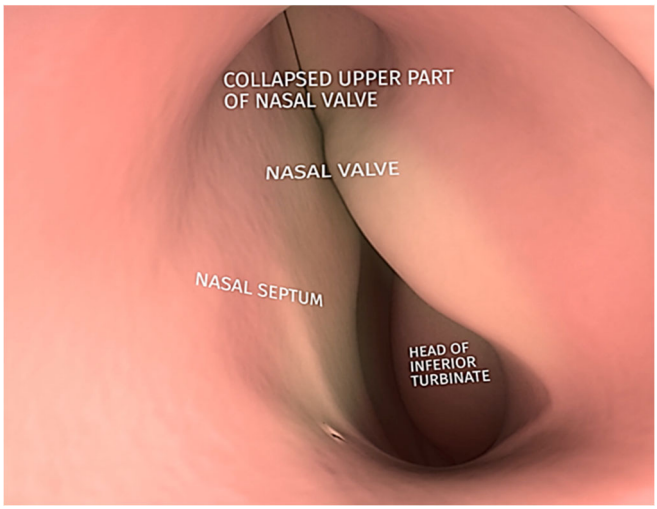
(1) Anatomy of the nasal cavity

The nose is divided by a midline septum from the anterior towards the posterior into two convoluted nasal passages that are joined into a common pathway behind the most posterior part of the septum in the nasopharynx. Each cavity starts with the vestibule just inside the nostrils where it is lined with non-ciliated squamous epithelium. The vestibule is supported by cartilage and transitions into a narrow anterior triangular dynamic segment of the nasal anatomy called the nasal valve. The nasal valve region includes the narrowest opening segment of the nose, and of the entire respiratory tract, and therefore is a primary flow-limiting segment of the nasal cavity.[36] It is not a vertically oriented structure, but "tipped forward" and includes a region that extends posteriorly to approximately the head of the inferior turbinate, about 2–3 cm from the nostril opening.[37] This slender, roughly triangular-shaped slit is much narrower at its upper part and acts as a dynamic valve to modify the rate and direction of airflow during respiration. Figure 4 below illustrates the nasal cavity, viewing the nasal valve from the nasal vestibule.

Figure 4[38]



The mucosal lining of the nasal cavity is not uniform in type or function. The squamous mucosal lining of the nasal valve region gradually transitions from columnar epithelium to ciliated respiratory epithelium.[39] The region lined with respiratory epithelium usually contains three nasal turbinates—the superior, the middle and the inferior—which project from the lateral wall of each half of the nasal cavity, and other complex structures such as the uncinate process, although there can be substantial person-to-person anatomic variation, including, for example,

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[36] L. Illum . Nasal Drug Delivery—Possibilities, Problems and Solutions. J Control Release. 2003 Feb. 21; 87(1–3):187–198 (attached hereto as Exhibit 22).

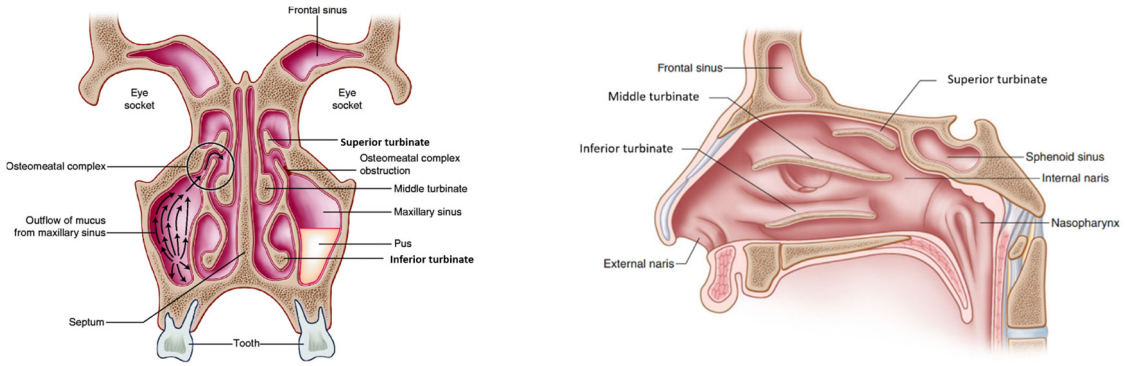
[37] P. Cole . The Four Components of the Nasal Valve. Am. J. Rhinol. 2003 Mar,–Apr.; 17(2):107–110 (attached hereto as Exhibit 23).

[38] Reprinted with permission from MediVisual (www.medivisual.com).

[39] A. Sahin-Yilmaz and R.M. Naclerio. Anatomy and Physiology of the Upper Airway. Proc. Am. Thorac. Soc. 2011 Mar.; 8(1):31–39 (attached hereto as Exhibit 24).

a fourth or "supreme" turbinate. The middle meatus, above the inferior turbinate and behind/lateral to the middle turbinate, is the area of the nose where the maxillary, frontal and anterior ethmoid sinuses drain and ventilate. In addition, this region is also where nasal polyps typically originate, as discussed below.[40] The ciliated respiratory mucosa is covered by a protective mucus blanket designed to trap particles and microorganisms[41] which is cleared via the beating action of cilia towards the nasopharynx.[42] The density and functional orientation of ciliated epithelium cells in different regions of the nasal cavity varies greatly, influencing the clearance rate and direction and the pathway of mucus clearance in different sub regions.[43] Figure 5 below illustrates coronal and sagittal sections through the nasal cavity.

Figure 5[44]



The distribution, density, and functional orientation of ciliated cells and non-ciliated cells, including goblet cells, in the nasal cavity and sinuses affect the mucus layer and mucociliary clearance rate, as well as the direction and patterns for particles/drugs deposited to different regions. Additionally, the chronic inflammatory disease process has a non-uniform influence on mucociliary activity (by anatomic location and by stage of disease).[45] Further, the distribution of goblet cells producing the mucus layer also has an important impact on the rate

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[40] P.L. Larsen, M. Tos. Origin of Nasal Polyps: An Endoscopic Autopsy Study. Laryngoscope. 2004 Apr.; 114(4):710–719 (attached hereto as Exhibit 25).

[41] D.F. Proctor. The Mucociliary System. *In*: Proctor DF, Andersen IB, eds. The Nose: Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical. 1982. p. 245–278 (attached hereto as Exhibit 26); A.R. Halama, S. Decreton, J.M. Bijloos et al. Density of Epithelial cells in the Normal Human Nose. A Scanning Electron Microscopic Study. Rhinology. 1990; 28(1):25–32 (attached hereto as Exhibit 27).

[42] Sahin-Yilmaz, *supra* note 39 (Exhibit 24).

[43] Halama 1990, *supra* note 41 (Exhibit 27); N. Mygind and R. Dahl. Anatomy, Physiology and Function of the Nasal Cavities in Health and Disease. Adv. Drug Deliv. Rev. 1998 Jan. 5; 29(1–2):3–12 (attached hereto as Exhibit 28); N. Jones. The Nose and Paranasal Sinuses Physiology and Anatomy. Adv. Drug Deliv. Rev. 2001 Sep. 23; 51(1–3): 5–19 (attached hereto as Exhibit 29).

[44] A.J. Sim , A.I. Levine, S. Govindaraj. Functional Nasal and Sinus Surgery. In: A.Levine, S. Govindaraj, Jr. S. DeMaria (eds). Anesthesiology and Otolaryngology. Springer, New York, NY. https://doi.org/10.1007/978-1-4614-4184-7_13; Chapter 13 (2013) (attached hereto as Exhibit 30).

[45] Mygind 1998, *supra* note 43 (Exhibit 28).

of dissolution, concentration, and clearance of drugs deposited, and also is greatly influenced by both anatomic location and the nasal polyp disease process. Available human data on these properties is very limited and largely includes information published in a 1990 study by Halama.[46] Authors attempting *in vitro* modeling of drug delivery into the nasal cavity to date have been forced to make unrealistic simplifying assumptions or have ignored these effects entirely, as discussed below in section B.III.A.3.c.[47]

(2) Complexity and dynamics of the nasal cavity

The nose and structures in the nasal cavity, as illustrated in Figure 5 above, are highly complex and dynamic. They may change in response to physiological, physical, endocrine, and emotional input. For example, the dimensions of the nasal cavity—in particular, the pliable segments at and beyond the valve region—dynamically expand and contract with airflow direction and the associated changes in pressure. The nasal valve, especially its upper narrow segment, is particularly susceptible to this effect. During inhalation, Bernoulli forces narrow the valve progressively with increasing inspiratory flow rate and may even cause partial or complete collapse with vigorous sniffing.[48] During exhalation, the valve acts as a "brake" to maintain a positive expiratory airway pressure that helps keep the pharyngeal and lower airways open and optimized gas exchange in the lungs.[49]

The complexity and dynamics of the nasal cavity make effective delivery of medication and assessment of nasal deposition patterns challenging. The nasal valve, for example, is a significant barrier to drug particles that are released anterior to the nasal valve.[50] The complex slender anatomy beyond the nasal valve also limits the amount of drug that can reach superior and posterior areas that may be remote and secluded but critical to efficacy in the treatment of nasal polyp disease, such as the olfactory epithelium (e.g., olfactory cleft) and middle meatus where the sinuses ventilate and drain and where nasal polyps typically originate. In addition, differences in the amount of drug that reaches these areas also can produce a different safety and adverse event profile due to regional differences in potential exposure to important structures such as the eye and cranial nerves. Actions such as sniffing at delivery, often performed by either instruction or spontaneously due to a wet sensation in the nasal vestibule, may further narrow the nasal valve, additionally limiting posterior deposition. Moreover, sniffing also draws the drug being administered along a pathway that is mostly along the floor of

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[46] Halama 1990, *supra* note 41 (Exhibit 27).

