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Review Article

Regulatory Dichotomy of Sucralfate, Its history and the new Bioadhesive polymerized Sucralfate barrier therapy for Oral health, Oncology support and Gastrointestinal disorders

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Abstract

Sucralfate is a biologically inert non-systemically acting compound. It requires polymerization for conversion into its biological active form, polymerized Sucralfate. Should this conversion occur in the body, using processes of the body to effect conversion subsequent to administering a dose, then the administered Sucralfate is a drug, as it enlists bodily functions to enact a chemical change. This form of Sucralfate should be regulated as drug. On the other hand, Sucralfate is manufactured as a polymerized product, requiring no bodily functions to enable its therapeutic effect, then this form of Sucralfate act as a medical device and should be regulated as such. This dichotomy of Sucralfate was first recognized by the US FDA in 2005 that subsequently cleared several polymerized Sucralfate barrier therapies as medical devices.

This review covers the history of the regulatory dichotomy or duality of Sucralfate, the biological basis for Sucralfate clinical effects and the regulatory position of several barrier therapies.

Keywords: Sucralfate barrier therapy, polymerized Sucralfate, Bioadhesive barrier, medical device, Polymerization, CE mark, GERD, US FDA 510k

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1. Introduction

Regulatory authorities define drugs as chemical or biological entities that operate systemically and require metabolic, pharmacologic or immunologic handling by the body to achieve their clinic effect. As such drugs are generally altered by the body to either activate or deactivate their effect, the latter resulting in a predictable half-life of clinical effect.

Alternatively, medical devices are generally non-systemic, locally acting, site specific and generally inert to the body's effort to alter them. Devices can be mechanical or chemical but must have a physical mode of action as their sole mechanism to achieve their desired clinical effect. Subsequent positive clinical responses to medical devices are indirect consequences of their physical action in or upon the body, an action for which the device had been designed.

Depending on its state prior to administration, Sucralfate can be either a drug or a medical device. The active therapeutic form of Sucralfate is polymerized. (1) As described by Nagashima (1): "on encountering gastric acid, (Sucralfate) becomes a highly condensed, viscous substance…", that is, polymerized. Polymerized Sucralfate has only a physical mode of action. Conversion from powder (or dilute suspension) to a polymerized complex is required for clinical effect. (1) This conversion may occur within or upon the body courtesy of mucosal moisture or of gastric acid. Alternatively, conversion may be accomplished independent of the body, through manufacture.

Any form of Sucralfate that requires the body's participation in its polymerization is a drug. If, on the other hand, Sucralfate is manufactured in its polymerized state then it is a device and is designated as pre-packaged polymerized Sucralfate, a medical device barrier therapy.

Drug Development History on Sucralfate

The 1968 discovery of Sucralfate, a synthetic analog unit of gastric mucin was a culmination of centuries-long quest dating from 1772 forward to understand why the stomach did not digest itself. (2-4) In 1907 theory of mucoprotection by gastric mucus, (5) sparked investigational interests in gastric mucus, with subsequent discovery of mucin and 'mucoids'. Efforts to decipher their compositional structure between 1911 (6) and 1918 (7) led to evidentiary conclusions in 1920 that the theory of mucoprotection by gastric mucus was indeed fact. (8) From 1930's through the 1950's investigational interests targeted the physiologic performance of gastric mucin, (9-10) its clinical application for the treatment of peptic ulcer (11) with the confirmation that the chondroitin sulfate fraction within gastric mucus was pepsin-suppressing and mucoprotective. (12) Understanding matured regarding the gastric mucus barrier and its secretions from 1940 to 1950 (13-16) and studies on the therapeutic antipeptic value of sulfonated polysaccharides expanded from the 1950's into the late1960's. (17-21)

Efforts in Japan diversified from sulfonated polysaccharides to sulfonated analogs of oligosaccharides (chain of three to nine sugars), disaccharides and monosaccharides. In 1966, this diversification led to the synthesis of octa-sulfonated sucrose, whose aluminum hydroxide salt is known as Sucralfate. (22) The 1969 US Patent on Sucralfate, (23) was followed by full descriptions of its antipeptic properties (24) and published results of multi-centered clinical trials. (25)

Regulatory History of Sucralfate as a Drug – First Japan then the US FDA 1982 to 2004

