

IFSCC MONOGRAPH

Number 6

Antiperspirants and Deodorants: Principles of Underarm Technology



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Published on behalf of the
**International Federation of Societies
of Cosmetic Chemists**
by



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General Preface to the Series

There are many excellent, authoritative textbooks covering the different areas which comprise Cosmetic Science. However, certain topics cut across these various disciplines and are best studied individually. From the study of such a topic, a better appreciation can be achieved of the practical use of that topic in the cosmetic field. This series of IFSCC monographs is a collection of such intersecting themes.

It is hoped that the knowledge gained from identifying activities common to a number of areas will be transferable when a chemist moves from project to project. This series of monographs will cover a wide range of themes compiled by experts in their fields, providing both the novice and the experienced individual with valuable reference books on the major topics of Cosmetic Science.

Monographs already published in this series are

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IFSCC Monograph No. 4: *Introduction to Cosmetic Emulsions and Emulsification*

and those in preparation include:

IFSCC Monograph No. 5: *An Introduction to Cosmetics Microbiology*

IFSCC Monograph No. 7: *Micro-emulsions in Cosmetics*

In a further series, the IFSCC has also published

Cosmetic Raw Material Analysis and Quality, Vol. 1: Hydrocarbons, Glycerides, Waxes and Other Esters, edited by Hilda Butler

Foreword

The technology and science associated with the development of safe, effective and cosmetically elegant antiperspirant and deodorant products have evolved rapidly over the past forty years. Advances in our understanding of aluminum and zirconium salt chemistry, the mechanism of action of agents in reducing perspiration, the microbiological efficacy of deodorant agents and claim support methodology, combined with the availability of new cosmetic raw materials and innovative formulation systems, have contributed to the dynamic developments described within this information monograph.

The IFSCC is grateful to Eric Abrutyn and John Wild for preparing this monograph on antiperspirants and deodorants.

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1 General Introduction to Underarm Technology

1.1 Historical perspective of underarm products development

Each region of the human body has a characteristic odor. Some cultures accept body odors as natural, even desirable — even as aphrodisiacs. However, in modern Western civilization, where underarm odor is regarded as unpleasant and socially unacceptable, hygienic and chemical control of both axillae odor and wetness has become a requirement.

Almost 4 000 years ago, offensive underarm odor was a noted concern in China [1,2]. In an effort to control body odors, resinous aromatic gums from trees were mixed with animal fat, then placed on various parts of the human anatomy (including the underarm area), where they melted and released a perfume. As civilizations advanced and people became fastidious about smelling socially acceptable, perfumes (now known as deo-colognes) assumed an important role. It is only during the last 100 years that formulations have been developed and marketed specifically to control and regulate underarm wetness and odor [3].

Table 1
The evolution of underarm odor control

<i>Date</i>	<i>Event</i>
1500 BC	Body deodorants used in China containing resinous aromatic gums mixed with animal fat.
Middle Ages	Personal disinfectant sachets used containing aromatic materials.
1888	MUM® markets an antimicrobial zinc oxide cream that controlled odor but not wetness.
1903	Ever-Dry® marketed as a simple aqueous solution of aluminum chloride that is applied by dabbing on with absorbent cotton.
1914	Odo-Ro-No® garners enough market volume to support a national advertising campaign.
1916	Dr. Stillians reports on the antiperspirant effectiveness of aluminum salts (application of 25% aluminum chloride applied every 2-3 days) [4].
1921	Introduction of buffered aluminum chloride with borax and alum [5].
Early 1930s	Introduction of first cream—Arrid®—which contains aluminum sulfate. Arrid, which was well liked because of its ease of use and aesthetically faster drying, dominates the cream market for the next 20 years; by 1946, creams dominated the underarm products market at 88%.

Table 1 (contd.)
The evolution of underarm odor control

<i>Date</i>	<i>Event</i>
1947	The 5-Day Deodorant® pad is marketed to simplify application.
1950	Van Mater H.C. [6] discloses use of zirconium salts for underarm (by 1973, three of the top four roll-ons contain zirconium salts).
1952	MUM Roulette® is marketed using new roll-on applicator (product fails due to design problems).
1953	Stopette® Spray Deodorant, the first deodorant/antiperspirant squeeze plastic bottle, further eliminates the use of fingers as an applicator.
1955	Ban® Roll-on (Bristol Myers) is introduced and becomes an immediate success (by 1963, it represented 37% of the underarm product market).
1960	Gillette's Right Guard® is introduced as first deodorant containing zinc phenolsulfate and hexachlorophene. In 1968 Gillette introduces Right Guard in an aerosol form for multiple family member hygienic use. In 1972 hexachlorophene was banned due to infant death in France.
Mid-1960s	Introduction of Arrid® Extra Dry as first, true antiperspirant aerosol (within three years, aerosols represent 75% of total underarm products market — 45% antiperspirants and 30% deodorants); by 1970, aerosols represent over 80% of the underarm market (60% antiperspirants and 20% deodorants)— suggesting that aesthetics and form are as important as efficacy for wetness control.
1970s	Elida Gibbs launches Sure® aerosol in the United Kingdom containing an activated antiperspirant active. Gillette launches antiperspirant aerosol with activated antiperspirant active in the US. Gillette's Dry Idea® is launched as anhydrous silicone suspensoid roll-on. Armour Dial launches an anhydrous silicone suspensoid solid stick. Fluorocarbons, considered ozone depleters, are banned in the US, which results in reformulation to lighter more flammable hydrocarbons. FDA bans zirconium-containing antiperspirant actives in aerosol form because of granuloma formation, found in lungs (based on studies conducted by Gillette Medical Laboratories, and believed to be related to aerosol spray inhalation.) Aluminum Zirconium Chlorohydrate complex with glycine buffering agent is introduced. Carter Wallace's Glide-On® as first clear water-in-silicone microemulsion. Mennen's Real® launches as first oil-in-water extrudable.

Table 1 (contd.)
The evolution of underarm odor control

<i>Date</i>	<i>Event</i>
1980s and 1990s	Elida Gibbs' Kyomi® is launched as first product to contain finely milled cellulose to adsorb water from the surface of the skin. Helene Curtis' Degree® and Revlon No-Sweat® are launched as first US products containing encapsulated fragrance and deodorant. Elida Fabergé's Sure® also launched in UK. Chesebrough Pond's launches clear water-in-cyclomethicone emulsion roll-ons, and both Carter Wallace and Gillette launch extrudable clear water-in-silicone gels—almost all other major markets follow suit. Procter & Gamble launches extrudable soft solid sticks. Bristol Myers (Ban®) and Gillette (Sensor Series®) launch first true clear sticks. High active solids antiperspirant as low dosage spray aerosol (Elida Fabergé). Fluorohydrocarbon replaces hydrocarbon (Dial).

1.2 Categorization of global markets

Although the terms *antiperspirant* and *deodorant* are often used interchangeably and are indistinguishable to most consumers, they are not synonyms. Deodorants inhibit or mask odor formation caused by the interaction of perspiration and bacteria, while antiperspirants work primarily to retard sweating by reducing the amount of perspiration excreted from the eccrine sweat glands. Regarding purchase, whether it is an antiperspirant or deodorant is not as important as the consumer's needs. A consumer's concern when purchasing with either an antiperspirant or deodorant is the control of underarm body odor. Thus, the three basic types of needs are: (1) control of underarm wetness, (2) elimination of underarm odor, and (3) provision of an aesthetically pleasing application that does not whiten axillae or stain garments. In the United States (US), Canada, the United Kingdom (UK), and Australia, antiperspirant products represent the dominant product category by as much as 80 percent. However, in many other parts of the world, where underarm wetness is socially acceptable, deodorant products dominate the market. Deodorant products are perceived as more natural without affecting the physiological function of the body.

