Swedish Match

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Justification of Final Product Specifications and Characterization Testing

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1 Introduction

Swedish Match initiated commercial production of ZYN in 2015. The company has since produced variants of the product included in this premarket tobacco application (PMTA). Over this period of time, a wealth of data from laboratory, pilot plant, and commercial production has been generated. This data has formed the basis to define product characterization and release specification, respectively, and to justify these criteria in comparison to the comparator product General Snus that received marketing orders from the Food and Drug Administration (FDA) in November 2015.

FDA Submission Tracking Number (STN)	Product Name
PM0000011	General Dry Mint Portion Original Mini
PM0000012	General Portion Original Large
PM0000014	General Mint Portion White Large
PM0000016	General Portion White Large
PM0000017	General Wintergreen Portion White Large

The comparator products General Snus have been produced by Swedish Match over many decades. In year 2000, Swedish Match voluntarily introduced GOTHIATEK®, Swedish Match's proprietary quality system that assures consumers that all Swedish Match products are subject to rigorous controls and maintain the highest quality throughout all the stages from tobacco plant to consumer. GOTHIATEK cannot be applied directly to ZYN production since ZYN is not a leaf tobacco product; however, the production of ZYN is inspired by the GOTHIATEK standard to ensure quality. An element of the GOTHIATEK quality standard is maximum level of certain Harmful and Potentially Harmful Constituents (HPHCs).

The maximum limit of constituents defined for the comparator products General Snus are pragmatic and largely based on considerations of what can technically be achieved in large-scale, routine production recognizing the importance of seed selection, growing and curing conditions, and all subsequent handling of the tobacco leading to manufactured finished product.

The chemical constituents of the ZYN products have been thoroughly investigated. The content of a great number of constituents relevant for this type of product, and many also listed by FDA as HPHCs, have been determined both at production and at best before date. Both internal and external limits have been set for these constituents. These limits are designed considering optimal production techniques, available analytical methods, and quantitative risk assessments.

Nicotine in its free base form is susceptible to oxidation and evaporation and is then fairly unstable. By providing a product where nicotine is present as a salt rather than in its free base form, the stability of the product is greatly increased. ZYN is produced using nicotine of pharmaceutical purity and refined excipients of high purity. All excipients are food grade quality. The nicotine salt and excipients are simply blended at ambient temperature in the manufacturing process of ZYN. In this blending operation, the integrity of each component is maintained, and no chemical reaction is intended between any of the components in the composition and no new HPHC constituents are formed in the manufacturing process. For these reasons, ZYN products contain constituents well below the HPHC levels of the comparator product General Snus, except for formaldehyde which is present in ZYN at a similar level.

This chapter is divided into two sections: justification of the ZYN product characterization and justification of the specifications. The definitions used for these two sections are the following:

1. **Characterization:**
   Swedish Match has established internal limits as well as external limits for several parameters that characterize the ZYN products, based on repeated analysis for a variety of ZYN products. Compliance with the product characterization criteria is ensured based on historical track record and a validated testing protocol. Characterization parameters do not constitute release nor shelf life specification.

   The main purpose of continued characterization analysis is to ensure that the ZYN products are within the internal limit for the respective constituent. Regular testing also enables identification of any unexpected and undesired trend. If such a trend is observed, an investigative process is initiated to identify the root cause with the objective of defining corrective actions. External limits are set for analytes that are included in GOTHIATEK to facilitate bridging to General Snus and characterize the product throughout the shelf life of the product at recommended storage conditions. The external limits are set based on all collective data collected for each parameter, raw material specifications and controls, stringent manufacturing process controls, and, where applicable, on safety considerations. The internal limits are used for monitoring and to guide continued improvements of the product.

2. **Release and Shelf Life Specifications**
   The ZYN release and shelf life specifications are based on two important overlapping criteria:

consumer health and safety, and consumer satisfaction. The release specification includes tests that will determine whether or not the product batch will be put on the market. Testing is performed on all batches with release criteria for each test. Product nicotine, product pH, product moisture, pouch weight and can weight constitute the release specification. The shelf life specification includes tests that are used to determine whether or not an appreciable change in quality is likely to occur after storage at recommended conditions.

2 Justification of ZYN Product Characterization

For each parameter, the internal limit as well as the external limit for ZYN and the limit from the GOTHIATEK standard are provided for easy comparison, when these values have been established. GOTHIATEK cannot be applied directly to ZYN production since ZYN is not a leaf tobacco product; however, the production of ZYN is inspired by the GOTHIATEK standard to ensure quality. For some ZYN characterizing parameters, when there is no defined GOTHIATEK limit, instead the internal limit for the comparator product General Snus is provided.