Sucralfate was first approved for clinical use in man in Japan in 1968. Thirteen years later in 1982, the US FDA approved New Drug Application (NDA) # 18333 (26) for Sucralfate solid dose form (Carafate) to treat duodenal ulcers. This was followed in 1993 by US FDA approval of NDA #19083 (27) for 10% suspension of Sucralfate also to treat duodenal ulcers. From 1993 to date there are over 214 brands of Sucralfate tablets, suspensions or powders formally regulated by more than 69 countries. (28) Each dose form of Sucralfate requires activation by gastric acid to polymerize it into its active form. Sucralfate has a reputation for being a safe drug, associated with few adverse reactions and non-specific absorption of concomitantly administered drugs that had electronegative properties. Despite widespread use, its safety profile has remained much the same as initially observed over the first 13 years of its initial approval in Japan. (29)

Regulatory authorities in several countries have granted over-the-counter (OTC) status to Sucralfate tablets, suspension and powders. Thus for 1.67 billion people, Sucralfate drug can be obtained without pharmacists' or physicians' orders, however for the remaining 5.8 billion people Sucralfate is by prescription only.

Regulatory History of Sucralfate as Bioadhesive Medical Device - US FDA 2005 to 2013

In 2005, the United States Food and Drug Administration recognized a regulatory dichotomy for Sucralfate. They clarified their position in an Agency Product Designation Ruling known as an RFD, request for designation. (30) The RFD process involved review of the original mechanism of action for Sucralfate whereby it had been classified as a non-systemic site protective agent that selectively engaged fibrinous debris and mucin in the form of an amorphous (polymerized) substance. (31, 32) Since the clarification by the 2005 Product Designation Ruling, the FDA has maintained two regulatory statuses for Sucralfate – a drug status for non-polymerized Sucralfate pre-packaged in its unpolymerized form, and a medical device status for Sucralfate polymerized and pre-packaged prior to patient use.

In 2013, the US FDA licensed the first commercially available polymerized Sucralfate barrier therapy medical devices. Orafate (OraHeal) and ProThelial licensed under the FDA's 510k program are prescription polymerized Sucralfate bioadhesive therapies for the management of oral health and chemoradiation toxic mucositis respectively.

2. Regulatory Acceptance of Barrier Therapies in US, Europe, India, China & Japan

There has been general regulatory acceptance to the concept of bioadhesive barrier therapy. Table 1 below list therapies licensed in differing regulatory jurisdiction each having claim from a lesser to greater extent of bioadhesion to the mucosal barrier as their chief mode of action.

Table 1 Bioadhesive Barrier Therapies in US, Europe, India, China and Japan

Barrier Therapy	Presentation	Composition	Clinical Syndrome	US FDA 510k	EU CE Mark	India	China	Japan
Caphosol 1999	Liquid Swish/Spit	Disodium & Monosodium Phosphate, Calcium and Sodium Chloride	Oral Mucositis pain	Class III	Class III	Class C	Class III	Class III
Gelclair 2001	Powder Sachets Swish/Spit	Hyaluronate, Polyvinylpyrrolidone, Propylene Glycol, PEG-40, Hydroxy ethylcellulose Hydrogenated Castor Oil	Oral mucositis pain	Class II	Class III	Class C	Class III	Class III
MuGard 2006	Liquid Swish/Spit	Carbomer, Homopolymer A, Polysorbate 60, Phosphoric Acid, Benzyl Alcohol,	Oral mucositis pain	Class II	Class III	Class C	Class III	Class III

		Glycerin, Citrate						
Episil 2010	Liquid Spray	Glycerol Dioleate, Soy Phosphatidyl Choline, Propylene Glycol, Polysorbate 80, Ethanol,	Oral mucositis pain	Class III	Class III	Class C	Class III	Class III
Orafate 2013 (OraHeal)	Gel	Polymerized Sucralfate	Gingivitis, Aphthous Ulcer, Periodontitis, Implant Mucositis, Oral wounds	Class III	Pending	Pending	Not yet	Not yet
ProThelial 2013	Paste Swish/Spit or Swallow	Polymerized Sucralfate	Chemoradiation toxic Mucositis, Lichen Planus	Class III	Pending	Pending	Not yet	Not yet
ProctiGard 2014	Liquid Enema	Carbomer, Homopolymer A, Polysorbate 60, Phosphoric Acid, Benzyl Alcohol, Glycerin, Citrate	Radiation Proctitis	Class III	Not yet	Not yet	Not yet	Not yet
Ziverel 2016	Powder Sachets Swallow	Hyaluronate/Chrondrotin Sulfate & Poloxamer 407	GERD, NERD	Not yet	Class III	Not yet	Not yet	Not yet
Esoxx 2017	Powder Sachets Swallow	Hyaluronate/Chrondrotin Sulfate & Poloxamer 407	GERD, NERD	Not yet	Class III	Not yet	Not yet	Not yet
Gelenterum 2017	Powder Sachets	Gelatin Tannic Acid	Diarrhea	Not yet	Class III	Not yet	Not yet	Not yet
Esolgafate 2019 (2005*)	Suspension Swallow	Polymerized Sucralfate	GERD	Not yet	Pending	Pending*	Not yet	Not yet
Colofate 2019	Enema Solution Per rectum	Polymerized Sucralfate	Radiation Proctitis, Pouchitis Ulcerative colitis	Not yet	Pending	Pending	Not yet	Not yet