On a global scale, the underarm market is represented by a number of product forms: sticks, aerosols, extrudables, roll-ons, creams, and pump or squeeze sprays. Preferences for use of them vary greatly around the world. For example, the European, Canadian, and Australian markets are dominated by aerosols (although a move to environmentally "friendly" product forms is growing), the US market is dominated by solid sticks (>55%), and the Mexican, Central American and South American markets favor roll-ons and sprays.

1.2.1 United States

Over the years, the US underarm products market has evolved due to: regulatory restrictions; breakthroughs in active performance and product aesthetics; and new product application delivery forms. Prior to the 1950s, the market was dependent on pads, creams, and solutions of harsh acidic salts or alcohol. However, as a result of the patenting of such things as the ball-point pen and the aerosol spray can [7,8], the antiperspirant/deodorant market changed. From the ball-point pen, roll-on deodorant applicators were developed (supported also by the commercialization of plastic for packaging); from aerosolized paint, fluorocarbon sprays for deodorant/antiperspirant applications were developed. These inventions, plus the patenting of a more basic antiperspirant salt — basic aluminum chloride later named aluminum chlorohydrate [9,10] — led to the creation of aesthetically improved, longer-lasting antiperspirants. Likewise, the development of hexachlorophene, which provided excellent antimicrobial activity, fueled the popularity and growth of deodorants, although the substance was banned in 1972 by the Federal Drug Administration [11] due to concerns about infant deaths in France.

The market again changed significantly in the 1970s, as, first, a concern arose over the safety of inhaling the aluminum and aluminum-zirconium salts released from aerosol spray cans [12,13], and, secondly, fluorocarbons, considered ozone depleters [14], were banned. With no readily acceptable aerosol replacement and consumers becoming environmentally concerned, the market shifted to cyclomethicone suspension sticks, which captured almost 50% of the market within two years. Subsequently, the late 1970s brought about a better understanding of the chemistry of aluminum-containing active salts [15a,b,c] and the development of "activated" [16a,b,c] versions of antiperspirant salt actives (based on controlled polymeric distributions) — further decreasing sweat production by an additional 25 – 50%.

Today over 90% of the US population uses some form of antiperspirant or deodorant on a daily basis [17a,b;18]. Roughly 80% of these consumers apply some type of antiperspirant (primarily solid cyclo-methicone suspensoid). The remaining $\approx 20\%$ apply some type of deodorant (primarily solid sodium stearate sticks and deo-cologne aerosols), with men representing the largest segment of this market.

Regarding purchase of an underarm product, the US consumer's decision-making process is driven by product claims and history of product performance. Claims made by manufacturers/marketers of underarm products include: "most effective antiperspirant ingredient available", "time release formula for longer lasting odor protection", "body-heat activation releases extra protection", "works harder", "sensitive skin formula", "clear formula leaves no white residue", "dermatologist tested", "goes on dry with no messy white residue", "pH balanced", "so effective you could even skip a day", and "more odor and wetness fighting ingredients". Additionally, antiperspirants must meet minimum efficacy and safety requirements as outlined in the Food and Drug Administration's tentative final monograph (documents describing how an antiperspirant can be manufactured, sold and used).

1.2.2 Europe

The European market has been undergoing rapid changes. Thus, forecasts of trends and demographic information become outdated almost immediately. Current European trends are based on the advent of multinational companies; an increase in the movement of people, opening Common Market borders, shared European advertising, depilatory hair removal in the underarm area (historically, European women have not shaved their underarms), and a changing personal hygiene attitude, especially of youth, toward control of underarm wetness and odor via aesthetically pleasing products [19].

Currently, the European market, comprising the United Kingdom and Continental Europe, appears to be switching to "dry" and "mild" underarm products. This switch is reflected by current advertisement claims: "effective and reliable", "24-hour protection against wetness and odor", "guarantees 24-hour total protection", "advanced formula that does not contain alcohol", "skin friendly, ultra mild-ultra protection", "formulated with effective deodorant and antiperspirant agents", and "super dry" [20].

The United Kingdom's underarm products market, dominated by the usage of aerosols, parallels the US in market segmentation for users of

antiperspirants and deodorants. However, Continental Europe's underarm market is divided into many differing cultural biases. For the most part, deodorants represent the majority of the continental European market, with fragrance-masking aerosols holding claim as the dominant application form.

France, focused on fragranced deodorant delivery, is starting to move toward a form of antiperspirants called "activated deodorants". This product category is based on a small amount of an antiperspirant active for drier underarms, but does not claim to "stop wetness". However, aerosol forms currently dominate the French market, with sticks starting to improve in market share.

Germany, typically against the chemical reduction of sweat and odor, has a growing antiperspirant market. At present, aerosols (44% and declining), pumps (23% and growing) and roll-ons (20%) lead the way.

Other European markets are growing: they tend to follow the German and French markets. For example, Italy has a growing market, geared towards a unisex antiperspirant (in various forms) — currently, aerosols represent 70% of Italy's market — and Spain has a mixed underarm products market of aerosols (49%), sticks (26%), and roll-ons (16%).

1.2.3 Latin America

The Latin American market has historically been based on simple aqueous-based products. However, with an improving standard of living, the underarm products market there has significantly improved. There has been a shift in the market to premium-valued, silicone-containing products that deliver more aesthetics. Fragranced deodorants lead in the market, but products with claims of super dry and extra protection are growing.

Latin America can be segmented into two areas: northern and southern. The northern portion tends to follow trends from the US and the southern portion tends to follow trends from Europe. Mexicans and Venezuelans tend to stay away from aerosols because of pollution and environmental concerns. Thus, 60% of underarm products users from Mexico and Venezuela use water-based roll-ons, and 40% use sticks. Furthermore, Brazilians focus more on use of hydro-alcoholic-based squeeze bottles (80% usage); Colombians favor finger application of water-based creams (80% usage); and Chileans and Argentinians primarily use aerosols (65%).

1.2.4 Far East/Australia

The Australian market tends to parallel the United Kingdom, with 80% antiperspirant users and greater than 50% applying via aerosol applicators. Antiperspirant actives are regulated under the Australian Therapeutic Goods Act (covering active level in finished product, type of acceptable actives, and label claims). New Zealand's market is similar to Australia's, except that roll-on applicators dominate. The rest of the Far East has traditionally focused on good hygiene and fragrance masking; however, there is a growing trend toward antiperspirant use. Part of this is the result of an influx of multinational companies in the Far East and Western business people working at these businesses. Antiperspirant/deodorant products in the Far East are classified closer to pharmaceuticals and controlled by regulations similar to those in Japan [21].

2 Governmental/Country Regulations

2.1 United States federal regulations: Tentative Final Monograph (TFM) review

As a result of several events, the US has led the way in defining food, drugs and cosmetics. Since the US is the primary market for antiperspirant products, its regulatory guidelines have formed and continue to form the basis for global clinical testing parameters required to label a product as an antiperspirant. First, in 1938, the US Congress passed the Federal Food, Drug, and Cosmetic Act [22]. This, in turn, led to the formation of the Food and Drug Administration (FDA) [23], which regulates adherence by businesses to the FDA regulations. Second, in 1962, a guideline on how to develop rule-making regulations for over-the-counter (OTC) purchases of non-physician prescribed drugs, was published in the Federal Register [24] (a federal publication on Congressional regulations). In 1972, the FDA followed this up by publishing rule-making procedures on: classifying OTC drugs as generally recognized as safe (GRAS) and/or generally recognized as effective (GRAE); and how properly to label drugs — defined in 21 US Code 32 (g)(1) section 201 (g)(1). Third, in 1974 a task force — the Antiperspirant Review Panel — was organized to develop an antiperspirant monograph that would define the elements to be considered as antiperspirant actives, how to register underarm products with the FDA, what information should be disclosed on antiperspirant and deodorant products (such as labeling and product claims), and inspection protocol.