All values are defined on a dry basis, unless otherwise stated, for both ZYN and the comparator product General Snus.

2.1 Characterization Parameters Subject to Annual Analysis

2.1.1 Product Nicotine (b) (4)

Product nicotine may diminish over time due to oxidation and evaporation. Product nicotine content has been extensively analyzed for ZYN products over time at different storage conditions.

Based on the observed manufacturing variability together with stability studies, Swedish Match has defined internal limits for nicotine. The allowed deviation from the target content during the shelf life amounts to (b) (4) Experience has shown that consumers cannot detect variation in nicotine content within these ranges, and thus these acceptance criteria are considered justified. It is considered justified to include nicotine content in the release and shelf life specifications.

ZYN Product Nicotine Strength	Unit	Internal Target	Internal Limits
ZYN 3 mg/pouch	mg/g as is	(b) (4)	
ZYN 6 mg/pouch	mg/g as is		

2.1.2 Product pH (b) (4)

The internal limits for pH are justified based on observed manufacturing variability, stability studies, as well as a general internal limit at Swedish Match limiting pH of our products to (b) (4). Product pH is included in both the release and shelf life specifications.

ZYN Product pH	Internal Target	Internal Limits
pH	(b) (4)	

2.1.3 Product Moisture (b) (4)

The internal limit for moisture content, (b) (4) %, is considered justified based on experience from the development of the product which shows that product stability is adversely affected by higher moisture contents. Moisture content is included in both the release and shelf life specifications.

ZYN Product Moisture Content	Unit	Internal Target	Internal Limit
Moisture Content	% as is	(b) (4)	

2.1.4 Tobacco-Specific Nitrosamines (b) (4)

NNN and NNK are both listed by the FDA as harmful and potentially harmful constituents (HPHCs). The FDA has issued a draft regulation of a maximum limit of 1 µg/g NNN on a dry weight basis for oral tobacco products. The World Health Organization Tobacco Regulation subgroup has recommended a combined limit for NNN and NNK of 2 µg/g on a dry weight basis.

If a high-purity nicotine source, that complies with the purity criteria of the United States Pharmacopeia (USP), is used to produce a tobacco-derived nicotine product, as is the case with ZYN, the levels of NNN and NNK are substantially reduced compared to the comparator product General Snus. The maximum limit of NNN and NNK of the comparator product General Snus, according to the GOTHIATEK standard, is 1.9 µg/g on a dry weight basis. Using the state-of-the-art analytical method available to Swedish Match, NNN and NNK are both below the limit of quantification (LOQ) of (b) (4) µg/g, which is less than one-thirtieth of the level of combined NNN and NNK of the comparator product General Snus.

The minimal levels of nitrite, nitrate, and microbial activity ensure that formation of TSNAs is highly unlikely to occur in the product. Because TSNAs have been consistently found to be lower than the LOQ, it is considered justified to not include TSNAs in the release specification. The choice of LOQ as the limit is considered justified. The total TNSA, NNN and NNK levels of all stock keeping units (SKUs) in production will be analyzed once every year, and are also included in the shelf life specification as required by the FDAs proposed rule for PMTA applications.

TSNA	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
NNN+NNK	µg/g	(b) (4) (LOQ)	(b) (4) (LOQ)	(b) (4)
Total TSNA	µg/g	(b) (4).	(b) (4) (LOQ)	

LOQ=limit of quantification; N.A.=not applicable; NNK=nicotine-derived nitrosamine ketone; NNN=*N*-nitrosonornicotine; TSNA=tobacco-specific nitrosamine.

2.1.5 Nitrite (b) (4)

Nitrite is not listed by the FDA as an HPHC. Nitrite is a precursor to NNN and NNK formation. During the drying of tobacco, (b) (4) . To minimize the risk of NNN and NNK formation, the comparator product General Snus has a maximum GOTHIATEK limit of nitrite of (b) (4) µg/g on a dry weight basis.

The levels of nitrite observed in common food stuffs and comparisons with estimated total daily exposure from food and drinking water suggest that the additional exposure to nitrite for a regular consumer of ZYN products is negligible. Because minimal levels of nitrite have been consistently found in ZYN products, it is justified to not include nitrite as part of the ZYN product release specification. The nitrite levels of all SKUs in production will be analyzed once every year, and are also included in the shelf life specification, along with nitrate, as required by the FDAs proposed rule for PMTA applications. The limit for nitrite, (b) (4) µg/g, is considered justified based on characterization data, stability study data and by comparison with the GOTHIATEK limit.