* 2005 Esolgalfate was manufactured in India under brand name GastrafateRx by Embiotics Laboratories but marketed as a branded generic sucralfate

In the US and Europe barrier therapies have been authorized for oral health, chemoradiation mucositis, GERD, NERD, diarrhea and radiation proctitis. Barrier therapy authorizations are pending for pouchitis and ulcerative colitis. Hence, the concept of therapeutic barrier protection for the entire GI tract is a regulatory reality established initially by the US FDA 510k program then harmonized into other regulatory jurisdictions.

However, for the most part the exact manner whereby barrier therapies protect the mucosal lining is not clear from literature review. All too often, in manufacturer's package insert, the details regarding manner of physical engagement are presented from the perspective of the device and rarely from the perspective of the lining to be protected. To a large extent, the biological basis of bioadhesive barrier does not begin with the device but rather with the mucosal barrier itself. Necessarily for a device mode of action, specific structural elements of the mucosal barrier must be targeted and engaged by the device to establish its clinical effect.

3. Biological basis for Sucralfate Barrier Therapies to Work

In principle medical conditions targeted by Sucralfate barrier therapies arise from a breach or breaches in the structure and/or functional homeostasis of the mucosal lining. To understand the nature of these conditions is to understand the mucosal lining in health and how it is structurally organized to maintain organized functions beneath it. Polymerized Sucralfate barrier therapies assert their physical mode of action here, at the outermost luminal interface of the mucosal lining.

Tasks of the Mucosal Lining Protected by Sucralfate Barrier Therapies

The mucosal lining is tasked with protecting underlying tissue of the host. Sucralfate barrier therapies protect the mucosal lining engaged in those tasks. The protection of the mucosal lining is both a physical separation (which is materially supported by polymerized Sucralfate) and a biofunctional separation of which polymerized Sucralfate plays no direct role. Physical separation is performed through biophysical resistance to invasive luminal contents. Functional separation is maintained by electrostatic thwarts to toxins, by hosting commensal bacteria which in turn attack other harmful microbials, and by deployment of defensive and offensive macromolecules. (33) Bioadhesive Sucralfate barrier therapies act here in this outermost milieu of the mucosal lining reinforcing the biophysical resistance mounted by the mucosal lining, which indirectly secures undisturbed continuation of underlying functional operations within the mucosal barrier.

Physical and Functional Barrier of the Mucosa

For the most part, as shown in Table 2, a healthy mucosal barrier is comprised of three histological compartments simultaneously performing any one of seven major functions to maintain structural and functional mucosal integrity.

Table 2 Structural Biology and Function of a Healthy Mucosal Barrier

Barrier Compartments	Barrier Functions		Functional & Cellular Elements
Mucin Gel	1	Cover, Capture, Deflect, Remove	Loose Mucin labyrinth, sterile dense Adherent Mucin, physical Mucin Transit flow
	2	Neutralize and Preserve	Neutralize using IgA, anti-microbial agents; Preserve epithelium using trefoil factors (TFF1, TFF2, TFF3)
Single Cell Epithelium	3	Antigen & non-antigen Surveillance, Detection, Barrier lubrication & Sustenance	Sample surveillance by αβ-IEL, δγ-IEL, M-cells, dendritic cells, goblet cells; detect mucin disturbance by epithelial transmembrane mucin; lubricate and sustain epithelium by Goblet cells producing mucin, trefoil factors; tuft cells and enteroendocrine cells.
	4	Cap and Close off Luminal Contents	Epithelial Cells with toll-like receptors, tight junctions, epithelial cytokine production, apical transmembrane mucin & cytosol signaling, basolateral growth factors
Lamina Propria and Submucosa to Subserosa	5	Pre-emptive Immune Actions	Innate Immune Cells (ILC)– Class I, II, III interacting with epithelial cells, IEL's, Goblet cells, Dendritic cells, M-Cells
	6	Adaptive Counter-Attack Immune Actions	Monocytes, Macrophages, Mast Cells, B- Lymphocytes, T-Lymphocytes, inflammasome formation
	7	Host Warning and Eliminate Effluent	Enteric glial neurons with 2 classes of voltage-gated receptors (ASIC, TRPV) on afferent neurons, with input to efferent neurons that are responsive to cytokine secretions from IEL, epithelial cells, mast cells and ILC's; these neurons extend from the epithelial cell layer (including tuft cells and enteroendocrine cells) downward into the submucosal plexus and myenteric plexus, with functions for sensory, epithelial, vascular, pain, nausea, emesis and motility.