On March 15, 1974, the Antiperspirant Review Panel convened, only to culminate on January 26, 1978, with a tentative final monograph — known henceforth as the OTC Antiperspirant Drug Products Tentative Final Monograph or TFM (this monograph was published in the Federal Register in October 1978 [25]). Since 1978, the TFM has been amended twice: in 1982 [26] and in 1990 [27]. In its amended form, the TFM, though not finalized and approved by Congress, serves as a reference for all aspects of manufacturing of underarm products, to include packaging, manufacturing, safety and effectiveness.

Packaging must (a) maintain stability; (b) not migrate to product; (c) bear labeling of directions for use, warnings, and active ingredient disclosure; and (d) bear only those claims supported by final product testing for safety and effectiveness. Manufacturers must (a) comply with good manufacturing procedure (GMP)

regulations; (b) meet FDA requirements for: personnel, building and facilities, equipment, production and process control, packaging and label controls, holding and distribution controls, laboratory controls, records and reports, returned product control, and documentation retention; and (c) register with FDA and undergo regular inspections.

As part of the TFM and Federal Food, Drug, Cosmetic Act, a drug, defined as anything that can affect the physiology of the human body, needs to be regulated to protect the public from misuse and misrepresentation. With regard to antiperspirants and deodorants, the TFM states that if the only action of a preparation is to stop perspiration, such a product is a drug. If, however, the only action of a preparation is to absorb perspiration or to mask its odor, it is a cosmetic. Also, depending upon the claims made by manufacturers/marketers, a product can be considered a cosmetic or a "cosmetic drug" [28]. Thus, manufacturers of deodorants are excluded from adhering to the stipulations of the TFM because deodorants have cosmetic claims, while the manufacturers of antiperspirants, which have drug claims [29], are subject to TFM guidelines.

Safety and effectiveness testing guidelines of antiperspirant products are regulated by required test protocol, which is discussed later (in addition to being delineated in the TFM). All antiperspirant products must meet a minimum 20% sweat reduction in 50% of a test population — via statistically validated methods.

Once approved by the FDA, an antiperspirant product is not to undergo changes in formulation, packaging, or manufacturing unless FDA and other regulatory agency requirements (e.g., Fair Packaging and Labeling Act, National Advertising Board, Environmental Protection Act, Federal Trade Commission, etc.) are met. Prior to manufacturing of proposed new antiperspirant actives (as defined in the TFM for safety and effectiveness), a business must file an Investigative New Drug Application (INDA) or a New Drug Application (NDA). To receive approval to proceed, a manufacturer must demonstrate that the proposed product will meet safety standards and be effective. Safety testing guidelines were also published in the Cosmetic, Toiletry, and Fragrance Association's (CTFA's) technical guidelines [30] in 1983. (The CTFA, the US trade association representing the cosmetic, toiletry, and fragrance industry, was founded in 1894. Currently, it has over 270 participating companies that manufacture or distribute the vast majority of the finished cosmetic products marketed in the US.)

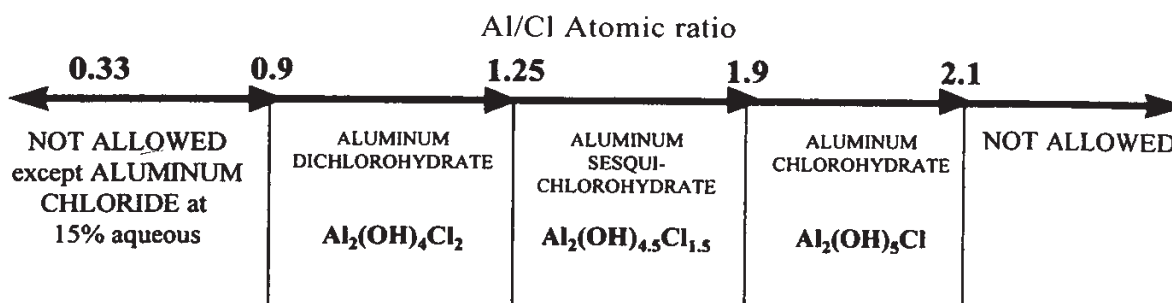
According to the original TFM draft, antiperspirant actives fell within two categories. Prior to developing categories, there were many products being used and claimed as antiperspirants. After drafting of the TFM, comments regarding all aspects of underarm products were allowed from the public. These comments, as well as scientific knowledge, were incorporated and as a result three categories of antiperspirants were proposed. Products not included in category I, *generally recognized as safe and effective*, were either placed in category II, *not generally recognized as safe and effective*, or category III, *available data are insufficient to classify as safe and effective and further testing is required*. In 1990 [31], category III was eliminated since it was assumed that if a product does not have sufficient data to determine its safety or effectiveness, then it really belongs in category II.

Category I contains the following actives:

Aluminum chlorohydrate
Aluminum sesquichlorohydrate
Aluminum dichlorohydrate
Aluminum zirconium pentachlorohydrate
Aluminum zirconium octachlorohydrate
Aluminum zirconium tetrachlorohydrate
Aluminum zirconium trichlorohydrate
15% aluminum chloride (aq. only)
Aluminum sulfate + sodium aluminum lactate (1:1)

Table 2

Allowable composition ranges for ACH in antiperspirant products



Equation 1

Aluminum chlorohydrates (ACH) empirical formula

where $1/0 < x/y < 1/3$, $y + z = 3$, and x , y and z are not necessarily integers

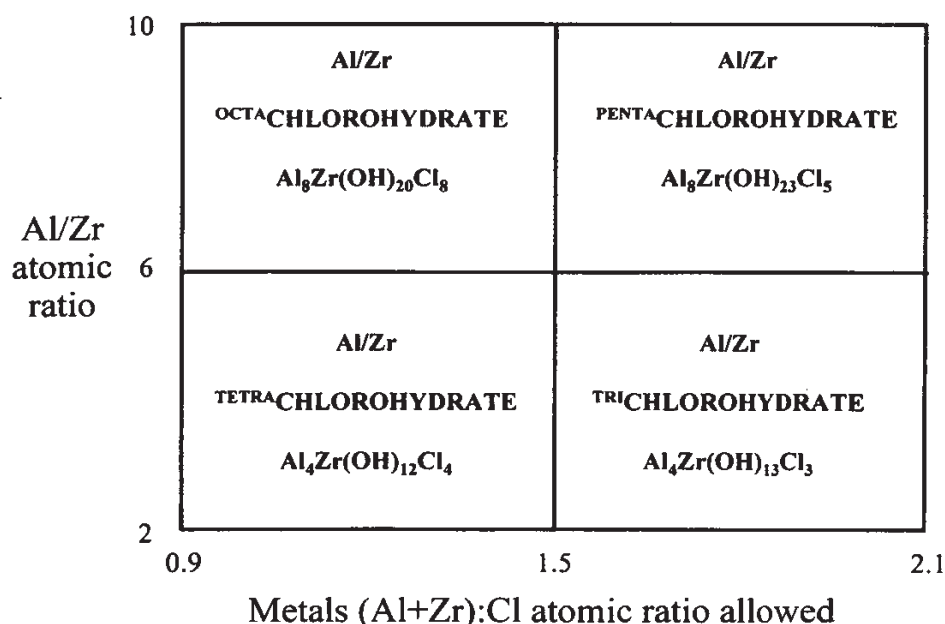
Allowable aluminum chlorohydrate (ACH) compositions for category I actives are outlined in table 2 [32] above to show atomic ratios of total metals to chloride. Equation 1 specifies the formula representations of the polymeric distributions of the ACH actives.