Tobacco Contaminant	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
Nitrite	µg/g	(b) (4)		

2.1.6 Aldehydes (QEMS-7-7322)

The aldehydes formaldehyde, acetaldehyde, and crotonaldehyde are listed by the FDA as HPHCs. These have all been found in the comparator product General Snus. Acetaldehyde and crotonaldehyde of the comparator product General Snus exclusively originate from the tobacco lamina while formaldehyde originates predominantly from the tobacco and the pouch wrapping material, which contains a binder with traces of formaldehyde as an unreacted crosslinking agent.

The ZYN powder enclosed in the wrapping material has been found to contain small quantities of formaldehyde and acetaldehyde (both below (b) µg/g). Formaldehyde contamination of the ZYN products originates predominantly from the pouch wrapping material containing a binder with traces of formaldehyde as an unreacted crosslinking agent. However, the formaldehyde content of ZYN products is similar to the corresponding value for the comparator product General Snus as the ratio of pouch wrapping material ("pouch paper") to pouch content is higher for ZYN than for General snus.

The levels of formaldehyde and acetaldehyde observed in common food stuffs such as fruit and vegetables compared to the potential exposure of formaldehyde of a regular consumer of ZYN product suggests that the additional exposure to formaldehyde of a regular consumer of ZYN products is negligible. The level of crotonaldehyde in ZYN products is less than the LOQ. For these reasons, and by comparison with the GOTHIATEK limits, the external limits are considered justified. Because the contents of aldehydes have been found to consistently be below the external limits, it is justified to not include aldehyde testing as part of the ZYN product release specification. The aldehyde levels of all SKUs in production will be analyzed once every year. Furthermore, to characterize any potential changes in formaldehyde or acetaldehyde contents during storage, it is justified to test the contents of these aldehydes in the first three stability studies for each SKU. On the basis of the results from the first three stability studies for each SKU, it will be evaluated whether it is justified to include testing of formaldehyde and acetaldehyde in the subsequent stability studies.

Aldehyde	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
Formaldehyde	µg/g	(b) (4)	(b) (4)	(b) (4)
Acetaldehyde	µg/g	(b) (4)	(b) (4)	
Crotonaldehyde	µg/g	(b) (4) (LOQ)	(b) (4) (LOQ)	

LOQ=limit of quantification.

2.1.7 Water Activity ((b) (4)) and Microbial Content ((b) (4))

All components of ZYN products are highly purified and (b) (4). The ZYN manufacturing process does not involve the use of (b) (4). However, the product has a moisture content in equilibrium with the air humidity. Two of the components, microcrystalline cellulose of the ZYN powder and the pouch paper, are known to absorb moisture in equilibrium with surrounding air. The release and shelf life acceptance criteria for moisture content, (b) (4)%, are considered justified based on experience from the development of the product which shows that product stability is adversely affected by higher moisture contents.

Water activity (a_w) is commonly used in the food industry to monitor conditions for microbial growth. Bacteria usually require an a_w of at least 0.91, and fungi require an a_w of at least 0.7. The comparator product General Snus has an a_w release criteria of (b) (4).

An external assessment of the risk of microbial growth in the ZYN products (Section H.2.1 Assessment of Product Risk, Microbiological Investigation) has been issued by (b) (4) (b) (4) realized in ZYN manufacture, ZYN products have a water activity of (b) (4). Very few microorganisms can grow below an a_w of 0.81. The organism known to grow at the lowest water activity is the mold *Xeromyces bisporus*, which grows at an a_w of 0.622. This means that even in a very conservative view, it can be stated that there is virtually no possibility for any harmful microorganism to grow in the ZYN products. As a result, the environment for microbiological growth within ZYN products is extremely poor. The total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) of ZYN products has been found to be consistently less than (b) (4) colony forming units/g ((b) (4) lgcfu/g).

Based on the low water activity of ZYN products and a ZYN manufacturing process devoid of (b) (4) and using (b) (4), there is no expectation that ZYN products will ever be contaminated by microbiological growth. Moisture content, related to water activity, is a release specification. For these reasons, it is considered justified to not include water activity testing in the ZYN product release specification. The water activity, TAMC and TYMC, of all SKUs in production will be analyzed once every year, and the microbial content (TAMC and TYMC) are included in the shelf-life specification.