IEL- intra-epithelial lymphocytes; ILC- Immune Lymphoid Cells; ASIC- acid sensing ion channels; TFF – trefoil factors; TRPV- transient receptor potential vanilloid

The three histological compartments of a healthy mucosal barrier include (a) the mucin compartment, (b) the epithelial compartment and (c) the lamina propria submucosa which extends downward away from the lumen toward (but just beneath) the subserosa. (34, 35) The epithelial compartment is a single layer of diverse cells comprised of enterocytes (the majority), two types of intra-epithelial lymphocytes (αβ-IEL, δγ-IEL), goblet cells, paneth cells, microfold cells, tuft cells (chemosensory) and enteroendocrine cells (containing serotonin). The lamina propria submucosa through to the subserosal compartment contains (a) a host of immune cells including three classes of innate immune cells (ILC1, ILC2, ILC3), dendritic cells, adaptive immune cells (mast cells, monocytes, macrophages, neutrophils, B-cells, T-cells); (b) sectional runs of capillaries and three layers of muscle (submuscularis, circular, longitudinal); and (c) a sprawling network of enteric neurons extending from the subepithelium of the lamina propria to the subserosal area having neuro-epithelial, neuro-immune, neuro-vascular and neuromuscular communications throughout all three compartments.

While polymerized Sucralfate barrier therapies have no direct engagement with the epithelial and lamina propria compartments, their physical engagement of the mucin compartment and that compartment's ability, in turn, to translate or convert signals of biophysical stability into intra-cellular directives act to modulate factors that determine mucosal health.

Mucin Compartment – Site of Action for Polymerized Sucralfate

The mucin compartment contains two layers of mucin, a loose more soluble layer (harboring commensal bacteria, defensive molecules, offensive agents) and an adherent gel layer (36, 37) which is largely free of bacteria. To a large extent, mucin at the lumen interface is substantially hydrated, while mucin deeper in the compartment is adherent to the apical epithelium. Adherence is facilitated by perpendicularly oriented transmembrane mucin (38) sprouting from apical portions of the epithelium and projecting into the overlying less hydrated adherent layer of mucin. Transmembrane mucin is a unique epithelial structure having its distal end extended into the extra-epithelial mucin, a membrane-bound portion that is fixed to the enterocyte, and an intra-cellular cytosolic portion that can detach to participate in signaling pathways (38) responsible for homeostatic, pro-inflammatory and anti-inflammatory processes.

Extracellular sections of transmembrane mucin complexes with trefoil factors, three-leaf clover shaped peptides with cysteine rich areas that facilitate multimeric complexation of adherent mucin and transmembrane mucin. (39, 40) Separately, trefoil factors facilitate continuous epithelial integrity through various processes including that of epithelial restitution. (39, 40)

Lumen-mediated disturbances in para-epithelial mucin can be biophysically detected and in turn physically translated to compartments below, particularly the epithelial compartment. Physical translation can signal structural alterations that are actual, impending or possibly disruptive to the adherent mucin sub-layer. Severe actual disturbances that breach the mucin compartment give rise to common clinical syndromes (symptoms and signs) that can be treated with polymerized Sucralfate barrier therapies. Physical stabilization of mucin through application of a Sucralfate barrier therapy is an effective approach to stave off clinical symptoms and signs due solely to loss of structural integrity in the mucosal lining.