The lower limit of equation 1 represents the non-neutralized acid, aluminum chloride, while the upper limit represents the complete neutralization/hydrolysis-aluminum hydroxide. Consequently, the many hydrolysis products between aluminum chloride and aluminum hydroxide are present in ACH and formed during the partial neutralization of aluminum salts.

Allowable limits for aluminum zirconium chlorohydrates (AZG) are shown in Table 3 [33]. Equation 2 specifies the formula representations of the polymeric distributions of the AZG actives.

Table 3

Allowable composition ranges for Al-Zr in antiperspirant products



Equation 2

Aluminum zirconium chlorohydrates (AZG) empirical formula



where $10/1 > x/w > 2/1$, $(x + w) < 7/12$, $y + z = 3x + 4w$, and x , w , y , z , and q are not necessarily integers

Lower limit = AlCl_3 (aq.) and ZrCl_4 , ZrOCl_2 (aq.)

Upper limit = $\text{Al}(\text{OH})_3$, $\{\text{Al}_2\text{O}_3 \cdot n \text{H}_2\text{O}\}$, $\text{Zr}(\text{OH})_4$, $\{\text{ZrO}_2 \cdot n \text{H}_2\text{O}\}$

Besides the type of actives allowable as antiperspirants, there are regulations defining the maximum amount of an active that can be used in a formulation and still be considered safe and/or effective. Therefore, in all delivery forms (except where noted):

- ❑ aluminum chlorohydrates cannot be used above a maximum of 25%, calculated on an anhydrous basis.
- ❑ aluminum zirconium chlorohydrates cannot be used above a maximum of 20%, calculated on an anhydrous basis and in only non-aerosolized products.
- ❑ aluminum chloride can be used to a maximum of 15% in non-alcoholic, non-aerosolized products.

An example of a calculation to determine the active level in a formula is as follows:

Assumption:

Aluminum chlorohydrate with an anhydrous empirical formula of $\text{Al}_2(\text{OH})_5\text{Cl} \cdot \text{H}_2\text{O}$ and having an analysis of 24.9% Al and 16.3% Cl as supplied (theoretical molecular weight equal to 174.5, 30.9 mole % Al, and 20.3 mole % Cl).

Calculation:

30.9 mole % Al (anhydrous) divided by 24.9% Al (actual in ACH powder) equals a factor of 1.241.

Therefore, 1.241 (factor based on aluminum content) times 25% allowable ACH active equals 31% ACH as purchased (actual).

20.3 mole % Cl (anhydrous) divided by 16.3% Cl (actual in ACH powder) equals a factor of 1.245.

Therefore, 1.245 (factor based on chloride content) times 25% allowable ACH active equals 31.1% ACH as purchased (actual).

Taken as the average from aluminum and chloride calculations, the maximum allowable ACH (as purchased) in formulations would be 30.85%.

3 Fundamental Understanding of Underarm Actives

3.1 Bacteriology of human axillae: the sweat glands

Underarm perspiration comes from the sudoriferous (sweat) glands and assists the body in three important ways: (1) in regulating body temperature (dispelling of heat); (2) in removing lactic acid (formed during muscular exercise); and (3) in moistening and protecting the skin from dryness (even though the moisture can be considered offensive) [34]. Basically, there are two types of underarm sudoriferous glands: apocrine and eccrine [35;36a,b;37]. The eccrine glands, although much smaller than the apocrine glands, are responsible for the majority of sweat production, and consequently have received major attention. Yet eccrine sweat, a highly dilute aqueous solution, has been proven to be of lesser importance in the production of axillae odor than that from apocrine glands [38,39]. Regardless, the moisture from eccrine glands promotes odor in two important ways:

- (1) Eccrine gland excretion is thought to form and cause a sticky oily material with axilla apocrine gland excretion, enhancing the spread over a wider surface;
- (2) Eccrine sweat, trapped in the warm axilla vault, provides an ideal environment for the proliferation of resident bacteria, which act upon the non-odorous sterile underarm excretion [40] to form the characteristic body odor.

Additionally, axilla hair has also been found to promote the development of odor. It is thought that axillae hair, with its particularly large surface area, provides a collecting site for apocrine and eccrine sweat, and subsequently bacterial proliferation.

It has been estimated that there are over two million eccrine glands distributed over the body surface. These glands differ in size and concentration depending upon where they are located on the body. Except for in the nail beds, glans penis, glans clitoris, labia minora, eardrums and lip margins, eccrine glands can be found throughout the skin.

Table 4 lists the distribution of eccrine glands throughout the body.

Table 4
Distribution of eccrine glands throughout the body

<i>Area</i>	<i>Number of sudoriferous glands (per cm³)</i>
Palm	370
Back of hand	200
Forehead	175
Forearm	155
Leg	80
Back	60 – 100
Axilla	90 – 200

Based on population density of the sudoriferous glands, age, sex, race, acclimatization to temperature change, and environmental humidity, there are differences in individual perspiration production levels. Sweat production, basically, is triggered as a response to either thermal changes (e.g. physical or environmental) or emotional responses (e.g., mental stress). For example, a person possessing about twenty thousand sweat glands in the axillae, can produce between 400 to 1000 milligrams of sweat per hour by sitting quietly in a warm environment; yet, should this same person undergo emotional stress, the volume could be increased four to eight times.

Of the sudoriferous glands, the eccrine glands, or small coil glands, are considered the true sweat glands. These simple coiled tubular glands are located in the subcutaneous layer of the skin with an excretory duct projecting up through the dermis and epidermis to a terminal pore at the surface of the epidermis. They excrete a clear, dilute, hypotonic, electrolyte salt solution composed primarily of sodium chloride, potassium ions, and carbonic acid. Other components include, but are not limited to, lactates, urea, and ammonia [41a,b]. As a consequence of osmotic gradient, these aqueous excrements are transported through the glandular membrane and then to the skin surface — resulting in wetness in the underarm area — utilizing a highly specific inhibitor of Na^+/K^+ ATPase enzyme [42a,b].

In contrast to the small coiled eccrine glands, there are the apocrine glands, or large coil glands. As these glands begin to function at puberty and under hormonal control, they have been associated with sexual development; they occur in relatively small numbers and are found primarily in the axillae, around the nipples, on the abdomen, and in the

pubic region. The secretory portion of an apocrine gland is in the dermis layer of the skin, with its relatively large (approximately 40 micron) excretory duct opening into a hair follicle. Axillae secretions from apocrine glands are sterile and odorless, yet have long been considered the major contributors to axillae malodor. This is because apocrine secretions — viscous, milky fluids rich in organic compounds [43a,b] — are readily attacked and decomposed by skin bacteria. The amount of apocrine secretion is increased by emotive stimuli such as fear and fright.

Decomposition of glandular secretion, both eccrine and apocrine, results from the efforts of various organisms residing in the axillae. In most axillae, well over 90% of the organisms present are either aerobic diphtheroid, coagulase negative staphylococci, or a combination of these two groups [44]. Axillae bacteria are almost exclusive to aerobic coryneform of the species *Corynebacterium xerosis* (71%) [45]. Other aerobic coryneform, such as *Corynebacterium psuedo-diphtheriticum*, *Corynebacterium minutissimum*, or *Brevibacterium epidermidis*, have also been reported present in the axilla.