There are no external limits for water activity, TAMC, or TYMC, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected levels be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Test Parameter	Unit	Internal Limit for ZYN	Internal Limit for General Snus
Water activity, a_w	N.A.	(b) (4)	
TAMC	lgcfu/g		
TYMC	lgcfu/g		

lgcfu/g=log_{10} colony forming units per gram; N.A.=not applicable; TAMC=total aerobic microbial count; TYMC=total yeast and mold count.

2.1.8 Nicotine Related Compounds (b) (4)

The internal limits for nicotine related compounds are identical to the criteria in the USP Monograph for Nicotine, and are therefore considered justified. Because the content of nicotine related compounds in newly produced ZYN products is consistently well below the internal limits, it is justified to not include this test in the product release specification. The content of nicotine related compounds will be analyzed once every year for each SKU in production.

There are no external limits for nicotine related compounds, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected levels be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Nicotine Related Compound	Unit	Internal Limit for ZYN
Anabasine	% of Nicotine	(b) (4)
Anatabine	% of Nicotine	
Cotinine	% of Nicotine	
Myosmine	% of Nicotine	
Nicotine-*N*-oxide	% of Nicotine	
β-Nicotyrine	% of Nicotine	
Nornicotine	% of Nicotine	
Total Related Compounds	% of Nicotine	

2.1.9 N-Nitrosodimethylamine (b) (4)

N-Nitrosodimethylamine (NDMA) is listed by the FDA as an HPHC. The comparator product General Snus has a maximum GOTHIATEK limit for NDMA of (b) (4) ng/g on a dry weight basis. NDMA is produced as an undesired by-product of several industrial food processing operations and may be present at very low levels in certain foodstuffs, especially those cooked, smoked, or cured. It is also a tobacco constituent.

NDMA content of ZYN has been found to consistently be below the LOQ of (b) (4) ng/g, which therefore is considered a justified external limit. Because production of ZYN is not based on tobacco, nor does its processing involve cooking, smoking or curing, it is deemed unrealistic that the product may ever contain NDMA. For this reason, it is justified to not include NMDA testing as part of the ZYN product release specification. The NDMA levels of all SKUs in production will be analyzed once every year.

HPHC	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
NDMA	ng/g	(b) (4) (LOQ)	(b) (4) (LOQ)	(b) (4)

HPHC=harmful or potentially harmful constituent; LOQ=limit of quantification; NDMA=N-Nitrosodimethylamine.

2.1.10 Benzo[a]pyrene and Other Polycyclic Aromatic Hydrocarbons (b) (4) (b) (4)

Benzo[a]pyrene is listed by the FDA as an HPHC. Benzo[a]pyrene content of the comparator product General Snus originates from the in-going tobacco. General Snus has a maximum GOTHIATEK limit for benzo[a]pyrene of (b) (4) ng/g on a dry weight basis. ZYN does not contain tobacco nor any other component that can be expected to contain traces of benzo[a]pyrene. Therefore, it was expected that benzo[a]pyrene would not be detectable in ZYN products, and the expectations have been confirmed by consistent benzo[a]pyrene levels of ZYN products below the LOQ of (b) (4) ng/g.

The levels of benzo[a]pyrene observed in common food stuffs, e.g. smoked or barbequed meat, and comparisons with estimated total daily exposure, suggest that the additional exposure to benzo[a]pyrene of a regular consumer of ZYN products is negligible. Because of the consistently minimal concentrations of benzo[a]pyrene in ZYN, is justified to not include benzo[a]pyrene as part of the ZYN product release specification. Because of the lack of a conceivable route of formation of benzo[a]pyrene in the product during storage, it is also justified to not include benzo[a]pyrene in the shelf life specification. The benzo[a]pyrene levels of all SKUs in production will be analyzed once every year.

HPHC	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
Benzo[a]pyrene	ng/g	(b) (4) (LOQ)	(b) (4) (LOQ)	(b) (4)

HPHC=harmful and potentially harmful constituent; LOQ=limit of quantification.

Benzo[a]pyrene is frequently used as a marker for polycyclic aromatic hydrocarbons (PAHs). However, it is just one out of many PAHs that are found in tobacco and tobacco products. The quantity of those PAHs listed by the FDA has also been measured in ZYN products. None of these, except naphthalene, was found to have a content above the LOQ. Because of the consistently minimal PAH contents found in the ZYN products, it is justified to not include PAH testing in the ZYN product release specification. Because of the lack of a conceivable route of formation of PAHs in the product during storage, it is also justified to not include PAHs in the shelf life specification.

All values for ZYN products are consistently below the LOQ, except for naphthalene, where occasional analytical results above the LOQ have been obtained. The LOQs, with the exception of the concentration listed for naphthalene, constitute the internal limits for the PAH in question.

