Weak organic acids (such as citric acid) and simple, strong acids like hydrochloric acid have shown positive outcomes on accelerated stability depending on the product matrix.

PACKAGING & PACE CONSIDERATIONS

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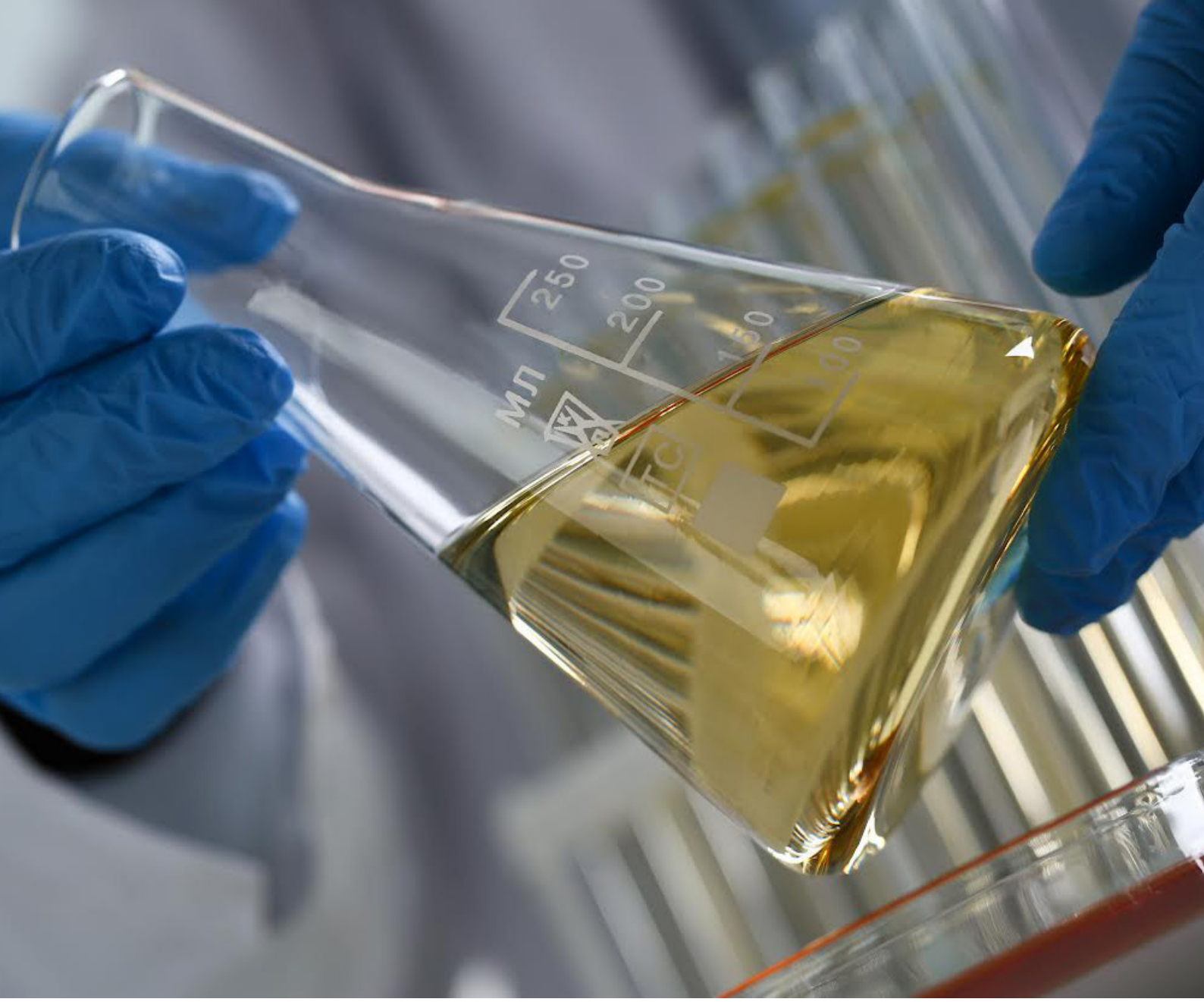

PACKAGING & PACE CONSIDERATIONS

What considerations should I make regarding packaging?
Understanding the permeability of the product packaging is a great tool for defining the potential risk factors your product might face during stability testing. While the typical concern of a stability study focuses on a loss in active ingredient levels after temperature stress and subsequent consumption, active ingredients also can fail stability by increasing above the upper certified limit due to loss of product matrix by evaporation, and is most commonly seen on accelerated stability. Thin plastic bags/bladders and spray bottles without closing nozzles are some of the more common packaging materials that can contribute to evaporation-based failures.

Can we go any faster?
In the fast-paced world of product development and registration, it can be frustrating to learn that a product will require a yearlong stability study before submission and final approval. The EPA has provided a pathway to accelerate these timelines, which have been used successfully by many applicants. Element offers a range of stability study options and can provide the guidance needed to provide appropriate stability results in the most efficient and effective manner possible. Understanding the testing requirements, acceptable limits, appropriate stability conditions and best packaging practices are ways we can help you move from product development to successful registration in the quickest time possible.

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