[47] S. Chari, K. Sridhar, R. Walenga. Computational Analysis of a 3D Mucociliary Clearance Model Predicting Nasal Drug Uptake. J. Aerosol. Sci. 2021 June; 155:105757 (attached hereto as Exhibit 31).

[48] P. Cole. Nasal and Oral Airflow Resistors. Site, Function, and Assessment. Arch. Otolaryngol. Head Neck Surg. 1992 Aug.; 118(8):790–793 (attached hereto as Exhibit 32).

[49] P.G. Djupesland, O. Skatvedt, A.K. Brogersen. Dichotomous Physiological Effects of Nocturnal External Nasal Dilation in Heavy Snorers: The Answer to a Rhinological Controversy? Am. J. Rhinol. Mar.–Apr. 2001; 15(2):95–103 (attached hereto as Exhibit 33); W.M. Hairfield, D.W. Warren, V.A. Hinton et al. Inspiratory and Expiratory Effects of Nasal Breathing. Cleft Palate J. 1987 July; 24(3):183–189 (attached hereto as Exhibit 34).

[50] Cole 1992, *supra* note 48 (Exhibit 32); R. Fodil, L. Brugel-Ribere, C. Croce et al. Inspiratory Flow in the Nose: A Model Coupling Flow and Vasoerectile Tissue Distensibility. J. Appl. Physiol. 2005 Jan.; 98(1):288–295 (attached hereto as Exhibit 35).

the nose (under the inferior turbinate) directly toward the oral cavity and away from sites more superiorly located that are targeted with nasal delivery in the treatment of nasal polyp disease.

(3) Variability of the nasal cavity and relevant adjacent structures

Further, the anatomy of the nasal cavity and mid-facial morphology is highly variable depending on race, ethnicity, and other factors in ways that interact with the structure and function of an exhalation delivery system. The XHANCE EDS was designed to provide effective delivery of fluticasone propionate across a range of anatomies.

First, nasal cavities are complex anatomical structures characterized by high inter-patient variability.[51] Anatomical variants of the nasal cavity, including the septum and middle turbinate, also play a role in the pathogenesis of inflammatory processes of the nasal cavity and paranasal sinuses and are more common in chronic rhinosinusitis. This type of variation has clear potential to interact with the nosepiece, airflow characteristics, and user behaviors with an exhalation delivery system, in ways that influence drug deposition in regions of interest for the treatment of nasal polyps. Further, external mid-facial morphology also exhibits an "exceptionally high level of between and within-group variation" across ethnic populations and will differently influence fit and function of exhalation delivery systems because they interact with both the nares and the mouth.[52]

Multiple studies have evaluated nasal variation in various populations, with the most commonly studied population being patients presenting to an ear, nose, and throat ("ENT") clinic, which is more representative of the population of interest suffering nasal polyp disease. Rates of anatomic abnormality are higher in the population of interest with chronic rhinosinusitis. The types and frequency of multiple relevant anatomic variations have been reported, with the most common being deviated nasal septum (up to 83% prevalence), various types of concha bullosa (lamellar, bulbous, or extensive types; collectively up to 55%), pneumatized pterygoid base (up to 73%), Haller cells, and other pneumatized bony structures.[53]

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[51] M. Cellina, D. Gibelli, A. Cappella et al. Nasal Cavities and the Nasal Septum: Anatomical Variants and Assessment of Features with Computed Tomography. Neuroradiol J. 2020 Aug.; 33(4) 340–347 (attached hereto as Exhibit 36).

[52] A. A. Evteev, A N. Grosheva. Nasal Vity and Maxillary Sinuses form Variation Among Modern Humans of Asian Descent. Am. J. Phys. Anthropol. 2019; 169:513–525 (attached hereto as Exhibit 37).

[53] Cellina 2020, *supra* note 51, (Exhibit 36); K. Devaraja, S.M. Doreswamy, K. Pujary. Anatomical Variations of the Nose and Paranasal Sinuses: A Computed Tomographic Study. Indian J. Otolaryngol Head Neck Surg. 2019 Nov. ; 71(Suppl 3):2231–2240 (attached hereto as Exhibit 38); K.M. Ozcan, A. Selcuk, O. Ozcan et al. Anatomical Variations of Nasal Turbinates. J. Craniofac Surg. 2008 Nov.; 19(6):1678–1682 (attached hereto as Exhibit 39); H.K.K. Tan, Y.K. Ong. Sphenoid Sinus: An Anatomic and Endoscopic Study in Asian Cadavers. Clin. Anat. 2007 Oct.; 20(7):745–750 (attached hereto as Exhibit 40); Y. Lu, J. Pan, S. Qi S et al. Pneumatization of the Sphenoid Sinus in Chinese: The Differences from Caucasian and its Application in the Extended Transsphenoidal Approach. J. Anat. 2011 Aug.; 219(2):132–142 (attached hereto as Exhibit 41); C.M. Özer, K. Atalar, I.I. Öz et al. Sphenoid Sinus in Relation to Age, Gender, and Cephalometric Indices. J. Craniofac Surg. 2018 Nov.; 29(8):2319–2326 (attached hereto as Exhibit 42); S. Tomovic, A. Esmaeili, N.J. Chan et al. High-Resolution Computed Tomography Analysis of the Prevalence of Onodi. Cells. Laryngoscope. 2012 July; 122(7):1470–1473 (attached hereto as Exhibit 43); M.A. Muñoz-Leija, M. Yamamoto-Ramos , F.J. Barrera-Flores et al.

These variations can severely distort the nasal anatomy. Other potentially important anatomic variants, including a 4th turbinate (the supreme turbinate or Santorini's concha), also occur.

Second, this "static" variation is further compounded by "dynamic" variation noted above. In addition to changes due to Bernoulli forces, dynamic variation is due to physiologic variability in the epithelium lining intranasal structures, which is dense with vascular capillaries and venus sinusoid structures that constantly swell and shrink in response to external conditions and endogenous stimuli, under the control of the sympathetic nervous system, in a process called the "nasal cycle" which causes dynamic congestion and decongestion of intranasal spaces.[54] Variable swelling of turbinate tissues due to factors such as inflammation, allergy, or environmental pollution can result in partial or complete blockage of the channel-like meatuses. Hormonal changes (pregnancy, premenstrual stage) can also determine prolonged or transitory turbinate congestion, further suggesting the need for both gender and age-specific modeling—in addition to modeling of the other sources of variation described—in order to understand population effects when attempting to simulate *in vivo* anatomy with *in vitro* simulations.

Third, race and ethnicity also are recognized as an important source of variation in not only the internal nasal cavity anatomy, but also in mid-facial morphology and anthropometrics of regions that directly interact with an exhalation delivery system (e.g., teeth/upper lip distance from nares), indicating that assessment of performance in a limited racial/ethnic population introduces significant risk of failure to indicate performance in a broader population even if intranasal cavity variation were to somehow be fully accounted for. "Systematic nasofacial analysis" is considered the standard of care by nasal surgeons contemplating rhinoplasty, and large differences are apparent in frontal, lateral, and basal views of regions that interact directly with an exhalation delivery system.[55] Some examples of this include the shape, size, and direction of the opening formed by the ala into which the nosepiece is inserted (which can vary dramatically from antero-posterior oriented to laterally-oriented, with short or long columella and different columella/lobule ratios) and the nasolabial angle (which can vary from acute to obtuse and, in conjunction with lip and front teeth, can influence the distance and angle between lips and nose and change spray angle and direction). Substantiating this recognized population variation, and as reflected in the design history file, the human factors studies conducted during design of the specific nosepiece and translating mouthpiece of the XHANCE EDS also identified a substantial anthropometric range of mid-facial structures that resulted in different interactions with differently designed devices.

Anatomical Variations of the Ethmoidal Roof: Differences Between Men and Women. Eur. Arch. Otorhinolaryngol. 2018 July; 275(7):1831–1836 (attached hereto as Exhibit 44); L. Badia, V.J. Lund, W. Wei et al. Ethnic Variation in Sinonasal Anatomy on CT-Scanning. Rhinology. 2005 Sept.; 43(3):210–214 (attached hereto as Exhibit 45); S.B. Hiremath, A.A. Gautam, K. Sheeja et al. Assessment of Variations in Sphenoid Sinus Pneumatization in Indian Population: A Multidetector Computed Tomography Study. Indian J. Radiol. Imaging. 2018 July–Sept.; 28(3):273–279 (attached hereto as Exhibit 46); V. Burulday, N.B. Muluk, M.H. Akgület al. Presence and Types of Anterior Clinoid Process Pneumatization, Evaluated by Multidetector Computerized Tomography. Clin. Invest. Med. 2016 June; 39(3):E105–110 (attached hereto as Exhibit 47).

[54] Cellina 2020, *supra* note 51 (Exhibit 36).

[55] N.L. Villanueva , P.N. Afrooz, J.A. Carboy. Nasal Analysis: Considerations for Ethnic Variation. Plast. Reconstr. Surg. 2019 June; 143(6):1179e–1188e (attached hereto as Exhibit 48).