Through investigation, it has been suggested that these organisms cause the degradation of sudoriferous gland excretions, resulting in malodors [46,47,48]. It has also been shown that the action of cocci bacterium on apocrine secretions produces a "sweaty" odor, which has been identified as short-chain fatty acids such as isovaleric acid and butyric acid [49]. In another vein, investigators [50,51] believe that the pungent/acrid musk-like odor generated in the axillae is strongly related to the formation of specific steroid 16-androstene compounds. The source of the 16-androstene odor is thought to be caused by action of coryneform on such materials as cholesterol and other steroid compounds present in apocrine secretions. Androsterone and androstenol exist in the apocrine secretions as water-soluble sulphates and glucuronides, produced only after the volatile free steroids are liberated due to bacterial hydrolytic enzymes, such as aryl sulphatase and β -glucuronidase. Although the levels of these steroids on the axillae surface are extremely low, the potency of 16-androstene compounds is so great that they have been postulated as a major contributor to underarm odor — the human olfactory threshold for androsterone, for example, is only 0.2 ppb.

3.2 Mechanisms for sweat reduction: theories and models for sweat reduction

There are a number of theoretical models to explain the action of antiperspirant salts on the eccrine gland. The most common antiperspirant salts — or active — used are aluminum chlorohydrate and aluminum-zirconium chlorohydrate-glycine (discussed in the next section). These antiperspirant actives work, first, toward retarding sweating by reducing the amount of perspiration from eccrine glands, and, second, toward inhibiting bacterial growth. These actives can cause a decrease in sweat production at the glandular level, via (1) formation of a blockage (or plug) deep within sweat ducts, (2) alteration of sweat duct permeability to fluids (as in a perforated water hose), as well as (3) bio-response near the surface entrance of eccrine sweat glands, forming a superficially obstructive plug to inhibit the excretion of sweat from the sweat glands.

Explanation of the various theories regarding axillae sweat inhibition can be found in various review articles, books, and authors' private communications [52a,b,c;53]. A general overview to some of the more important theories follows:

- (1) Formation of a "keratin plug" — an antiperspirant salt denatures and binds to keratin protein, disrupting the stratum corneum and causing a functional closure of sweat duct.
- (2) Formation of an "occlusive plug" — functions to form an obstructive plug of hydrolyzed metallic cationic salt (through the action of pH change upon entering the eccrine duct), closing the sweat gland by forming an occlusive metal hydroxide salt plug.
 - (a) "Modified occlusive plug" [54] — takes into account the rate of formation of an obstructive plug due to the rate of complete hydrolysis of the metallic cationic salt, since antiperspirant actives may have a dependency on the thermodynamic stability of hydrolysis by-products.
- (3) The "leaky hose" — metal cationic actives alter permeability of the electrolytic fluid across an eccrine duct membrane, causing re-adsorption rather than transportation of sweat.
- (4) The "electropositive charge" — an antiperspirant salt causes an electropositive charge, which reverses a sweat gland's negative charge potential to a strong positive charge on the skin surface, thus inhibiting sweat production.
- (5) "Anticholinergic activity" — prevents cholinergic neurological triggering.

Today, the "occlusive plug" theory is the most recognized theory of inhibition of glandular excretion from the eccrine gland. This theory was first proposed by Reller and Leudders [55]; However, groundwork for the theory was laid earlier by Papa et al. [56] and Gordon et al. [57]. In 1981, Quatralle et al. published a series of articles [58,59] delineating the "occlusive plug" theory with ACH, AZG, and aluminum chloride salts. Quatralle's Scotch® tape stripping techniques — histological examining of a morin dye stain strip specimen with transmission electron microscopy and optical fluorescence — demonstrated that an obstructive material was located near the surface entrance of eccrine gland ducts shortly after application of an antiperspirant salt. They also noticed that (1) after stripping of the occlusive plug, about 50% of treated sweat glands resumed producing sweat after the obstructive plugs were removed; (2) that aluminum chloride plugging was deeper than either ACH or AZG, and ACH was deeper than AZG; and (3) aluminum chloride treated eccrine glands took longer to resume functioning. One interesting observation was that even though AZG-caused plugs were not as deep as ACH-caused plugs, the AZG sweat reduction effectiveness was greater. Consequently, the theory that a deeper plug would result in a greater degree of sweat reduction was weakened.

3.3 Mechanism for deodorancy: odor development and controlling actives

We have discussed how to control eccrine gland excretion, but there is also a need to control the underarm malodors. Most approaches center around either (a) the control of malodor by use of deodorant actives (e.g., antimicrobials, antioxidants, and enzyme inhibitors — acidifiers) or (b) the counteracting of malodor by use of odor absorbers (e.g., sodium bicarbonate) and perfume masking agents (these can also possess antibacterial or enzymatic properties which contribute toward their effectiveness). Perfumes and antimicrobial deodorants are widely considered the norm and most popular in controlling axilla odor.

A variety of materials have been promoted for reducing malodor [60,61]. They include:

- ▣ Topical application of antiperspirants (e.g., aluminum chlorohydrate [62a,b,c]) and aromatic ethers (e.g., 2,4,4'-trichloro-2'-hydroxydiphenyl ethers [63]) possessing antibacterial activity and resulting in localized reduction of sweat gland activity (typically called "Activated Deodorants" in Europe).

- ❑ Antioxidants (e.g., vitamin E, BHT, BHA) which generally complement the action of antibacterial agents although vitamin E and BHT are no longer recognized as safe for use in US deodorant marketed products [64].
- ❑ Esters (e.g., derivatives of hydroxycarboxylic acid—triethyl citrate) which deactivate/inhibit degradative enzyme system of bacteria, thus causing a breakdown of the bacteria wall integrity.
- ❑ Odor suppressers which adsorb low molecular weight odoriferous organic compounds (e.g., zinc ricinoleate) and neutralize low molecular weight fatty acids (such as mild bases, e.g., sodium bicarbonate).
- ❑ Vapor pressure modifiers which cause reduction of volatile malodorous substances.
- ❑ Odor modifiers (e.g., perfumes) which blend with axillae malodor, making it less offensive.

There are three different approaches used for controlling underarm malodor:

(1) *Odor masking/disguise*: This method involves masking unwanted odor by overpowering or disguising it. Strong perfumes are typically used in deodorants to overpower underarm odor. Levels of perfumes in deodorants can vary from fairly low levels (0.5% of total formulation) to levels as high as 10%. Both Sturm [65] and Morris et al. [66] provide reviews of fragrance components and combinations of fragrances with deodorant actives.

(2) *Odor reduction/removal*: Materials can be added to underarm deodorant formulations to adsorb or absorb odors, particularly low molecular weight excretion components. However, these materials usually work on specific chemical types and thus have limited use. Other materials can be added to deodorant formulations to adsorb glandular excretion physically, therefore slowing down bacterial growth. Also, acid salts can act chemically as either mild alkalis or mild acids (e.g., sodium and potassium bicarbonates). Different hybrid powders, fiber systems, and elastomeric systems have been suggested for this purpose.

(3) *Odor Prevention*: This approach is aimed at inhibiting the growth of surface bacterial micro-organisms in the axilla. Antibacterial agents are by far the most often used materials in deodorant formulations to prevent or slow down odor formation. Other actives provide enzyme inhibition or anti-oxidation.