4. Physical Mode of Action asserted by Bioadhesive Sucralfate

The principle of physical engagement utilized by any barrier therapy should be physiologically plausible and preferably demonstrable in some manner. Polymerized Sucralfate barrier therapies preferentially engage mucin. (42-44) Neither denuded epithelium nor basolateral growth factors (located in the subepithelium) provide areas of engagement for polymerized Sucralfate, contrary to reports and assertions made by some without supporting corroborations. (45) Countermanding assertions that sucralfate directly engages epithelial structures or associated growth factors are published transmission electron micrographs, scanning electron micrographs and unfixed freeze-fractured and freeze-dried electron micrographs demonstrating that post-administration, no Sucralfate lays on or near apical epithelium. (42-44) Instead post-ingested Sucralfate is found bound to mucin gel compartment with a decreasing gradient from the outer to inner aspect of the mucin layer. (44)

Polymeric Sucralfate physically engages mucin within the two layer mucin compartment. This physical contact stabilizes it. This physical stabilization of mucin is the device mechanism of action used by polymeric Sucralfate to manage the signs and symptoms of gingivitis, oral surgical wounds, aphthous ulcers, oral lichen planus, chemoradiation toxic mucositis, GERD, radiation proctitis, ulcerative colitis and pouchitis.

5. Relationship between Sucralfate Polymerization and its Clinical Effect

The entire clinical effect of Sucralfate resides in the surface concentration it achieves and maintains over time. Polymerization is Sucralfate's preferred means of achieving and maintaining optimal surface concentration to exert clinical effect. However, all processes of polymerization do not create versions of polymerized Sucralfate that are equivalent in capacity to achieve and maintain surface concentrations sufficient for desired clinical effects. Specifically, if electrostatic and intermolecular ionic charges within resulting polymerized Sucralfate are worn away by hydrogen bonds of surrounding water, then polymerization breaks down, and with it the ability for Sucralfate to achieve and maintain clinically effective surface concentrations.

There are three common processes of Sucralfate polymerization: (i) self-annealing facilitated by moisture of no more than 40% of its dry weight, (ii) gastric acid or mineral acid polymerization and (iii) organic acid (e.g., acetic acid) polymerization. Moisture polymerized Sucralfate is most susceptible to hydration, and thereby dilution, by water. Gastric acid (or mineral acid) polymerized Sucralfate is less susceptible. Organic acid polymerized Sucralfate is least susceptible, and as such most capable of achieving and maintaining Sucralfate surface concentrations sufficient to generate meaningful clinical effects. Sucralfate-based medical devices containing organic-acid polymerized Sucralfate include Orafate/OraHeal gel for oral health, ProThelial paste for chemoradiation mucositis, Esolgafate suspension for GERD, and Colofate enema for management of radiation proctitis, pouchitis and ulcerative colitic conditions.

6. Specific Sucralfate Barrier Therapies

Polymerized Sucralfate Bioadhesive (Orafate/OraHeal) for Dental, Gingival & Labial Uses

Moisture facilitated polymerized Sucralfate applied by caking bulk amounts of powdered Sucralfate to gingival disorders like periodontitis, chronic purulent gingivitis and tooth extraction wounds have resulted in rapid resolution of those medical conditions. (46) The organic acid-facilitated polymerized Sucralfate in Orafate/OraHeal requires but a fraction of amount of moisture-facilitated polymerized Sucralfate to achieve similar outcomes (47) for gingivitis, for cold/hot dental pain, for post-cleaning gingival pain and for labial aphthous ulcers. Orafate (OraHeal) is a Class III medical device authorized by US FDA 510k division with pending CE marks for Europe and Class C authorization in India.

Polymerized Sucralfate Bioadhesive (ProThelial) for Chemoradiation Mucositis of the Oropharynx, Esophagus, Small and Large Intestine

Due to inadequate clinical effects, Sucralfate suspension and gastric acid facilitated polymerized Sucralfate are not recommended for treatment or prevention of chemoradiation toxic mucositis of the oropharynx and GI tract respectively. (48) However, polymerized Sucralfate in ProThelial is associated with complete prevention and rapid sustained elimination of chemoradiation toxic mucositis (49, 50) in the oropharynx and throughout the GI tract, reducing its overall duration by 97%. ProThelial is a Class III medical device authorized by US FDA 510k division with pending CE marks for Europe and pending Class C authorization in India.

