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## ZYN Stability Studies

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### Protocol Summary

#### 1 Purpose

The aim of these long-term studies is to document chemical and physical parameters of the different flavors and strengths of ZYN in cans during (b) (4), and thereby provide a basis for establishing a shelf life for the products.

This summary describes the general implementation of the stability studies, including material, storage and testing. An overview in tabular form shows details and highlights minor differences in the individual stability study protocols.

#### 2 General

##### 2.1 Description of Product

ZYN consists of nicotine bitartrate blended with microcrystalline cellulose, maltitol, sodium bicarbonate, sodium carbonate, hydroxypropyl cellulose, and flavors, and is enclosed in non-woven pouch paper. The product has (b) (4) and the contents of the pouches have the appearance of a free-flowing powder.

##### 2.2 Likely Changes of Product on Storage

The likely changes on storage can be classified into three main categories; physical, chemical and microbiological changes.

(b) (4)

From product development, it is known that the compounds regarded by FDA as Harmful and Potentially Harmful Constituents (HPHCs) in smokeless tobacco do not increase during storage of the product. In order to further corroborate these findings, the full abbreviated list of HPHCs are tested at the start of the study and at the end of the proposed shelf life.

The product is unlikely to promote microbiological growth, (b) (4). However, in order to demonstrate compliance with applicable regulatory guidelines for drugs for oromucosal use, the product is tested with respect to total aerobic microbial count (TAMC) and total yeast/mold count (TYMC).

### 3 Test Design

#### 3.1 Test Material

The material used in the study is detailed in Table 1. For details regarding batches and number of units, see the flavor-specific stability protocols.

**Table 1: Overview of Material Used in the Study**

Product Name	ZYN 3 mg/6mg
Product format	(b) (4)
Content per can	
Pouch weight	
Proposed shelf life	
Intended storage conditions	
Can	
Banderole	
Secondary packaging	
(b) (4)	

#### 3.2 Storage Conditions

During the stability storage period, samples will be stored at (b) (4) and either (b) (4) or (b) (4) as shown in Table 4. (b) (4)

##### 3.2.1 Labeling

The boxes (or equivalent) that hold the cans are labeled (not the cans themselves). At a minimum, this label should contain the following information:

- Request number
- Project (stability study)
- Product name, format and stock keeping unit (SKU)
- Storage conditions

### 3.3 Sampling Time Points and Sample Handling

#### 3.3.1 Sampling Intervals

(b) (4)

Table 2: Sampling Time Points for the Long-Term Studies

(b) (4)

#### 3.3.2 Analytical Testing

The analyses to be performed for samples withdrawn at different storage times during long-term studies are shown in Table 3. (b) (4)

#### *Number of Replicates*

Analyses should be performed in triplicate. (b) (4)

**Table 3:** Analyses to be Performed for Samples Withdrawn at Different Time Points During the Long-Term Studies

(b) (4)

### 3.3.3 Sample Storage until Analysis

(b) (4)

### 3.4 Specification

(b) (4)



## 4 Evaluation and Reporting

All analytical results will be listed in a spreadsheet document, along with summaries in graphical and tabular forms for the following parameters versus storage time:

- pH
- Moisture Content (%)
- Nicotine (mg/g as is)
- Nicotine related compounds (total and individual; % of Nicotine)

A written report will be produced, in which any peculiarities of the data are discussed and in which the shelf life supported by the data is established.

(b) (4)

## 5 Stability Study Overview

Differences between the stability studies for the various ZYN flavors are summarized in Table 4.

(b) (4)

**Table 4: Overview of Long-Term Stability Studies**

Flavor	SKU		Stability Study Start
	3 mg	6 mg	
Cool Mint	8105	8106	(b) (4)
Peppermint	8107	8108	
Spearmint	8109	8110	
Wintergreen	8111	8112	
Citrus	8122	8123	
Coffee	8124	8125	
Cinnamon	8128	8129	
Smooth	8134	8135	
Chill	8136	8137	
Fresh	8140	8141	