The static and dynamic variation in anatomy can interact with the specific pressure and airflow produced by an exhalation delivery system in ways that are potentially sensitive to even millimeter variation in initial conditions (for example, angle of delivery resulting from position, or degree of nasal valve stenting in the most superior aspect versus inferior aspect).

In summary, anatomical characteristics, including anthropometrics, of the nose, mid-face, nasal cavity, and paranasal sinuses exhibit considerable variation, and many of these variations depend on age, gender, geography, race, and ethnicity.[56] This is further complicated by a high degree of additional variation due to the indicated disease process (nasal polyps) which is known to further alter static and dynamic anatomy and physiology due to both the effects of inflammation (e.g., swelling, impairment of mucociliary motility, epithelial barrier dysfunction) and the polyp structures themselves. These patient-based sources of variation interact directly and/or functionally with an exhalation delivery system device, introducing the risk that non-identical devices may produce materially different drug deposition that is difficult to predict *in vitro*. *In vitro* to *in vivo* correlation models for exhalation delivery system devices have not been established and are difficult to develop for the reasons further articulated below; however, even if they should become possible in the future, a failure to assess a suitable range of variation in anatomy due to within-population intranasal anatomic variants, and of a suitable range of racial and ethnic variants in anthropometrics of the midface, would restrict the generalizability of any conclusions of comparability. Failure to assess a suitable range of disease-related variation would have a similar consequence. A non-inferiority assessment of clinical safety and efficacy outcomes is necessary, as discussed below, because for this topically acting product, the distinct profile of deposition and local absorption is equally or more important than simply the amount of drug delivered or systemically absorbed and cannot be predicted in non-generalizable *in vitro* models.

b) Nasal polyps are variable and arise in the upper parts of the nasal cavity, typically in the region of the middle meatus or superior turbinate as well as inside the sinuses, and not on or below the inferior turbinate.

Nasal polyps are benign lesions that arise from chronically inflamed tissue within the nasal cavity and are associated with nasal congestion, rhinorrhea, facial pain and pressure, loss of sense of smell, halitosis, fatigue, impaired sleep, and frequent episodes of acute sinusitis. These symptoms, among others, contribute to serious morbidity as measured by impairment of quality of life. The harm to quality of life has been found to be on a par with that associated with other serious chronic diseases such as chronic obstructive pulmonary disease ("COPD"), chronic angina, and congestive heart failure ("CHF").[57]

Nasal polyps typically arise from the region of the middle meatus but also can be found higher up on the superior turbinate or on the posterior septum. Nasal polyps also can form on inflamed mucosa within the paranasal sinuses (typically the ethmoid cells or maxillary sinus). This polypoid tissue eventually can reach into the nasal cavity via the ostia in the unoperated

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[56] Devaraja 2019, *supra* note 53 (Exhibit 38); Tan 2007, *supra* note 53 (Exhibit 40); Lu 2011, *supra* note 53 (Exhibit 41); Özer 2018, *supra* note 53 (Exhibit 42); Tomovic 2012, *supra* note 53 (Exhibit 43); Muñoz-Leija, *supra* note 53 (Exhibit 44); Badia 2005, *supra* note 53 (Exhibit 45); Hiremath 2018, *supra* note 53 (Exhibit 46); Burulday 2016, *supra* note 53 (Exhibit 47); Evteev 2019, *supra* note 52 (Exhibit 37).

[57] Z.M. Soler, E. Wittenberg, R. J. Schlosser et al. Health State Utility Values in Patients Undergoing Endoscopic Sinus Surgery. Laryngoscope. 2011 Dec.; 121(12):2672–2678 (attached hereto as Exhibit 49).

patient or through a surgically created antrostomy. Nasal polyps do not form on the more inferior structures within the nasal cavity, such as the inferior turbinate or floor of the nasal cavity. Polyps may be mobile (stalked), in which case they can move with respiration, or comparatively immobile and be in the form of bulk tissue extending from the lining of the mucosal surface. They almost always present bilaterally and often are quite different in conformation (shape/size) on each side of the nose. Left untreated, nasal polyps typically will expand, filling up the spaces within the nasal cavity, inhibiting airflow, and contributing to the symptoms of congestion and hyposmia commonly reported by patients suffering from this condition. As polyps continue to expand, they will extend inferiorly and even can reach beyond the nares if left untreated.[58]

Although nasal polyps originate from chronically inflamed tissue, they also exacerbate the inflammation within the nasal cavity. Nasal polyps release large amounts of IL-5, which is a cytokine known to attract eosinophiles that degranulate within the nasal cavity, exacerbating the inflammatory burden and further worsening the associated swelling that is typical of this disease. They also are associated with increased tissue IL-4, IL-13, *S. Aureus* enterotoxin (superantigens), and other inflammatory mediators, which may help explain why patients with nasal polyps are known to suffer from "epithelial barrier dysfunction" (including loss of tight junction functioning) which has obvious potential to alter drug tissue penetration in specific segments of the nasal cavity that are so affected. Patients with nasal polyps also tend to have impaired ciliary clearance. The degree and specific anatomic locations of this impairment can be quite variable and highly influenced by the severity of inflammation and, therefore, should be assumed to be inconsistent in different regions of the nasal cavity. Moreover, this impairment is thought to be reversible with effective treatment, introducing an additional variable in modeling mucociliary clearance that depends on treatment effects and disease progression; the rate and degree of improvement varies substantially.[59]

Patients with nasal polyps often undergo sinus surgery, and a large fraction of patients who are candidates for nasal medication for nasal polyps have undergone prior sinus surgery (approximately 30% in one XHANCE pivotal trial and 60% in the other pivotal trial).[60] Endoscopic sinus surgery ("ESS") is not standardized, and multiple variations in the magnitude of surgical intervention are common. Typically, ESS involves removal of tissue (for example, nasal structures such as the uncinate process and/or middle turbinates), and the creation of variably-sized antrostomies between some or all of the paranasal sinuses and nasal cavity, greatly increasing variability of nasal geometry. This additional "surgically induced" anatomic variation in polyp patients can influence airflow, pressure, site of polyp recurrence, and other factors material to prediction of deposition, safety, and efficacy associated with exhalation delivery system delivery.

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[58] W. W. Stevens, R. P. Schleimer, R.C. Kern. Chronic Rhinosinusitis with Nasal Polyps. J. Allergy Clin. Immunol. Pract. 2016; 4(4): 565–572 (attached hereto as Exhibit 50).

[59] K. E. Hulse, W. W. Stevens, B. K. Tan. Pathogenesis of Nasal Polyposis. Clin. Exp. Allergy. 2015 Feb.; 45(2): 328–346 (attached hereto as Exhibit 51).

[60] D.A. Leopold, D. Elkayam, J.C. Messina, et al. NAVIGATE II: Randomized, Double-Blind Trial of the Exhalation Delivery System with Fluticasone for Nasal Polyposis. J Allergy Clin. Immunol. 2019 Jan.; 143(1):126–134.e5 (attached hereto as Exhibit 52); R. Sindwani, J.K. Han, D.F. Soteres et al. NAVIGATE I: Randomized, Placebo-Controlled, Double-Blind Trial of the Exhalation Delivery System With Fluticasone for Chronic Rhinosinusitis With Nasal Polyps. Am. J. Rhinol. Allergy. 2019 Jan.; 33(1):69–82 (attached hereto as Exhibit 53).

Because fluticasone propionate is a topically acting medication, deposition on the nasal polyps themselves is required for them to be reduced, and the magnitude of polyp reduction will be dependent upon the amount of steroid that can reach the tissue, the polyp tissue surface area that is coated, and the amount of drug that continues to reach the tissue as it shrinks. The same is true for mucosal tissues swollen due to inflammation related to the underlying nasal polyp disease process.

c) The XHANCE EDS is designed to deliver the fluticasone propionate suspension to the most superior and posterior regions of the nose.

The XHANCE EDS is specifically designed to deposit drug aerosol on structures and tissues that are in more superior and more posterior obstructed spaces in the nasal cavity (e.g., olfactory region, middle meatus, osteomeatal complex, ethmoid sinus cavity). Through the XHANCE EDS, the product produces a different distribution of intranasal drug deposition than a conventional nasal spray and disproportionately places topically acting steroid in the region of the nasal cavity where nasal polyps typically originate and where paranasal sinuses ventilate and drain. In addition, the XHANCE EDS has been shown to deposit drug inside sinus cavities that have been surgically opened to the nasal cavity, which is often the case in the context of patients with nasal polyp disease[61].

The XHANCE EDS achieves this particular deposition pattern through known and unknown factors sensitively related to critical device components and also to dynamic interactions with patients' variable anatomy and physiology. The critical components and dimensions of the device constituent of XHANCE include not only those for a conventional nasal spray, such as spray pump and applicator, but also include the device subassembly and its components that affect the mechanics of the overall performance of the device, including the nosepiece, mouthpiece, geometry between the nosepiece and mouthpiece, T-valve, grip, and others.

Specifically, the XHANCE EDS contains a spray pump that produces a metered dose of medication that is synchronized to be released with the "burst" of exhaled breath when actuated. The XHANCE EDS also interfaces with both the external nares and nasal valve and the mouth and serves as conduit for the exhaled breath and the associated pressure to move from the user's mouth into the nose in a way that allows for the aerosol droplets to be entrained into the airflow. Lastly, the asymmetrical nosepiece of the XHANCE EDS seals at the nostril to allow transfer of a balancing, or proportional, amount of pressure into the nose from the oral cavity (to control the degree of soft palate elevation), stents the narrow nasal valve (especially superiorly), and displaces soft tissue without obstructing drug exit from the device, all facilitating deposition of a larger proportion of medication both beyond the nasal valve and above the inferior turbinate (i.e., superiorly and posteriorly) in order to reach regions of the nose targeted for treatment of nasal polyps.