All the PAHs listed below, together with benzo[a]pyrene, are classified by the FDA as HPHCs.

Polycyclic Aromatic Hydrocarbon	Unit	Internal Limit for ZYN
(b) (4)		

LOQ=limit of quantification.

The contents of the above identified PAHs for all SKUs in production will be analyzed once every year. There is no external limit for the contents of these PAHs, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected increase in the characterizing contents of PAHs be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

2.1.11 Heavy Metals (b) (4)

The heavy metals arsenic, cadmium, chromium, lead, mercury, and nickel are all defined as HPHCs by the FDA. Heavy metals in the comparator product General Snus originate from the tobacco component of the product. The content of heavy metals in tobacco is determined predominantly by the heavy metal content of the soil where the tobacco is grown. Heavy metal constituent levels of ZYN are considerably lower compared to General Snus, since ZYN does not contain tobacco, but rather highly refined components. The content of heavy metals in ZYN products are all at or near the LOQ, which in effect means that on average, the heavy metal content of ZYN is one tenth of the heavy metal content of the comparator product General Snus.

The heavy metal levels observed in common food stuffs and comparisons with estimated total daily exposure from food and drinking water suggest that the additional exposure to heavy metals of a regular consumer of ZYN products is negligible. For this reason and because of the consistently minimal levels found in the ZYN products, it is justified to not include heavy metals testing as part of the ZYN product release or shelf life specifications. The heavy metal levels of all SKUs in production will be analyzed once every year.

Heavy Metal	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
Lead	µg/g	(b) (4)		
Arsenic	µg/g			
Cadmium	µg/g			
Chromium	µg/g			
Nickel	µg/g			
Mercury	µg/g			

LOQ=limit of quantification.

2.1.12 (b) (4)

(b) (4) is not listed by the FDA as an HPHC. (b) (4) is an additive to the comparator General Snus product as a humidifier with a maximum level of [redacted] % as an internal limit. In the manufacturing of ZYN, (b) (4)

There is no external limit for the contents of (b) (4), and consequently, the analysis will be performed for monitoring purposes. Should any unexpected increase in the characterizing contents of (b) (4) be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Flavor Component (ZYN Manufacture)	Unit	Internal Limit for ZYN	Internal Limit for General Snus
(b) (4)			

2.1.13 (b) (4)

(b) (4) is not listed by the FDA as an HPHC. (b) (4) is used as a solvent for flavor additives in the production of General Snus. General Snus has an internal limit of (b) (4) of (b) (4) % on a dry weight basis. ZYN production involves the use of (b) (4) as solvent for encapsulating and granulating agent. The internal limit of (b) (4) for ZYN products is (b) (4) %.

The level of (b) (4) observed in common food stuffs such as fruit compared to the potential exposure to (b) (4) of a regular consumer of ZYN product suggests that the additional exposure of (b) (4) by a regular consumer of ZYN products is negligible. For these reasons, (b) (4) [redacted]. The (b) (4) levels of all SKUs in production will be analyzed once every year. There is no external limit for the contents of (b) (4) and consequently, the analysis will be performed for monitoring purposes. Should any unexpected increase in the characterizing contents of (b) (4) be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Solvent (ZYN Manufacture)	Unit	Internal Limit for ZYN	Internal Limit for Snus
(b) (4)			

2.1.14 Pouches per Can

ZYN products are designed to contain 15 pouches per can, with a tolerance of (b) (4) pouch/can. The number of pouches per can is not included in the release specification, which is justified by the inclusion of the related parameter net can content weight. The number of pouches per can will be tested once every year for each of the SKUs in production.

There are no external limits for the number of pouches per can, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected values be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Can Content	Unit	Internal Target	Internal Limits
Pouches/Can	#	(b) (4)	

2.1.15 Pouch Dimensions

The pouch dimension design specification and tolerances are shown in the table below. Based on manufacturing experience, it is justified to not include pouch dimensions in the release specification. The number of pouches per can will be tested once every year for each of the SKUs in production.

There are no external limits for the pouch dimensions, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected values be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Pouch Dimension	Unit	Target	Internal Limits
Length	mm	(b) (4)	
Width	mm		
Height	mm		

2.2 Characterization Parameters Subject to Precursory Analysis

2.2.1 Mycotoxins - Aflatoxins B_1, B_2, G_1, G_2 and Ochratoxin A (b) (4)

Aflatoxin B_1 is listed by the FDA as an HPHC.