In the US, zinc oxide and aluminum chloride were the first antibacterial agents used in deodorants. There was no doubt about the performance of these substances; however, their form of application, their objectionable odor, and the safety of the formulations in which they were used were not totally acceptable. In 1941, researchers at Givaudan Corporation discovered that halogenated bisphenol structures (e.g., hexachlorophene) exhibited bacteriostatic qualities when incorporated in soap. Thus, for aesthetic and mildness reasons, hexachlorophene replaced the then popular zinc oxide and aluminum chloride. But, in mid-1971, the FDA issued a report stating that brain lesions could be produced in test animals by feeding them high dosages of hexachlorophene. As a result, in 1972, the FDA banned the use of hexachlorophene in all non-prescription products [67]. Consequently, trichlorocarbanilide (also known as triclocarban — effective against Gram-positive bacteria [68a,b]) and 2,4,4'-2-hydroxydiphenyl ether (also known as triclosan and effective against Gram-positive and Gram-negative bacteria [69a,b,c]) along with aluminum salts [70a,b,c;71a,b,c], began to be used in place of hexachlorophene. Europe tends to follow the US guidelines.

The most common underarm antimicrobial agent is triclosan. Used in underarm deodorants and bar soaps [72], it is an effective broad spectrum antimicrobial agent against Gram-positive and Gram-negative bacteria; typical use levels are between 0.03 – 0.3%. It is thought that the antimicrobial mode of action is the result of interference of the amino acid uptake through a bacterium's membrane.

Other underarm malodor-controlling materials that can provide deodorant activity include:

- (1) Surface active agents — act as antimicrobial agents (e.g., monoesters of lauric acid [73] and quaternary ammonium compounds [74a,b,c]), although there is concern for irritation and sensitization.
- (2) Ethanol — used as a vehicle in deodorant products; also acts as an active antibacterial agent.
- (3) Terpenes — found to have good antibacterial activity and typically found as one of the components in underarm fragrance.
- (4) Blend of magnesium nitrate, magnesium chloride, 5-chloro-2-methyl-4-isothiazolin-3-one, 2-methyl-4-isothiazolin-3-one acts as antimicrobial agent, but not considered safe for leaving on the underarm skin surface.
- (5) Metallic salts of ricinoleic acid (e.g., zinc ricinoleate) cause a deodorizing effect that can be intensified by adding small quanti-

ties of derivatives of polyhydroxy fatty acids or resinic acids; show marked reactivity toward low molecular weight organic compounds with functional groups containing amino hydrogen and mercaptol sulfur.

(6) Antioxidants such as BHT and tocopherol (these prevent or hinder the oxidation of axillae components).

Unfortunately, most of these classes of materials have either health or regulatory issues associated with them. Thus, before using any of them in a deodorant product, it is necessary to pay attention to regulations and manufacturer's safety data regarding intended use.

4 Antiperspirant Active Salts

4.1 Chemistry

Little has been written about the characterization of active antiperspirant salts, such as aluminum chlorohydrate, and their relationship to the hydrolysis chemistry of aluminum and, to some extent, zirconium. Yet reviews by White et al. [75a,b,c] (structural determination of aluminum chlorohydrate), Fitzgerald [76] (summary literature on aluminum-containing actives), and others [77,78], begin to discuss the complexity of the structure-physical property-chemistry relationship of active antiperspirant salts and their hydrolysis chemistry.

Aluminum- and zirconium-containing antiperspirant salts (AP actives) are finite distributions of various structures of polycationic, protonated oxohalides. When aluminum is the only metal present, the AP active is known as aluminum chlorohydrate ("ACH"). When zirconium is present along with aluminum, the AP active is known as aluminum-zirconium chlorohydrate. As the aluminum-zirconium chlorohydrate active is most often buffered with glycine, it is also known as "ZAG" or "AZG". The various synthesis routes of ACH involve the partial hydrolysis of an acidic aluminum salt. AZG involves the subsequent reaction of the ACH product with a zirconium-containing complex such as zirconyl chloride or zirconyl hydroxychloride [79a,b]. Through heat and dilution processing steps, these species of aluminum and aluminum-zirconium chlorohydrates can further be modified or "activated". An "activated" AP active is based on controlling the polymer distributions, where both the molecular weight and structure are modified when compared to historical "standard" AP actives, and they are reported significantly to improve sweat reduction.

To understand the potential impact on sweat reduction efficacy, one first needs to understand the synthesis mechanism and inter-relationship of hydrolysis chemistry of various poly-oxo-aluminum species of aluminum-containing AP actives. Equation 3 below depicts the overall hydrolysis relationship and kinetics that result in polymer formation of aluminum oxides/hydroxides. The monomeric aluminum oxide/hydroxide, $\text{Al}(\text{OH}_2)_6^{3+}$, is the least hydrolyzed, and the solubilized aluminum oxide/hydroxide, $\text{AlO}(\text{OH})_2$, network is the most neutralized material that can exist prior to precipitation of insoluble aluminum oxide/hydroxide, $\text{Al}(\text{OH})_3$. As discussed earlier, it is postulated that inhibition of sweat excretion from the eccrine glands is based somewhat on the for-