[61] P. G. Djupesland, J.C. Messina, J.N. Palmer. Deposition of Drugs in the Nose and Sinuses With an Exhalation Delivery System vs Conventional Nasal Spray or High-Volume Irrigation in Draf II/III Post-Surgical Anatomy. Rhinology 2020; 58: 2, 175–183 (attached hereto as Exhibit 54).

d) The design of the XHANCE EDS and the interaction of the device with the patient's anatomy and physiology are central to the clinical effect of the drug product.

The design of the XHANCE device and the interaction of the device with the patient's anatomy and physiology are central to the product's drug deposition, and, accordingly, XHANCE's clinical effects.

First, the XHANCE EDS creates an airflow that has a key impact on the deposition of drug within the nose. The XHANCE EDS releases the user's breath as the bottle is depressed and simultaneously opens the internal valve inside the device to create an abrupt "burst of air" synchronized with the release of the spray. The device has important design aspects that influence the flow of the air into the nose. For example, the XHANCE EDS can prevent "leakage" of air, and associated pressure, as the breath travels through. This flow efficiency affects both the volume and velocity of the airflow that enters the nose, and varies depending on the exhalation pressure and flow. Additionally, the XHANCE EDS synchronizes the release of the breath with the release of the spray such that the droplets are entrained in airflow at a particular point in time within the variable airflow curve (flow rate by time curve), contributing to the product's unique drug deposition.

For example, at one extreme, if the breath instead were to be released largely after the drug aerosol spray, many of the droplets would be deposited before being entrained in the breath, producing highly altered drug deposition within the nose. Similarly, if the drug aerosol spray were to be released after the peak of the exhaled air "burst," the airflow carrying the droplets would be substantially different purely on the basis of timing. The direction, volume, and velocity of airflow directed into the nasal cavity will change both the initial deposition of the spray and the subsequent movement of initially deposited drug, in part by altering the plume and spray pattern inside the nose and changing droplet size (as airflow causes droplets to impact one another, thereby altering size). As airflow continues beyond the initial deposition of the spray (during both the initial breath and during a subsequent breath when using the 2-spray dose), laminar airflow along mucosal surfaces will continue to move the deposited liquid further back into the nasal cavity for the duration of the exhalation process, typically lasting 2-3 seconds. This effect of moving already deposited drug particles more superiorly and posteriorly is further accentuated when a second dose is administered to the same nostril, a dose that is consistent with currently labeled use of the product. Therefore, the amount of air and the velocity and pressure of the airflow that is passed through the device will have important effects on the deposition of fluticasone suspension at the specific sites of action within the nasal cavity that are relevant for the treatment of nasal polyps.

Airflow and pressure after exiting the device within the nasal cavity also are changed by the resistance of the air circuit. In a nasal geometry congested by anatomic variation, mucosal inflammation, and/or nasal polyps, more of the exhaled force will be transferred to pressure and therefore may change the conformation of the narrow cavity anterior to the obstruction, with a lower flow rate. The expansion and lower flow rate will enhance the drug deposition on the obstructing tissues localized anteriorly. With less mucosal swelling and polyp volume, with variation not only due to intrinsic or disease-related patient differences, but also during treatment due to the effects of the treatment, there may be less resistance, and the flow rate will increase and propel droplets progressively deeper into the nasal cavity. This dynamic interaction between the physiological and pathological status of the sinonasal airway and the deposition is difficult to model across the full range of expected variation in the target population, further calling into question the validity of *in vitro* models that do not account for

this variation for assessing equivalence and highlighting the need for non-inferiority clinical endpoint studies in a suitable target population, as discussed below.

Second, the transfer of the positive pressure associated with the airflow is another important design feature of the XHANCE EDS and impacts drug deposition within the nasal passages and target sites. Per the approved Instructions for Use, the user blows into the device and, while continuing to blow, presses the vial upward.[62] The valve within the XHANCE EDS prevents airflow release through the nosepiece until the valve is opened. This allows pressure to build within the device before actuation. The amount of "leakage" of air through other parts of the device ("flow efficiency") will impact the amount of pressure that will be transferred from the device into the nasal cavity during use. These pre- and post-actuation flow efficiencies will affect the force and associated velocity of the airflow through the nosepiece once actuated, which, as noted above, will influence deposition along with spray pattern, plume geometry, and droplet size within the nasal cavity.

The transfer of the positive pressure also has a dynamic effect on the nasal cavity itself. This positive pressure transfer will cause the soft tissues within the nasal passages to expand in a manner that depends on the magnitude, timing, and direction of the pressure applied. The positive pressure will affect airflow parameters within the entire nasal cavity circuit, thereby affecting drug deposition within the nasal passages and target sites.

This is especially true for the area where the nasal valve is located. The transfer of positive pressure that occurs with the spray release from the nozzle will influence the size and shape of the opening produced in the nasal valve, which is a key factor in determining the amount of drug that reaches targeted parts of the nasal passages. Similarly, if the soft palate is either not sealed, or if the counterbalancing pressures across the soft palate (the oral cavity pressure from below the vellum balanced against the "mid-circuit" pressure in the nasopharynx from above the vellum) produce a different positioning of the soft palate during delivery, then the airflow circuit also will be altered, which will in turn alter airflow, pressures, and deposition. Notably, this is different from the considerations that apply to conventional nasal sprays, which interact differently with the patient and nasal cavity. With conventional nasal sprays, not only is there no transfer of proportional positive pressure to consider, but the opposite: negative pressures associated with "sniffing" a conventional nasal spray can collapse narrow spaces due to Bernoulli's forces. This highlights how dramatic device-related differences can be depending on device design. Even small differences in the device, such as nosepiece stenting design, soft-tissue obstruction of device outflow, and others will have potential to influence drug deposition when deposition is assessed with the anatomic specificity appropriate to nasal polyp disease and to the wide degree of variation in the target population.

Third, the nosepiece of the XHANCE EDS plays an essential role in achieving the product's drug deposition. The nosepiece is designed specifically with a form that achieves a number of functions that influence drug deposition. The specific XHANCE EDS nosepiece is designed to slide into the anterior part of the nose to create a seal with the tissue at its base in a broad range of nasal sizes and shapes and, at the same time, stent open the upper segments of the narrow nasal valve. For airflow and the associated positive pressure to be proportionately transferred into the nasal cavity from the device, the pressure drop across the device must be controlled and, notably, the nosepiece must create a seal with the nostril to prevent air and pressure from escaping retrograde out of the nostril of administration.

[62] XHANCE Instructions for Use (Apr. 2021) (Exhibit 6).

At the same time, it is important that the position and angle of the inserted nosepiece remain stable. For this to be achieved, the user must be able to insert the mouthpiece between the lips while still maintaining a seal around the nostril and a consistent position with the nosepiece ("2-point fixation"). The XHANCE EDS has a flexible mouthpiece that is designed, and has been demonstrated in human factors studies, to accommodate substantial differences in the distances between the mouth and nose in different people in order to ensure that a seal within the nostril and a stable position of the nosepiece can be achieved while still placing the mouthpiece between the lips. The physical design and architecture of the body of the XHANCE EDS are engineered to maximize fit in a diverse patient population as it relates to their mid-facial and nasal anatomic features and dimensions. Elements of the mouthpiece design and device geometry are important to assure the fit needed to correctly accommodate the anatomic diversity of a large portion of users.

Variations, such as in the angles between the mouthpiece and the device body or in the shape or size of the mouthpiece or nosepiece, have the potential to alter the "2-point fixation" between the mouth and nose and, therefore, the angle of the spray applicator and direction of delivery of the drug aerosol, and also to alter the interaction of the nosepiece and soft tissues of the nasal vestibule and nasal valve in ways that change drug deposition.

The nasal valve is the narrowest part of the entire respiratory tract and plays an important role in the physiology of the nose and interacts closely with the lower airways in many ways. The nasal valve is located between 2-3 cm into the nostril and is one of the significant barriers to delivering drug to the more superior and posterior parts of the nasal cavity targeted for treatment of nasal polyps. The multi-dimensionally asymmetrical nosepiece used on the XHANCE EDS is elongated and shaped in such a way that it stents the nasal valve at its narrowest point without creating undue discomfort, or risk of mucosal erosion, at the site of device interaction because the generally "triangular" form of the nasal valve is mimicked. This ensures that the air and associated positive pressure exiting the device at the time of actuation can create the maximum opening of the nasal valve and posterior soft tissues, allowing more of the spray droplets to get beyond the nasal valve into the target regions of the nasal passages.

Another key consideration is that the nosepiece design was intended to reduce unintentional obstruction of the spray that could be caused by compression of intranasal soft tissues during insertion, and to be acceptably comfortable to a broad range of end users. Ultimately, the nosepiece shape was selected with a specific configuration that best conformed to the patient's anatomy and the XHANCE EDS's intended functions.