Polymerized Sucralfate Bioadhesive (Esolgafate) for Gastroesopohageal Reflux Disease (GERD)

In recent years CE marked barrier devices have been introduced into Europe for the management of GERD and NERD. Their physical mechanism of action involves a multi-component medicinal, which when mixed with water and immediately ingested forms a bioadhesive protective film over the distal esophagus. Ziverel and Esoxx are Class III medical devices containing hyaluronate chrondroitin sulfate and Poloxamer 407. (51, 52) Polymerized Sucralfate in Esolgafate has demonstrated efficacy for GERD. (53) In a 7 day, randomized controlled comparative effectiveness trial, 80% of GERD patients experienced symptomatic relief associated with 83% healing of GERD erosions. (53) Esolgafate is a Class III medical device with pending CE marks for Europe and pending Class C authorization in India. Interestingly, an identical formulation of Esolgafate was previously manufactured by Embiotics Laboratories, but marketed as a branded generic Sucralfate suspension in 2005.

Polymerized Sucralfate Bioadhesive (Colofate) for Radiation Proctitis, Pouchitis and Ulcerative disorders of the Distal GI Tract

Moisture facilitated polymerized Sucralfate has long been used as enema management of rectocolon ulcerative disorders. It has guideline recommendation for radiation proctitis though there are conflicting studies. Key in these reports is the use of either Sucralfate suspensions, i.e. 10% Sucralfate versus a Sucralfate paste. (54) Both enemas, having no exposure to gastric acid, are moisture facilitated-polymerized Sucralfate and have been used to manage ulcerative colitis and pouchitis. (55) Polymerized Sucralfate in Colofate holds promise for the management of radiation proctitis by using Sucralfate polymerized by an organic acid, polymerization that is more resistant to hydration and capable of maintaining prolonged surface concentrations. Colofate is a Class III medical device with pending CE marks for Europe and pending Class C authorization in India.

7. Conclusions

Sucralfate as a therapeutic intervention represents the history of how a quest to understand the biological basis of mucosal health became a door to create therapies that support mucosal health. The peak of a centuries' long mission to comprehend how the stomach does not digest itself was an intervention that facilitate the health of stomach and related mucosal linings. Mucin is the mucosa's physical means to protect itself and Sucralfate, when polymerized in a manner resistant to water hydration, is the physical means whereby the mucin compartment or any accessible mucus lining can be protected because it requires polymerization to exert clinical effect on the mucosal lining, Sucralfate powder, tablets and suspensions are biologically inactive compounds. If the body's participation is required to convert biologically inactive Sucralfate into it biologically active polymerized form, then regulatory speaking, Sucralfate is a drug and should be, as it has been, regulated as a drug.

If, on the other hand, Sucralfate is polymerized outside the body during a process of manufacture, then Sucralfate is a medical device, having only a physical mode of action, and should be regulated as such, as indeed it is in the US and soon to be in Europe and India. As to a physical mode of action, the site of action for polymerized Sucralfate appears to be the mucin compartment of the mucosal barrier. The molecular mode of action for sucralfate has been investigated since 1969, and from 1980 through 2010, (45) no evidence has been published to support a non-physical mode of action for sucralfate. Rather, as stated earlier, transmission scanning and freeze-fracture electromicrographs show (42-44) that post-administration, polymerized Sucralfate has no direct engagement with the apical epithelium where tyrosine kinase receptors reside or with its basolateral lining which harbors growth factors within the lamina propria. There is only physical engagement of the mucin compartment in a manner of decreasing gradient from the outer mucin layer downward to the inner mucin layer. It would appear that inherent to the mucin compartment is an ability to translate signals of biophysical stability from the mucin compartment across the epithelial cell into its cytosol to provide intra-cellular directives that directly modulate factors shaping mucosal health.

Orafate gel (OraHealth), ProThelial paste, Esolgafate suspension and Colofate enema are first generation polymerized Sucralfate bioadhesive barrier therapies trekking through international regulatory bodies. Sucralfate barrier therapies represent the latter half of the regulatory duality of Sucralfate. Sucralfate, a compound first synthesize in Japan in 1967, and subsequently approved by nearly all international regulatory bodies over succeeding 50 years has been regarded by regulatory authorities serving 22% of world's population (or 1.67 billion people) as safe for OTC use. Of course the safety of Sucralfate the drug and of Sucralfate the device is best determined by the regulatory officials serving their respective populations.

For now this first generation of polymerized Sucralfate bioadhesive barrier therapies continues a journey through regulatory authorities one jurisdiction at a time – in a journey inaugurated by the US FDA in 2005, (30) then actualized through its licensing of Orafate (OraHeal) and ProThelial in 2013, and currently progressing through the CE Mark and Class C medical device processes in the EU and in India, respectively.

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Conflict of Interest

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