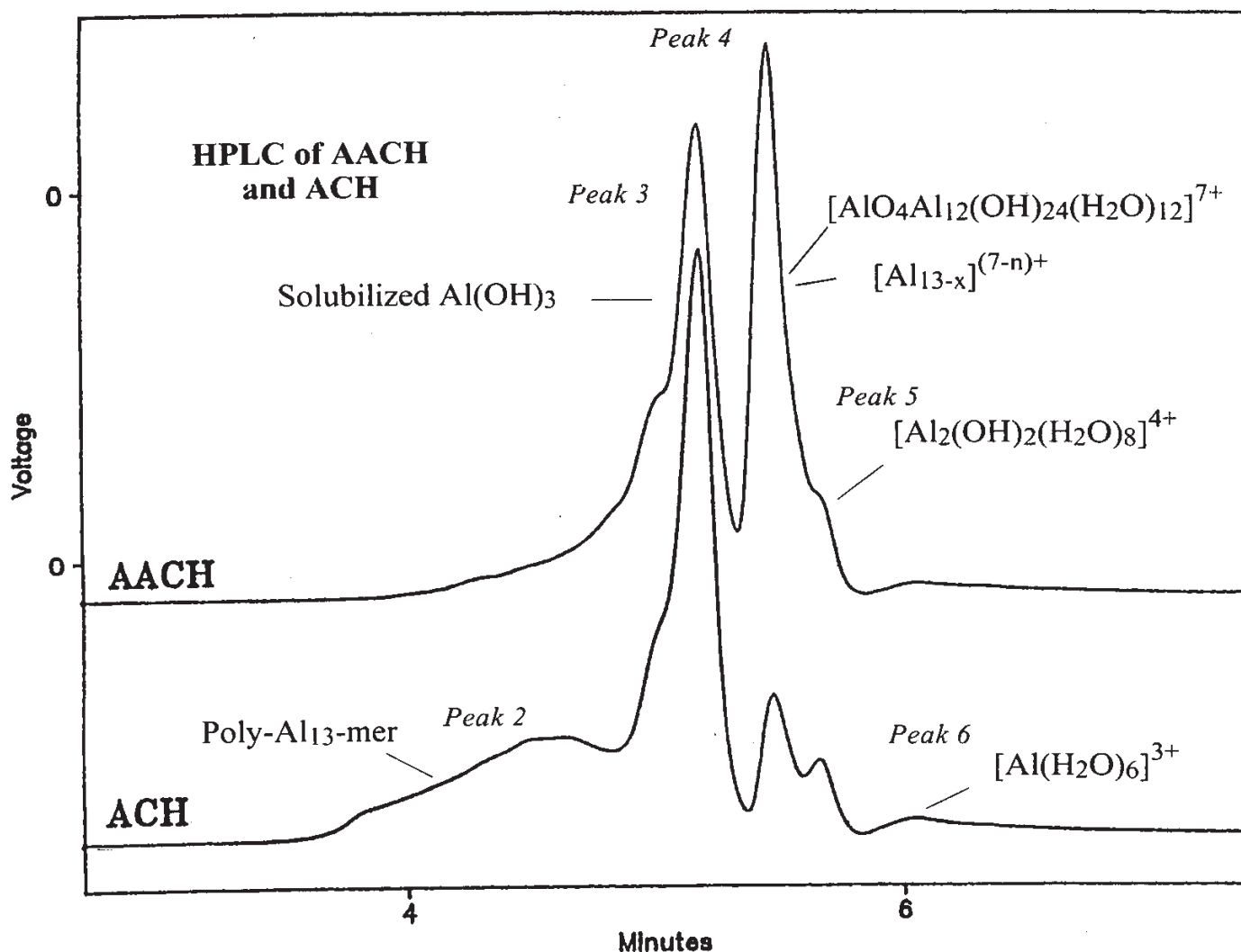


Figure 1
Typical SEC/GPC structural distribution of ACH

acid), and subsequent hydrolysis of aluminum metal to hexaquo Al^{+3} . This method of synthesis is described in early patents [85a,b]. The species $\{\text{Al}_2(\text{OH})_5\}^+$, most commonly written in the neutral form $\text{Al}_2(\text{OH})_5\text{Cl}$, has come to be recognized as "ACH". This empirical formula specifies the most commonly encountered atomic/molecular ratio of Al/Cl in commercial ACH salts. In the commercial world, ACH antiperspirant actives are provided in many different forms, although most often as an aqueous solution (50 percent) or a dry powder. In powder

form, ACH has a particle size which may vary from spherical (>100 micron) to super-fine micronized powders (<10 micron). Table 5 provides additional information on the physical properties of typical ACH actives.

Table 5
Physical properties of typical ACH actives

<i>Test method</i>	<i>50% Aqueous solution</i>	<i>Milled powder</i>
%Al	12.2-1.27	24.4-25.6
%Cl	7.9-8.4	15.8-17.0
Atomic ratio Al/Cl	(1.9-2.1)/1	(1.9-2.1)/1
Specific gravity at 15°C	1.335-1.345	—
pH (15% solids)	4.2-4.4	4.2-4.4
Particle size	—	100% < 75 micron

Figure 2 shows a typical particle size distribution for a few different ACH actives.

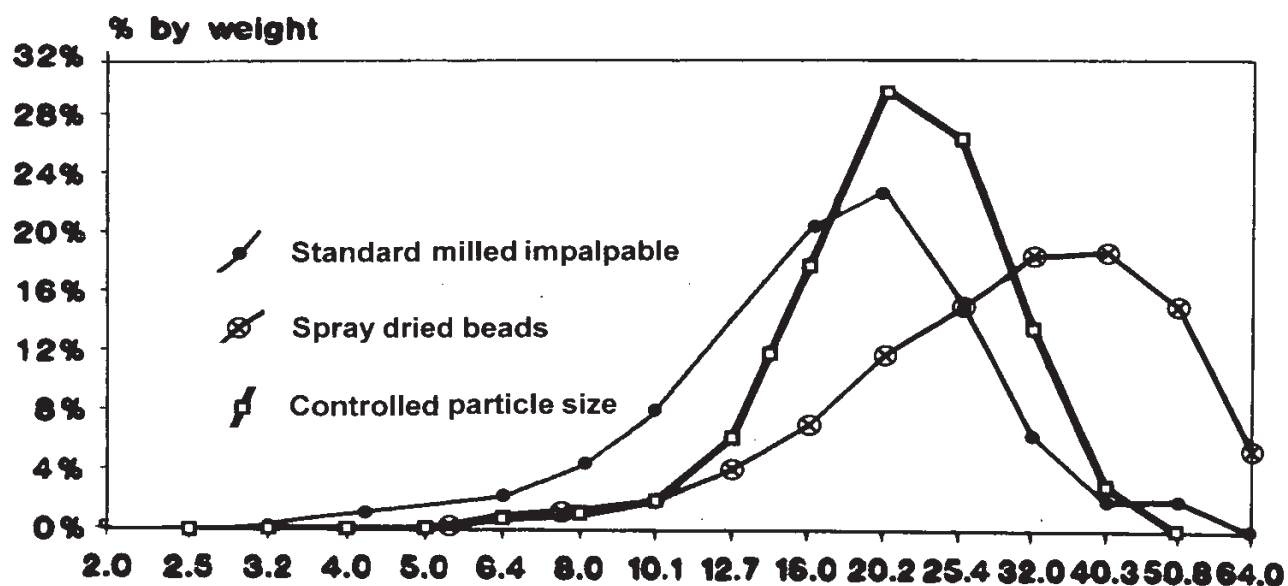


Figure 2
Controlled particle size distribution of various ACH powders

In the late 1980s, enhanced activity antiperspirants entered the market [86a,b,c]. They were developed to improve the performance of aerosol antiperspirants and to bring sweat reduction closer to that achieved with roll-ons and solid forms. The polymer distribution in these "activated" antiperspirant actives was controlled (*see* fig. 1); both the molecular weight and structure were modified compared to previous historical AP actives. Equation 4 depicts the most commonly reported process route for the preparation of activated aluminum chlorohydrate:

Equation 4

AACH chemical reaction equation



Activated ACH can also be made *in situ* during a controlled reaction of aluminum metal and an acid (e.g., aluminum chloride, hydrochloric acid) [87]. Activated ACH is provided as a spray-dried powder, since in an aqueous solution the product can deactivate back to the larger poly-oxo species.

Activated ACH differs from unactivated ACH in that there is present a Al_{13} -mer cluster (a small, almost spherical $\{\text{AlO}_4 \text{Al}_{12} (\text{OH})_{24} (\text{H}_2\text{O})_{12}\}^{7+}$ oligomer) which is associated with increased sweat reduction performance. SEC/GPC and NMR are employed to detect the presence of Al_{13} -mer cluster in the activated ACH. If found to be present, using the same tests, the amount of an Al_{13} -mer cluster is then determined. With the SEC/GPC test, peak 4 is indicative of an Al_{13} -mer cluster (reference fig. 1). With the NMR, a chemical shift of 62.9 ppm in the NMR spectroscopy spectra is indicative of an Al_{13} -mer cluster (reference table 6 and fig. 3).

In the early 1970s, aluminum-zirconium chlorohydrate complexes (AZG or ZAG) were developed [88] and marketed to provide significant improvements in performance in non-aerosolized [89] product forms, such as roll-ons and sticks. AZG salts are prepared by mixing (cold or hot) ACH with zirconyl hydroxy chloride $\{\text{ZrO} (\text{OH}) \text{Cl}\}$, or zirconyl chloride $\{\text{ZrOCl}_2\}$, at various ratios in the presence of glycine [90a,b]. Equation 5 depicts a typical reaction path.