Relatively minor variations from the specific design may behave differently in all, or some, individual users across a diverse population. Results from human factors evaluations identified potentially important differences in nosepiece design with regard to risk of obstruction of the exit due to compression primarily of lateral soft tissue, reliability of producing a seal at the nostril entrance, adequate stenting of the superior aspect of the narrow nasal valve, and reported comfort, particularly in individuals with smaller noses and/or "shorter" nasofacial dimensions. As a result of these evaluations, the specific shape and opening at the tip of the nosepiece were determined to be important to assure a seal at the nostril with varying nostril shapes and sizes, to achieve the desired in-use performance (e.g., stenting pattern and relief of soft tissue obstruction), to reduce risk of discomfort or harm when in contact with nasal tissues, and to accommodate diverse users. The specific configuration of the nosepiece itself, and its relationship with the mouthpiece, is an important component of the design for any exhalation delivery system and will have an impact on the factors described above and, therefore, on both the airflow and positive pressure transferred into the nasal cavity. Different nosepieces also will influence the number and size of droplets able to pass beyond the nasal valve region, and in

what direction and with what force and flow, to reach the specifically targeted subset of regions that are behind the nasal valve and above the inferior turbinate, and will behave differently across a spectrum of patients due to patient-level variation.

Additionally, the grip of the XHANCE EDS has a shape that permits a patient to use the product with either a one-handed or two-handed hold, and also was evaluated with either same-sided or opposite-sided administration. These grip differences can alter the angle of the device nozzle in the nostril and greatly influence the direction of spray. Alterations to the grip have the potential to change the manner in which a patient uses the device in ways that change the direction of spray or position of the nosepiece in the nasal valve, resulting in potentially major differences in the amount of drug passing beyond the nasal valve and above the inferior turbinate.

The XHANCE EDS also offers potential therapeutic effects, including those related to carbon dioxide, nitric oxide, change in pH, or positive pressure, the direct effects of which are not well characterized, that are independent and/or complementary to the therapeutic effect of the drug being delivered.[63] As noted in the XHANCE labeling, for example, the carbon dioxide present in the exhaled breath delivered into the nose through the XHANCE EDS may influence inflammatory mediator activity and neuropeptide activity.[64] These effects would have to be replicated by a differently designed device in order for a proposed generic product to be "expected to have the same clinical effect and safety profile" as XHANCE, and, therefore, to achieve therapeutic equivalence to XHANCE.[65]

In summary, the design of the XHANCE EDS, including its critical components, acts in a particular way to achieve drug deposition that is the result of both the device design and by interaction with the nose and nasal cavity, and mouth and oral cavity, and with the static and dynamic anatomy and physiology of the patient. Deposition of the topically acting drug is central to the safety and efficacy of XHANCE for the treatment of nasal polyps. Even if a proposed generic liquid drug formulation is identical, differences in the delivery device can produce materially different activity, especially through different drug deposition, with the clear potential to alter safety or efficacy in ways that would cause the proposed product not to be therapeutically equivalent to XHANCE.

2. The in vitro methods that FDA recommends for conventional nasal spray products are necessary but not sufficient to identify safety and efficacy differences resulting from differences from the XHANCE EDS.

FDA's Nasal Spray Draft Guidance recommends the following seven *in vitro* methods to evaluate bioequivalence for locally acting drugs delivered by nasal aerosol or nasal spray: (1) single actuation content through container life; (2) droplet size distribution by laser diffraction; (3) drug in small particles/droplets, or particle/droplet size distribution by cascade impactor; (4) drug particle size distribution by microscopy; (5) spray pattern; (6) plume geometry; and (7) priming and repriming.[66] These methods are necessary, but insufficient without additional data, to establish that a proposed ANDA product generates an equivalent drug deposition within the

[63] *See* note 7, *supra*.

[64] XHANCE Prescribing Information § 12.1 (Apr. 2021) (Exhibit 6).

[65] 21 C.F.R. § 314.3(b) (defining "therapeutic equivalents").

[66] Nasal Spray Draft Guidance, *supra* note 23, at 9–10 (Exhibit 17).

nose to that produced by the XHANCE EDS, including through the interaction of the device with the patient's anatomy and physiology.

The XHANCE EDS introduces multiple new variables into the intranasal delivery process that influence drug deposition in the nasal cavity in ways that are difficult to predict. Some of these variables relate to the device itself, and other variables relate to the device's interaction with the patient, patient's anatomy (static, dynamic, and disease-related), and patient's normal physiology. The *in vitro* assessments of droplet size, plume geometry, spray pattern, and other properties that FDA generally recommends for conventional nasal spray devices are insufficient to fully evaluate a proposed generic version of the XHANCE EDS. As discussed, the XHANCE EDS interacts directly with the nasal anatomy (e.g., sealing the nostril, stenting the nasal valve, providing an initial burst of air at actuation synchronized with spray emission, and generating a subsequent continuous high airflow lasting up to 2-3 seconds which dynamically expands the nasal cavity as well as—along with subsequent actuations—moving already-deposited drug even higher and deeper). These interactions will influence droplet size, spray pattern, and plume geometry in the nose, and will modify the nasal valve and other nasal geometry, in addition to re-routing airflow and modifying the "air resistance circuit" as air that reaches the nasopharynx reverses course due to the sealed soft palate. Physiologic behavior and anatomy have the potential to be different based on race, gender, disease state, and other factors. Therefore, *in vitro* testing of droplet size, spray pattern and plume geometry between XHANCE and a test product remain necessary in the assessment of equivalence; however, an evaluation of these factors alone is insufficient to establish equivalent drug deposition within the nose in a diverse target population.

Similarly, the *in vitro* morphologically-directed Raman spectroscopy ("MDRS") method that supported FDA's approval of generic versions of NASONEX® (mometasone furoate nasal spray) is insufficient to assure equivalent drug deposition within the nose between XHANCE and a proposed generic product.[67] MDRS measures particle morphological characteristics (size and shape) using its microscopic component, and performs chemical identification by analyzing Raman spectra.[68] The MDRS method was used to characterize the particle size distribution ("PSD") of active pharmaceutical ingredient ("API") in the suspension drug product by distinguishing the API from excipients in the liquid drug suspension. FDA's general draft product-specific guidance for proposed generic products referencing FLONASE includes this MDRS method as a potential alternative to an *in vivo* clinical endpoint study to support bioequivalence. However, MDRS is insufficient to assess the bioequivalence and therapeutic equivalence of a proposed generic version of the XHANCE EDS. MDRS does not assess intranasal drug deposition at all, and only assesses the distribution of particles suspended in the liquid formulation in the vial prior to administration. Therefore, it does not address important potential differences between differently designed exhalation delivery system devices, either dimensionally or in functional interaction with the patient. Most notably, it does not address whether there may be differences in the deposition of the aerosol droplets introduced into the nasal cavity by differently designed devices. It also does not address differences in potential direct device therapeutic effects independent of the drug delivered.

Lastly, we recognize that FDA has issued draft product-specific guidance documents for certain orally inhaled drug products that provide for *in vitro* studies in conjunction with other

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[67] Liu 2019, *supra* note 27 (Exhibit 18).

[68] *Id.* at 16.

types of data as an alternative approach to conducting comparative clinical endpoint studies.[69] However, methods used for the evaluation of orally inhaled drug products cannot be presumed to be appropriate for locally acting nasal sprays. Orally inhaled drugs are introduced into a much larger organ system, the lungs, with a dissimilar degree of normal or disease-related variation relative to the nasal cavity. Additionally, there is a greater sensitivity to small distances in the (significantly smaller) nasal cavity, where a fraction of a centimeter can be material, and because of major differences in anatomic specificity and other disease effects between nasal polyp disease and more diffuse diseases such as COPD or asthma.

3. There is no alternative to a non-inferiority study to ensure that a proposed generic product is as safe and effective as XHANCE.

In recent years, alternative methods for modeling nasal cavity deposition have been proposed, including imaging using radiolabeled drug and gamma scintigraphy cameras in humans, *in vitro* models using 3D-printed silicone casts, and computational fluid dynamics ("CFD"). However, no standard has been established for any of these methods, none has established an *in vitro*-to-*in vivo* correlation, and none accounts for the relevant population variations that are known to occur. Therefore, none of these methods is valid for establishing equivalence in drug deposition at the sites of action for the target population. These methods cannot support a conclusion that a proposed generic product would be expected to have the same safety and efficacy as XHANCE. Below we briefly address some of the limitations associated with these methods.

a) *In vivo* imaging

Many studies have sought to quantify deposition by using radiolabeled solutions coupled with scintigraphy measurement of deposition.[70] The high degree of technical difficulty of these studies has resulted in small patient sample sizes, limiting generalizability to diverse populations. Further, there are limits on the dose of radioactivity that safely can be administered to the nose in these experiments, particularly because of concerns over ocular exposure. As a consequence, in order to obtain sufficient sensitivity of measurements at the radioactivity doses that are used, even with comparatively coarse image resolution, gamma emissions must be recorded over a relatively prolonged time period of 1-2 minutes (a "long exposure image"). The coarse image resolution limits precise characterization of deposition in the small but relevant anatomic target regions that are relevant in nasal polyp disease. Despite these limitations, *in vivo* imaging can be a useful tool for illustrating dramatic differences in deposition patterns such as those produced by a conventional nasal spray and exhalation delivery systems, *see* Figure 1A, *supra*. However, the sensitivity with which drug delivery to specific locations within the nose is delineated and quantified and methodological factors addressing spatial scattering of the radioactivity and differences in tissue attenuation in different regions of the nasal airway, preclude the use of such imaging for establishing

[69] *See, e.g.*, FDA, Draft Guidance on Tiotropium Bromide Spray, Metered; Inhalation (Nov. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021936.pdf (attached hereto as Exhibit 55).