Mycotoxins have been found in all major food crops and contamination may occur both before and after harvesting. Any tobacco-based product may contain traces of mycotoxins formed by microbiological activity during growing, harvesting, and storage of the tobacco. The comparator product General Snus has a GOTHIATEK maximum limit for aflatoxin of (b) ng/g on a dry weight basis, defined as the sum of B_1, B_2, G_1, and G2. The corresponding limit for ochratoxin A is (b) (4) ng/g on a dry weight basis.

Since ZYN products do not contain tobacco or any other raw material that may reasonably contain aflatoxins B_1, B_2, G_1, G_2 or ochratoxin A, it is deemed highly unlikely that the product may ever contain

any of these constituents. Consequently, the external limits are set to the LOQ and are thus considered justified. Mycotoxin testing was performed as part of ZYN product characterization, confirming the absence of quantifiable levels of mycotoxins. It is therefore justified to not include mycotoxin testing as part of the ZYN product release or shelf life specifications. Swedish Match does not propose to perform mycotoxin testing on an ongoing basis.

Mycotoxin	Unit	External Limit for ZYN	Internal Limit for ZYN	GOTHIATEK Limit for General Snus
Aflatoxin B_1	ng/g	(b) (4)		
Aflatoxins (sum $B_1+B_2+G_1+G_2$)	ng/g			
Ochratoxin A	ng/g			

LOQ=limit of quantification; N.A.=not applicable.

2.2.2 Ethyl Carbamate (b) (4)

Ethyl carbamate is listed by the FDA as an HPHC. Ethyl carbamate can be formed in comparator product General Snus. General Snus has an internal limit of ethyl carbamate of (b) (4) ng/g.

ZYN production is based on highly purified components. The ethyl carbamate level in ZYN products has been found to be consistently below the LOQ ((b) (4) ng/g). On the basis of the consistent absence of quantifiable contents of ethyl carbamate, it is justified to not include this test in the ZYN product release or shelf life specifications. Swedish Match does not propose to perform ethyl carbamate testing on an ongoing basis.

Potential Byproduct (ZYN Manufacture)	Unit	Internal Limit for ZYN	Internal Limit for General Snus
Ethyl carbamate	ng/g	(b) (4)	

LOQ=limit of quantification.

2.2.3 Acrylamide (b) (4)

Acrylamide is listed by the FDA as an HPHC. Acrylamide can be formed in the heat treatment/pasteurization process in the manufacturing of the comparator product General Snus. The comparator product General Snus has an internal limit of acrylamide of (b) (4) ng/g on a dry weight basis.

ZYN is produced (b) (4), and it is therefore deemed highly unlikely that acrylamide may ever be formed in the production. The acrylamide content of ZYN has been found to be consistently below the LOQ ((b) (4) ng/g), and it is therefore justified to not include this test in the ZYN product release or shelf life specifications. Swedish Match does not propose to perform acrylamide testing on an ongoing basis.

Potential Byproduct (ZYN Manufacture)	Unit	Internal Limit for ZYN	Internal Limit for General Snus
Acrylamide	ng/g	(b) (4)	

LOQ=limit of quantification.

2.2.4 Radioisotopes (QEMS-7-7898/External Labstat)

The radioisotopes, polonium 210, uranium 235 and uranium 238, are listed by the FDA as HPHCs. These three radioisotopes have been quantified in ZYN products, and the levels were found to be below the LOQ, except for polonium 210 where a few results just above the LOQ have been obtained.

The absorbed radiation dose for a regular ZYN user is insignificant compared to the natural background radiation. The levels consistently below, or occasionally just above, the LOQ, justify that radioisotope testing is not included in the ZYN product release or shelf life specifications. Swedish Match does not propose to perform radioisotope testing on an ongoing basis.

Radioisotope	Unit	Internal Limit for ZYN	Internal Limit for General Snus
Polonium 210	Bq/kg	(b) (4)	
Uranium 235	Bq/kg		
Uranium 238	Bq/kg		

Bq=Becquerel; LOQ=limit of quantification.

2.2.5 Maximum Level of Agrochemicals (b) (4)

The comparator product General Snus is characterized by defined limits for agrochemical residues based on CORESTA Guide No. 1 – The Concept and Implementation of CPA Guidance Residue Levels (GRL); November 2019. However, the ZYN product is made (b) (4) Swedish Match GRLs are equal to or lower than any current regulatory limits. No traces (below LOQ) of the 365 agrochemicals mentioned above were found analyzing the nicotine source (nicotine bitartrate dihydrate) for residual agrochemicals. ZYN does not contain tobacco or any other raw material that may reasonably contain agrochemicals. For this reason, agrochemical testing is not part of the ZYN product release or shelf life specifications. Swedish Match does not propose to perform agrochemical testing on an ongoing basis.