[70] A. Skretting, P.G. Djupesland. A New Method for Scintigraphic Quantification of Deposition and Clearance in Anatomical Regions of the Human Nose. Nucl. Med. Commun. 2009 Aug.; 30(8):629–638 (attached hereto as Exhibit 56).

equivalent drug deposition produced by different exhalation delivery system devices at the site of nasal polyps where differences can be expected to affect each product's safety and efficacy.[71]

b) Use of nasal airway models

Similar to *in vivo* imaging, nasal casts can detect the dramatic difference in deposition patterns generated by a conventional nasal spray and the XHANCE EDS, *see* Figure 1B, *supra*; however, they are subject to significant limitations which preclude the use of such models for establishing equivalent drug deposition produced by different exhalation delivery system devices at the site of nasal polyps. These limitations include, among others, challenges in defining air tissue boundaries when producing the airway model and the inaccurate static and/or dynamic anatomy at the nasal valve and in other areas, unrepresentative tissue pliability, and inaccurate simulation of the soft palate, and the impact of these items on nasal aerodynamics.[72] Additionally, there is a lack of *in vitro* to *in vivo* correlation using nasal casts as it relates to the efficacy and safety of a topically acting medication in regions of the nose affected by nasal polyps, and no clear pathway to simulate the exceptionally broad range of patient and disease population variation that occurs in this context.[73] This correlation is further limited by the large *in vivo* intra-patient variability in anatomy in particular as regards the location, shape and dimensions of the nasal valve area and the lack of pathological models. Given the various targets pursued through nasal drug deposition (including the middle meatus, olfactory region, sinuses, and nasal polyps, among others) and the complexity and dynamics of the nasal anatomy, the correlation between nasal drug deposition and some biological effects may be less straightforward than for other targets of inhaled drug delivery, such as lung deposition.[74]

c) Computational fluid dynamics

An alternative approach to examining the deposition of drug from nasal sprays is "*in silico*" using 3D computer modeling. While many studies have "validated" the observed *in silico* results against *in vitro* tests (e.g., nasal casts; see limitations discussed above), this has typically involved simply confirming the amount of drug that is deposited on either side of a simplified assumption for the nasal vertical valve location.[75] A key challenge for diseases such as sinusitis

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[71] Skretting 2009, *supra* note 70 (Exhibit 56); A.S. Shah, R. L. Berger, J. McDermott et al. Regional Deposition of Mometasone Furoate Nasal Spray Suspension in Humans. Allergy Asthma Proc. 2015 Jan.–Feb.; 36(1):48–57 (attached hereto as Exhibit 57).

[72] Fodil 2005, *supra* note 50 (Exhibit 35); K. Zhao, J. Jiang. What is Normal Nasal Airflow? A Computational Study of 22 Healthy Adults. Int'l Forum Allergy Rhinol. 2014 June; 4(6):435–446 (attached hereto as Exhibit 58).

[73] S. Le Guellec, S. Ehrmann, L. Vecellio. In Vitro - In Vivo Correlation of Intranasal Drug Deposition. Adv. Drug Deliver Review. 2021 Mar.; 170:340–352 (attached hereto as Exhibit 59).

[74] R.L. Walenga, P.W. Longest. Current Inhalers Deliver Very Small Doses to the Lower Tracheobronchial Airways: Assessment of Healthy and Constricted Lungs. J. Pharm. Sci. 2016. Jan.; 105(1):147–159 (attached hereto as Exhibit 60).

[75] Chari, *supra* note 47 (Exhibit 31); S. Hosseini, T.A. Schuman, R. Walenga et al. Use of Anatomically-Accurate 3-Dimensional Nasal Airway Models of Adult Human Subjects in a Novel Methodology to Identify and Evaluate the Internal Nasal Valve. Comput. Biol. Med. 2020 Aug.; 123:103896 (attached hereto as Exhibit 61); Shah 2015, *supra* note 71 (Exhibit 57).

and nasal polyps is that the targeted regions are far more specific and are in deeper, more posterior regions of the nose (e.g., the middle meatus, olfactory cleft, or ethmoid sinus cavity), and the degree of relevant variation (patient- or delivery-related) is much greater.[76] Simply demonstrating that the amount of drug reaching beyond the nasal valve (vertical dividing line often incorrectly called the nasal valve) is the same between a test product and reference product is inadequate for establishing equivalence of drug deposition, both in the context of a condition such as nasal polyps and in the context of an exhalation delivery system.[77]

The impact of mucociliary clearance on the location where fluticasone penetrates through the mucus layer into a target site of action is another important factor in attempting to model efficacy and safety and also is a challenge for computational fluid dynamics ("CFD").[78] To accurately use *in silico* modeling of intranasal drug deposition, the distribution of ciliated/non-ciliated cells and of goblet cells in the nasal cavity and sinuses must be understood, as must the functional variation in different internasal anatomic sites, including the mucus layer, relative production rate of mucus (affecting drug dissolution/penetration), density of ciliated cells, mucociliary clearance rates, and direction of clearance.[79] Due to the different density and distribution of ciliated cells and goblet cells, mucociliary clearance is highly variable in different regions of the nasal mucosa. Total clearance patterns for the entire nose become misleading, even if separated into anterior and posterior segments.[80]

Even if data on cell density and distribution (squamous epithelium, ciliated cells, goblet cells, olfactory cell/filaments) are taken into account, it is essential to be aware that the available data are based on biopsies from cadavers of 4 individuals aged 58 to 78 who died from

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[76] Larsen 2004, *supra* note 40 (Exhibit 25); R. Richard, Orlandi et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021. Int'l Forum Allergy Rhinol. 2021; 11:213–739 (attached hereto as Exhibit 62); W.J. Fokkens, V.J. Lund, C. Hopkins et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb. 20; 58(Suppl S29):1–464 (attached hereto as Exhibit 63); Djupesland 2013 *supra* note 3, (Exhibit 2).

[77] P.G. Djupesland, A. Skretting, M. Windern et al. Breath Actuated Device Improves Delivery to Target Sites Beyond the Nasal Valve. Laryngoscope. 2006 Mar.; 116(3):466–472 (attached hereto as Exhibit 64); P.G. Djupesland , A. Skretting, Nasal Deposition and Clearance in Man: Comparison of a Bidirectional Powder Device and a Traditional Liquid Spray Pump. J Aerosol. Med. Pulm. Drug Deliv. 2012 Oct.; 25(5):280–289 (attached hereto as Exhibit 65).

[78] Shah 2015, *supra* note 71 (Exhibit 57); P.G. Djupesland, R. Mahmoud. Letter to the Editor: Incorrect Conclusions Regarding Deposition of Conventional Mometasone Furoate (MF) Nasal Spray. Allergy Asthma Proc. 2015 Sept.–Oct. 36(5): e104–e105 (attached hereto as Exhibit 66); Djupesland 2006, *supra* note 77 (Exhibit 64); Djupesland 2012, *supra* note 77 (Exhibit 65).

[79] S. Gizurarson. The Effect of Cilia and the Mucociliary Clearance on Successful Drug Delivery. Biol. Pharm. Bull. 2015; 38(4):497–506 (attached hereto as Exhibit 67); Halama 1990, *supra* note 41 (Exhibit 27); C. Rusznak, J.L. Devalia, S. Lozewicz et al. The Assessment of Nasal Mucociliary Clearance and the Effect of Drugs. Respir. Med. 1994 Feb.; 88(2):89–101 (attached hereto as Exhibit 68); F. Féron, C. Perry, J.J. McGrath et al. New Techniques for Biopsy and Culture of Human Olfactory Epithelial Neurons. Arch. Otolaryngol. Head Neck Surg. 1998 Aug.;124(8):861–866 (attached hereto as Exhibit 69).

[80] Shah 2015, *supra* note 71 (Exhibit 57); Djupesland 2015, *supra* note 78 (Exhibit 66); Djupesland 2006, *supra* note 77 (Exhibit 64); Djupesland 2012, *supra* note 77 (Exhibit 65).

cardiopulmonary incidents and who lacked sinonasal pathology.[81] These limitations are not recognized and addressed in the recent CFD studies arguing that CFD analysis may serve as a model to predict nasal drug deposition and uptake.[82] Furthermore, the impact of acute and chronic inflammatory sinonasal disorders causing mucosal congestion and modifying the rate of secretion production and mucociliary clearance is not taken into account in the simplified model applied.[83] Chronic inflammation causes remodeling of the entire sinonasal mucosa with entirely changed cell distribution.[84] In addition, polyp formation, surgical procedures, and medical intervention will significantly alter the anatomy, physiology, and aerodynamics of the sinonasal geometry. Assumptions related to these factors intended to simplify and enable *in silico* modeling must be accurate and well-substantiated, which so far has not been possible despite published efforts.[85] Accurate modeling of the nasal valve (e.g., not a simplified assumption of a vertical plane) and other intranasal features, all subject to a high degree of static and dynamic disparity across patients and over the course of time, also is necessary. It is crucial to understand that there is great variation, relevant to both efficacy and safety in the treatment of nasal polyps, among regions that have historically been characterized simply as "behind the nasal valve." Recent studies accurately have described the complexity and variability of the nasal valve and the significant inter- and intra-subject variability in deposition in nasal replicas from healthy individuals.[86] Nonetheless, more recent publications by some of the same authors do not address these important findings regarding the dynamic features of the nasal valve anatomy, airflow, and the impact of inflammation, polyp formation, and surgery,[87] in favor of a simplified model of mucociliary clearance and drug uptake.[88] Furthermore, with the introduction of novel devices like the XHANCE EDS—a device where delivery and drug

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[81] Halama 1990, *supra* note 41 (Exhibit 27).