2.2.6 (b) (4) and (b) (4) (b) (4)

(b) (4) and (b) (4) are not listed by the FDA as HPHCs. (b) (4) and (b) (4) in the oral cavity, may cause tooth decay as a result of acid formation in the metabolism by bacteria. An alkaline pH regulator is included in the composition of the ZYN product, and the buffering activity of nicotine itself limits acid formation, but it is nevertheless desirable to minimize the content of (b) (4) and (b) (4) for oral nicotine products such as ZYN.

The content of (b) (4) in ZYN products has consistently been found to be less than (b) (4) The sum of (b) (4) and (b) (4) has been found to be less than (b) (4) (LOQ). A separate study has shown that consumption of ZYN does not reduce tooth plaque pH. It can be concluded that ZYN has no discernable impact on tooth decay. For these reasons, the proposed internal limits are considered justified, and it is also justified to not include these tests in the release or shelf life specifications. Swedish Match does not propose to perform this testing on an ongoing basis.

	Unit	Internal Limit
(b) (4)	(b) (4)	

LOQ=limit of quantification.

2.3 ZYN Component Parameter Characterization

2.3.1 Particle Size Distribution (b) (4)

The particle size distribution pertains to the ZYN powder/granulate contained inside the pouches, and is considered a parameter of the powder component, rather than a parameter of the product as such. Testing has shown highly consistent mass distributions of particle sizes, and it is therefore justified to not include these parameters in the release or shelf life specifications. The continued consistency of particle size distribution will be verified once every year for each of the SKUs in production. There are no external limits for particle size distribution, and consequently, the analysis will be performed for monitoring purposes. Should any unexpected values be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Particle Size Mass Distribution	Unit	Internal Target	Internal Limits
(b) (4)	µm	(b) (4)	
	µm		
	µm		

2.3.2 ZYN Powder Density

The powder density pertains to the ZYN powder/granulate contained inside the pouches, and is considered a parameter of the powder component, rather than a parameter of the product as such.

On the basis of the results from powder density testing was performed during ZYN product characterization, it is considered justified to not include this parameter in the release specification. Swedish Match does not propose to perform powder density testing on an ongoing basis.

ZYN powder density	Internal Target	Internal Limits
Powder Density (g/mL)	(b) (4)	

(b) (4) .

2.3.3 Pouch Wrapping Material

ZYN powder is wrapped in an enclosing material, sometimes called pouch paper, to make individual pouches for consumption by the consumer. The pouch paper consists of (b) (4) (b) (4) and (b) (4)

Swedish Match requires that pouch paper suppliers certify that paper and all in-going components conform to relevant EU and FDA regulations. The vendor tests thickness and basis weight. Swedish

Match will test thickness, basis weight and air permeability on an annual basis. There are no external limits for the pouch paper parameters, and consequently, analyses will be performed for monitoring purposes. Should any unexpected values be observed, an investigative process will be initiated to identify the root cause with the objective of defining corrective actions.

Parameter	(b) (4)	Unit	Internal Target	Internal Limits
Thickness	(b) (4)			
Basis weight				
Air permeability				

(b) (4) .

3 Justification of Product Specifications

3.1 Tests Included in Both Release and Shelf Life Specifications

3.1.1 Nicotine (b) (4)

Based on the observed manufacturing variability together with stability studies, Swedish Match has defined acceptance for nicotine at release and at the end of the shelf life. The allowed deviation from the target content amounts to (b) (4) during the shelf life. Experience has shown that consumers cannot detect variations in nicotine content within these ranges, and thus these shelf life acceptance criteria are considered justified. The release criteria, amounting to a deviation by (b) (4), are justified on the basis of observed manufacturing variability together with stability data. It is considered justified to include nicotine content in the release and shelf life specifications.

ZYN products	Unit	Target	Acceptance Criteria	
			Release	Shelf Life
ZYN 3 mg/pouch	mg/g as is	(b) (4)		
ZYN 6 mg/pouch	mg/g as is			

3.1.2 pH (b) (4)

The lower release acceptance criterion for pH, (b) (4), is justified based on observed manufacturing variability, and the lower shelf life criterion, (b) (4) is lower by an amount that is justified based on the observed variation in pH during stability testing. (b) (4) Experience has shown that consumers cannot detect variation in pH within these ranges. The ZYN product pH specification range falls completely within the manufacturing and consumer satisfaction experience for the comparator General Snus products.

The upper acceptance criterion for product release, (b) (4) has been tightened relative to the shelf life criterion, based on the observed change during stability studies. Observed manufacturing variability further supports the upper release criterion.

ZYN products	Target	Acceptance Critera	
		Release	Shelf Life
pH	(b) (4)		

3.1.3 Product Moisture (b) (4)

The release and shelf life acceptance criteria for moisture content, (b) (4) %, are considered justified based on experience from the development of the product which shows that product stability is adversely affected by higher moisture contents. On the basis of the very small observed manufacturing variability with respect to moisture content, it is possible that the inclusion of this parameter in the release specification is not justified, and the inclusion is therefore subject to upcoming investigation.

ZYN products	Unit	Target	Acceptance Criteria	
			Release	Shelf Life
Moisture Content	% as is	(b) (4)		

3.2 Tests Included Only in the Release Specification

3.2.1 Can Content Weight

The can content weight release acceptance criteria, (b) (4) g, correspond to a deviation by 10% from the target value (b) (4) g) and is considered justified based on manufacturing experience. (b) (4)) (4) It is considered justified to not include this parameter in the shelf life specification.

ZYN Products	Unit	Target	Release Acceptance Criteria
Net Content	g/can	(b) (4)	

3.2.2 Pouch Weight (b) (4)

The pouch weight release acceptance criteria, (b) (4) g, correspond to a deviation by 10% from the target value (b) (4) g) and is considered justified based on manufacturing experience. It is considered justified to not include this parameter in the shelf life specification.

ZYN products	Unit	Target	Release Acceptance Criteria
Pouch Weight	g/pouch	(b) (4)	

3.3 Tests Included Only in the Shelf Life Specification

3.3.1 NNN+NNK and Total TSNA (b) (4)

Testing of TSNAs during stability studies are required by the PMTA proposed rule, and results should be reported as separate amounts for Total TSNAs, NNN and NNK. Based on the absence of detectable amounts of TSNAs in ZYN, the shelf-life acceptance criteria, ≤LOQ, are justified.

TSNA	Unit	Shelf Life Acceptance Criterion
NNN+NNK	µg/g	(b) (4)
Total TSNA	µg/g	

LOQ=limit of quantification; NNK=nicotine-derived nitrosamine ketone; NNN=N-nitrosonornicotine; TSNA=tobacco-specific nitrosamine.

3.3.2 Nitrite and Nitrate (b) (4)

Testing of nitrate and nitrite during stability studies are required by the PMTA proposed rule. Based on the absence of Nitrate in the product, the acceptance criterion for Nitrate, (b) (4)% (LOQ), is justified. (b) (4) Nitrate have been observed during stability studies, and therefore an acceptance criterion o(b) (4) µg/g is considered justified.

Nitrate and Nitrite	Unit	Shelf Life Acceptance Criterion
Nitrate	%	(b) (4)
Nitrite	µg/g	

LOQ=limit of quantification.

3.3.3 TAMC (b) (4) and TYMC (b) (4)

Testing of microbial content (including TAMC and TYMC) during stability studies are required by the PMTA proposed rule. Based on existing stability study data, and in comparison to the internal limit for snus, (b)(4) lgcfu/g as is, the acceptance criteria for these parameters, (b)(4) lgcfu/g as is, is considered justified.

Microbial Content	Unit	Shelf Life Acceptance Criterion
TAMC	lgcfu/g	(b) (4)
TYMC	lgcfu/g	

lgcfu/g=$\log_{10}$ colony forming units per gram; TAMC=total aerobic microbial count; TYMC=total yeast and mold count.

3.3.4 Nicotine Related Compounds (b) (4)

The shelf life acceptance criteria for related compounds are identical to the criteria in the USP monograph for nicotine, and are therefore considered justified.

Nicotine Related Compound	Unit	Shelf Life Acceptance Criterion
(b) (4)		

3.3.5 Aldehydes (b) (4)

To characterize any potential changes in formaldehyde or acetaldehyde contents during storage, it is justified to test the contents of these aldehydes in the first three stability studies for each SKU. On the basis of the results from the first three stability studies for each SKU, it will be evaluated whether it is justified to include testing of formaldehyde and acetaldehyde in the subsequent stability studies. The shelf-life acceptance criteria for Acetaldehyde, (b) (4) µg/g, and Formaldehyde, (b) (4) µg/g, are justified based on product characterization data and stability study data.

Aldehyde	Unit	Shelf Life Acceptance Criterion
Acetaldehyde	µg/g	(b) (4)
Formaldehyde	µg/g	