[82] Chari, *supra* note 47 (Exhibit 31); Y. Shang, K. Inthavong, J. Tu. Development of a Computational Fluid Dynamics Model for Mucociliary Clearance in the Nasal Cavity. J. Biomech. 2019 Mar. 6; 85:74–83 (attached hereto as Exhibit 70).

[83] V.K. Pandya, R.S.Tiwar. Nasal Mucociliary Clearance in Health and Disease. Indian J. Otolaryngol Head Neck Surg. 2006 Oct.; 58(4):332–334 (attached hereto as Exhibit 71); Gizurarson 2015, *supra* note 79 (Exhibit 67); S.M. Birdi, S. Singh, A. Singh. Mucociliary Clearance in Chronic Sinusitis. Indian J. Otolaryngol Head Neck Surg. 1998 Jan.; 50(1):15–19 (attached hereto as Exhibit 72).

[84] Fokkens 2020, *supra* note 76 (Exhibit 63); Hulse 2015, *supra* note 59 (Exhibit 51).

[85] Chari 2021, *supra* note 47 (Exhibit 31); P. W. Longest, A. Rygg, and M. Hindle. Bioequivalence Testing: Can Systemic Pharmacokinetic Profiles from Corticosteroid Nasal Sprays Be Used to Elucidate Local Drug Deposition within the Nose? Respiratory Drug Delivery 2016 (attached hereto as Exhibit 73); Shang 2019, *supra* note 82 (Exhibit 70).

[86] Hosseini, 2020, *supra* note 75 (Exhibit 61); M.D. Manniello, S. Hosseini, A. Alfaifi et al. In Vitro Evaluation of Regional Nasal Drug Delivery Using Multiple Anatomical Nasal Replicas of Adult Human Subjects and Two Nasal Sprays. Int'l J. Pharm. 2021 Jan. 25; 593:120103 (attached hereto as Exhibit 74).

[87] K. Zhao, P.W. Scherer, S.A. Hajiloo et al. Effect of Anatomy on Human Nasal Air Flow and Odorant Transport Patterns: Implications for Olfaction. Chem. Senses. 2004 June; 29(5):365–379 (attached hereto as Exhibit 75); M. R. Wofford, J.S. Kimbell, D.O. Frank-Ito. A Computational Study of Functional Endoscopic Sinus Surgery and Maxillary Sinus Drug Delivery. Rhinology. 2015 Mar. ;53(1):41–48 (attached hereto as Exhibit 76).

[88] Chari, *supra* note 47 (Exhibit 31).

deposition occur through an active and dynamic interaction between the patient, the device design, and flow and pressure properties that constantly change with the state of sinonasal pathology—such simplified CFD models lack utility.

One of the functions of the nasal cavity is olfaction, the loss of which is a safety concern for intranasal treatments and also a cardinal symptom of nasal polyp disease. Olfactory sense is highly location-dependent across small anatomic regions, reinforcing the critical importance of precision and sensitivity of deposition and clearance determination in assessing clinical equivalence for *in vitro* models. Olfactory nerve filaments extend through the olfactory cleft and, variably and with less density, into anterior and posterior parts of the middle turbinate.[89] Trigeminal nerve fibers, which interact with olfactory fibers in a complex way and contribute to the "common chemical sense," also modulate olfactory receptor activity and are involved in reflexes to minimize exposure to potentially noxious substances by altering nasal patency and airflow and by changing properties of the mucus blanket.[90] Loss of trigeminal function, in addition to olfactory nerve function, may underlie the loss of sense of smell.[91] These considerations further highlight the importance of an accurate (i.e., precise and specific) understanding of drug deposition and movement in the nasal cavity after delivery from different devices, something which cannot currently be achieved *in vitro* or *in silico*, particularly in consideration of the degree of population heterogeneity which must be considered.

An *in silico* model for an exhalation delivery system would present particular complexities. There are a number of factors related to the device that could influence the velocity and volume of air delivered, including, for example, the efficiency of the device in preventing leakage of air before reaching the nasal cavity and whether or not a sealing nosepiece is employed. A key challenge for CFD modeling is that there is no definitive way of knowing how these factors impact deposition in the nose itself. Additionally, a model would have to take into consideration the pressure transfer that occurs with the XHANCE EDS and the efficiency of the device in the transfer of pressure, as well as how a change to the shape or form of the nosepiece (and its relationship to the mouthpiece) in a test product would affect placement, the geometry and dimensions of the nasal tissues adjacent to the tip of the nostril, "trap conditions" for movement of drug along mucosal surfaces under conditions of continuing airflow (variable length and strength of breath and variable number of actuations), changes in droplet size distribution due to two-way interactions with the intranasal airflow after exiting the device, and the intranasal circuit resistance to airflow, among other factors.

4. A non-inferiority clinical endpoint study is necessary to demonstrate bioequivalence and therapeutic equivalence to XHANCE.

No existing *in vitro* method or any of the emerging technologies described above can adequately assess the drug deposition that will result from a proposed generic product's device and the interaction of that device with the patient's anatomy and physiology. As discussed,

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[89] Féron 1998, *supra* note 79 (Exhibit 69); D. Leopold, T. Hummel, J.E. Schwobet al. Anterior Distribution of Human Olfactory Epithelium. Laryngoscope. 2000 Mar. ;110(3 Pt 1):417–421 (attached hereto as Exhibit 77).

[90] T. Hummel, A. Livermore. Intranasal Chemosensory Function of the Trigeminal Nerve and Aspects of its Relation to Olfaction. Int'l Arch. Occup. Environ. Health. 2002 June; 75(5): 305–313 (attached hereto as Exhibit 78).

[91] A. Husner, J. Frasnelli, A. Welge-Lüssen et al. Loss of Trigeminal Sensitivity Reduces Olfactory Function. Laryngoscope. 2006 Aug.; 116:1520–1522 (attached hereto as Exhibit 79).

those approaches lack sufficient precision, accuracy, reproducibility, and validity across a sufficient range of patient-related and disease-related variation to establish equivalence of nasal deposition at the small and anatomically specific sites that are most relevant in this disease. Given the absence of any suitable alternatives, a non-inferiority clinical endpoint study is necessary to demonstrate bioequivalence and support therapeutic equivalence to XHANCE.

The site of deposition is expected to be central to the safety and efficacy of a proposed generic product. Because fluticasone propionate is a locally acting medication, deposition on the nasal polyps themselves is required for them to be reduced and the magnitude of polyp reduction will be dependent upon the amount of steroid that can reach the tissue, the polyp tissue surface area that is coated, and the amount of drug that continues to reach the tissue as it shrinks. Importantly, the same is true for mucosal tissues swollen due to inflammation related to the underlying nasal polyp disease process.

The ability to reach these target regions is essential even when treating patients who have extensive polyp tissue that extends inferiorly or anteriorly to regions accessed by any nasal delivery system. This is because the mechanism of XHANCE EDS delivery not only deposits drug on large polyps, but introduces the potential for the deposition profile to change as the patient anatomy changes, enabling drug to reach increasingly posteriorly (up to and including the middle meatus, the typical site of origin) as polyps shrink during treatment. This is consistent with the observation in pivotal trials of patients taking XHANCE in whom all polyp tissue inside the middle meatus was resolved during treatment. Products which are different in ways that have the potential to alter deposition cannot be assumed to produce the same clinical outcomes in all patients with the disease throughout the course of therapy. Both the physical presence of the polyps and the inflamed mucosa in the upper regions of the nasal cavity contribute to symptoms experienced by a patient. It therefore is inadequate, especially when comparing exhalation delivery system devices, to simply rely on crude segmentation, such as the proportion of drug that reaches beyond a single region of interest in the nasal passages (for example, an arbitrary segmentation between "anterior" and "posterior" at a vertical nasal valve) to determine equivalent deposition. Exactly where the nasal fluticasone suspension is deposited has obvious potential to influence the efficacy of the product. There also is potential for regional differences to influence safety, as, for example, might be considered with regard to the amount of steroid deposited in regions near the eye (contributing to existing concerns over risk for glaucoma or cataract), deposition at the nasolacrimal duct, or deposition in the olfactory cleft or sphenopalatine ganglion, which may introduce different risks to nerve function. Importantly, accurate assessments are not available to establish which specific aspects of device design contribute in what way to the particular pattern of deposition produced by the XHANCE EDS.

As noted, the XHANCE EDS also offers potential therapeutic effects, the direct effects of which are not well characterized, that are independent of and/or complementary to the therapeutic effect of the drug being delivered.[92] These effects would have to be replicated by an alternatively designed device in order for a proposed generic product to be "expected to have the same clinical effect and safety profile" as XHANCE, and, therefore, to achieve therapeutic equivalence to XHANCE.[93]

Based on these considerations, the only valid approach to ensure bioequivalence and therapeutic equivalence between a proposed generic product and XHANCE is through a

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[92] *See* note 7, *supra*.

[93] 21 C.F.R. § 314.3(b) (defining "therapeutic equivalents").

comparative clinical endpoint study that demonstrates non-inferiority of safety and efficacy in patients with nasal polyps.

There are two particularly important considerations for the design of such a comparative clinical endpoint study. First, any such study should be required to demonstrate non-inferiority on the same co-primary endpoints—improvement in nasal congestion and improvement in nasal polyp grade—as evaluated in XHANCE's pivotal studies. There is a risk of non-equivalence being missed (i.e., Type 1 error) if reduction in polyp grade is not observed starting from the same baseline degree of disease, since topical drug will differently reach polyps extending to different parts of the nasal cavity. Additionally, given the fact that most nasal polyps originate in the middle meatus, the non-inferiority of a test product on polyp grade should be demonstrated not only for mean change in this measure from a comparable baseline, but also for the proportion of subjects who achieve a polyp score of 0=no polyps, demonstrating comparable activity in the middle meatus. In pivotal studies with XHANCE, it was shown that between 14-20% of patients treated with the high dose of XHANCE had polyps eliminated (grade=0; not observed in the middle meatus or elsewhere) in at least one nostril after 16 weeks and up to 28% after 24 weeks.[94] This likely reflects the particular intranasal deposition associated with XHANCE that enables continued deposition of topical steroid on the polyp tissue as it shrinks back to its site of origin. Although this activity through different stages of treatment is not necessary for all drugs that treat the disease, equivalent intranasal deposition is necessary to produce a therapeutically equivalent effect; therefore, any proposed generic version of XHANCE should be able to produce an equal rate of polyp elimination to ensure bioequivalence and therapeutic equivalence.

Second, the subjects included in the study need to be representative of the population in which XHANCE has been demonstrated to be effective in order to accurately assess whether the test product has equivalent effects on shrinking nasal polyps. The need for representativeness applies to both polyps and patients. Regarding polyps, in the XHANCE pivotal studies, subjects with grade 1-3 polyps were enrolled. Larger polyps extend further down into the nasal cavity, and therefore are more easily reached by products that produce limited deposition in more difficult-to-access regions. Smaller polyps (grades 1 and 2) do not reach much further than the middle turbinate, and the amount of drug deposition in more superior/posterior regions will have a substantial impact on the magnitude of polyp reduction in the population of patients with that grade of disease. Therefore, the inclusion criteria for the clinical study should allow for a sufficient number of subjects with both large and small polyps. Regarding patients, given the important patient-based population variations that interact with the design and functioning of an exhalation delivery system device in domains including not only the extent of disease, but also behavior, intranasal anatomy, and mid-facial morphology (sometimes but not always linked to race/ethnicity/age/gender), even minor changes in the design or handling of the delivery device require validation of equivalence of clinical performance in a suitably diverse population.

5. A pharmacokinetic study is a necessary element of an ANDA product's demonstration of bioequivalence and therapeutic equivalence to XHANCE.

Additionally, a demonstration of bioequivalence and therapeutic equivalence to XHANCE should include a pharmacokinetic study to assess systemic absorption, consistent with

[94] Leopold 2019, *supra* note 60 (Exhibit 52); Sindwani 2019, *supra* note 60 (Exhibit 53).

FDA's recommendations in the Nasal Spray Draft Guidance.[95] Requiring an ANDA applicant to conduct a pharmacokinetic study also is consistent with FDA's precedents. For example, the applicant for the generic mometasone furoate nasal spray conducted a pharmacokinetic study and obtained measurable plasma concentrations at a therapeutic dose.[96] The general draft product-specific guidance for fluticasone propionate nasal spray also recommends a single-dose, two-way crossover pharmacokinetic study.[97] Accordingly, FDA should require a pharmacokinetic study to ensure equivalent systemic absorption between XHANCE and a proposed generic drug product.

6. An ANDA formulation product should be Q1/Q2 the same as XHANCE.

FDA also should require an ANDA product formulation to be qualitatively (Q1) and quantitatively (Q2) the same as XHANCE. This reflects a recommendation in FDA's Nasal Spray Draft Guidance and also aligns with FDA's recommendations for generic products referencing FLONASE.[98]

7. A generic device should have equivalent design and performance characteristics to the XHANCE EDS and should not include differences in user interface that would preclude approval in an ANDA.

Finally, as part of the required showing of bioequivalence and therapeutic equivalence, FDA should require that a generic device have equivalent design and performance characteristics to those of the XHANCE EDS. The elements of the XHANCE EDS that are believed to play the greatest role in XHANCE's safety and efficacy are described above in sections B.II.A and B.III.A.1.c-d. Additionally, FDA should require an ANDA applicant to analyze any differences in user interface and show that such differences do not prevent the proposed generic combination product from being substituted for XHANCE without the intervention of a health care provider and/or without additional training prior to use. These requirements are essential given the central role played by the device constituent in the safety and efficacy of XHANCE.

FDA included similar recommendations in the general draft product-specific guidance for fluticasone propionate nasal spray and in the Nasal Spray Draft Guidance. First, in the general draft PSG for products referencing FLONASE, FDA recommended that prospective applicants consider the following characteristics of the reference ("R") product in designing the test product: external operating principles and external critical design attributes of the R product, size and shape of the R product and number of doses in the R product[99]

FDA further recommended that prospective applicants refer to the draft guidance entitled "Comparative Analyses and Related Comparative Use Human Factors Studies for a

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[95] Nasal Spray Draft Guidance, *supra* note 23, at 7, 24–26 (Exhibit 17).

[96] Liu 2019, *supra* note 27 (Exhibit 18).

[97] FLONASE Draft Guidance, *supra* note 28, at 4–5 (Exhibit 19).

[98] Nasal Spray Draft Guidance, *supra* note 23, at 6–7 (Exhibit 17); FLONASE Draft Guidance, *supra* note 28, at 8 (Exhibit 19).

[99] FLONASE Draft Guidance, *supra* note 28, at 9 (Exhibit 19).

Drug-Device Combination Product Submitted in an ANDA."[100] This draft guidance recommends that an ANDA applicant "analyze the overall user interface of a proposed generic combination product to identify differences in design when compared to the RLD," including through comparative use human factors studies if the differences "may not be minor."[101] In assessing whether such design differences are acceptable, FDA "intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product."[102]

Similarly, in FDA's Nasal Spray Draft Guidance, FDA recommended that the container and closure system of the test product formulation be comparable to that of the reference listed drug, and that an applicant include a side-by-side comparison of the components of the container and closure system, listing brand and model, dimensions of critical components, and engineering drawings, if possible.[103]

Although these analyses are an essential part of an ANDA applicant's showing of bioequivalence and therapeutic equivalence, they are insufficient, without the additional data described in this petition, to establish the equivalence of a proposed product. This is because it is not possible to accurately establish, particularly in light of patient variability, how each design feature of the XHANCE EDS, individually or collectively, contributes to the drug deposition achieved by XHANCE, including through the interaction between the XHANCE EDS and the nose and nasal cavity and mouth and oral cavity, and the patient's physiology, and the product's resulting clinical effect.

B. FDA should issue a draft product-specific guidance for ANDAs referencing XHANCE that is consistent with these requests.

In 2020, FDA added XHANCE to the Agency's list of planned new product-specific guidance documents for complex generic drug products.[104] To provide clarity to ANDA applicants and other stakeholders on FDA's current thinking on the appropriate methods for showing bioequivalence and therapeutic equivalence to XHANCE, OptiNose requests that FDA issue a draft product-specific guidance for ANDAs referencing XHANCE that aligns with these requests.

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[100] *Id.*; FDA, Draft Guidance for Industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan. 2017) ("Comparative Analyses Draft Guidance") (attached hereto as Exhibit 80).

[101] Comparative Analyses Draft Guidance, *supra* note 100, at 5, 8 (Exhibit 80).

[102] *Id.* at 4.

[103] Nasal Spray Draft Guidance, *supra* note 23, at 7 (Exhibit 17).

[104] *See* FDA, Upcoming Product-Specific Guidances for Complex Generic Drug Product Development (current as of Mar. 2, 2020),https://web.archive.org/web/20200516235430/https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development (attached hereto as Exhibit 81).

C. FDA should require the same type of non-inferiority clinical endpoint study for a section 505(b)(2) product to receive an "A" rating.

Generally, a section 505(b)(2) product may be approved with a range of differences from the listed drug relied upon. For example, a section 505(b)(2) product is unlikely to be Q1/Q2 the same as XHANCE and also can be expected to differ from XHANCE in the device design. The same type of non-inferiority *in vivo* clinical endpoint study described above should be required to show the bioequivalence and therapeutic equivalence of a section 505(b)(2) product if the applicant seeks a determination that the product is therapeutically equivalent to XHANCE (i.e., an "A" rating in the Orange Book).

IV. Conclusion

For the foregoing reasons, OptiNose requests that FDA not approve an ANDA referencing XHANCE unless the applicant demonstrates bioequivalence and therapeutic equivalence through the type of non-inferiority clinical endpoint study described above in addition to *in vitro* studies, pharmacokinetic study data, and an adequate showing of device equivalence. Additionally, OptiNose requests that FDA issues a draft product-specific guidance document that is consistent with this approach. Finally, OptiNose asks that FDA require a section 505(b)(2) applicant to demonstrate bioequivalence and therapeutic equivalence through the same type of non-inferiority clinical endpoint study in order to obtain an "A" rating in the Orange Book.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

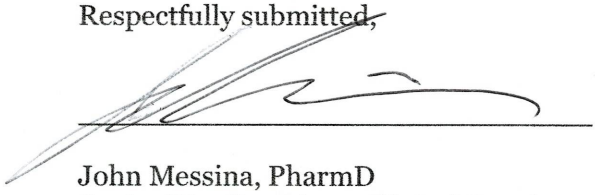
D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only upon the request of the Commissioner.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: January 21, 2021. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on behalf of OptiNose US, Inc. as part of my responsibilities as an employee of OptiNose US, Inc.; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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