Table 6
 ^{27}Al NMR parameters for various oxo-aluminum cations

<i>Oxo-aluminum cation</i>	<i>Chemical shift ppm</i>	<i>Line width (Hz)</i>
$\text{Al}(\text{H}_2\text{O})_6^{3+}$ (peak 6: monomer)	0	7
$[\text{Al}_2(\text{OH})_2(\text{H}_2\text{O})_8]^{4+}$ (peak 5: dimer)	4.5	500
$[\text{AlO}_4 \text{ Al}_{12} (\text{OH})_{24} (\text{H}_2\text{O})_{12}]^{7+}$ (peak 4a)	62.9	10
$>5000[\text{Al}_{13-x}]^{(7-n)+}$ (peak 4b)	69	1000
$\text{Al}(\text{OH})_4^-$ (peak 2)	80.5	23
Condensed hydro-oxo-aluminum polymer	8–11	900–3500

^{27}Al NMR of "Activated" ACH
 in 25% w/w D_2O

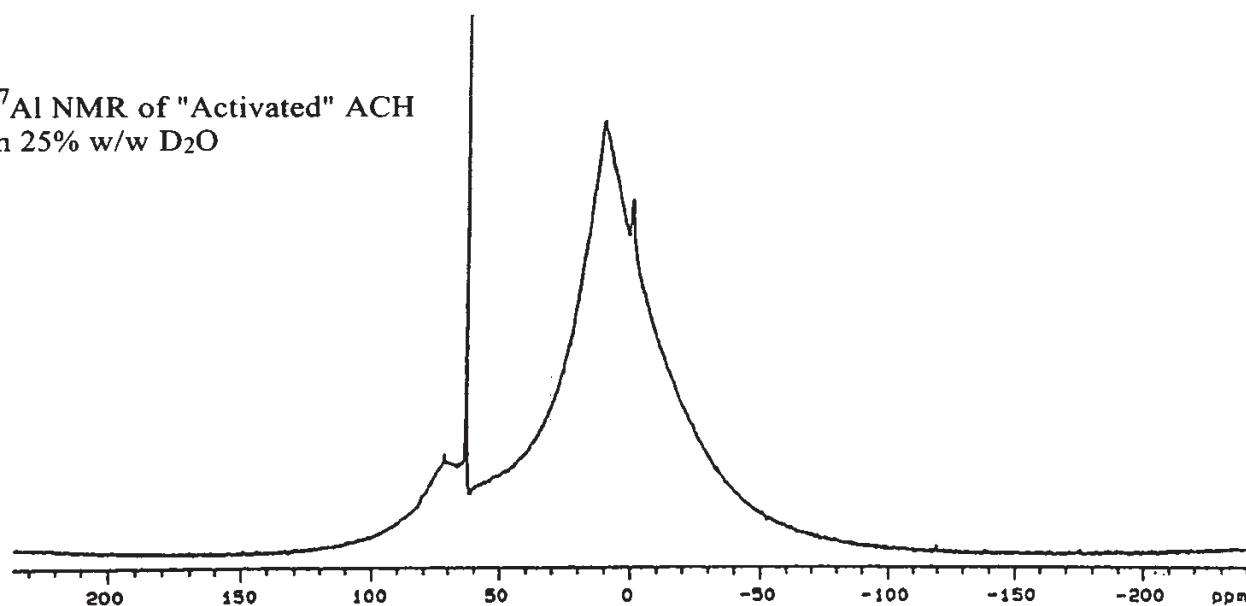


Figure 3
 Typical NMR distribution of ACH

Equation 5

AZG chemical reaction equation



The most commonly used AZG product, which contains an Al/Zr atomic/molecular ratio of 4/1, corresponds to the empirical formula $\text{Al}_4\text{Zr}(\text{OH})_{12}\text{Cl}_4(\text{H}_2\text{NCH}_2\text{COOH}) \cdot n\text{H}_2\text{O}$. Commercial AZGs are typically offered as an aqueous (35–50%) solution, spray-dried spherical beads and micronized powders of various particle sizes.

Table 7 shows physical properties for a few different AZG actives.

Table 7
Physical properties for tetra-AZG actives

<i>Test method</i>	<i>35% Aqueous solution ("tetra")</i>	<i>Powder ("tetra")</i>
%Al	5.0–5.7	14.5–15.5
%Zr	4.4–5.7	13.0–15.5
%Cl	5.9–6.7	17.0–18.5
Atomic ratio Al/Zr	(3.4–3.8)/1	(3.4–3.8)/1
Atomic ratio Metals/Cl	(0.9–1.5)/1	(0.9–1.5)/1
pH (15% solids)	3.7–4.1	3.7–4.1

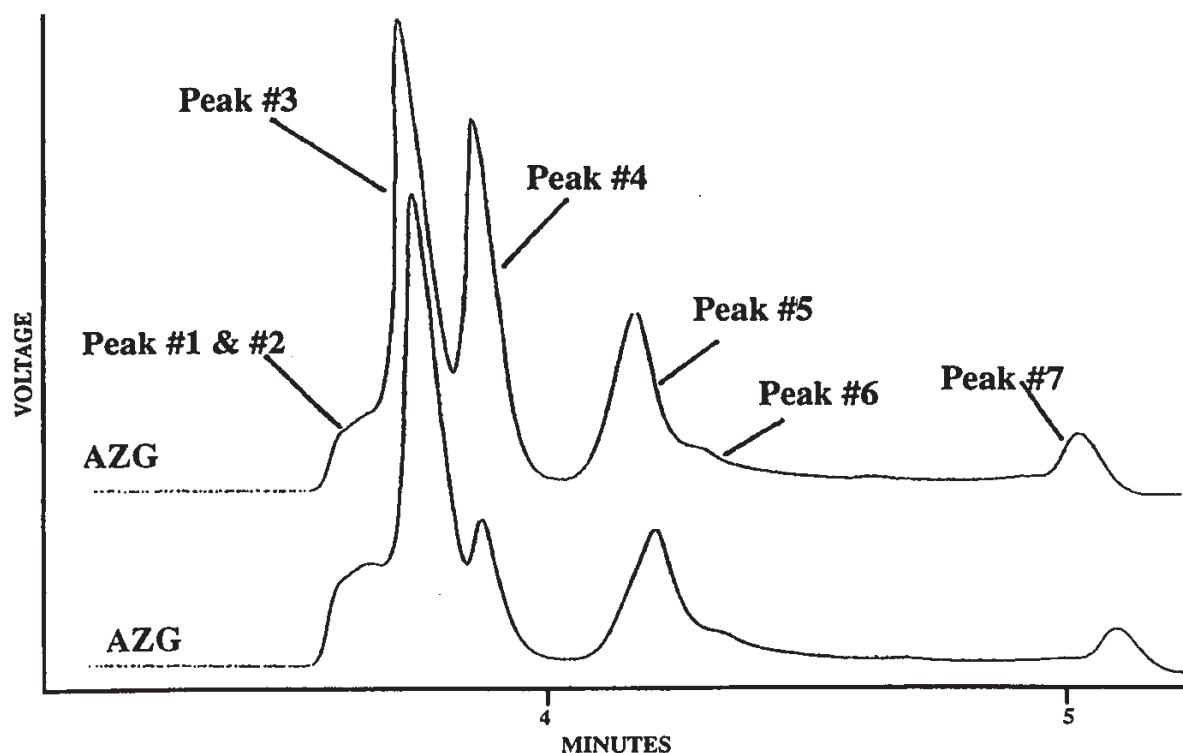


Figure 4
Typical SEC/GPC structural distribution of AZG

There is less information on structures and compositions of AZG salts than there is on ACH salts. SEC/GEC for a typical AZG (Fig. 4) reveals a lot of similarities to ACH (reference Fig. 1). ^{27}Al NMR spectroscopy of AZG salts in solution reveals the presence of hexaquo Al^{3+} monomers and Al_{13}^{7+} oligomers (Fig. 5) although the concentration of the latter is significantly reduced from that of the analogous ACH starting materials. This is attributed to a destructive hydrolysis of the Al_{13}^{7+} components (dissociation) towards lower molecular weight oligomers by the more acidic zirconyl species. What is known is that in addition to the homonuclear oligomeric aluminum clusters and zirconium oxohalides [zirconium tetramer $\{\text{Zr}_4(\text{OH})_8(\text{H}_2\text{O})_{16}\}^{8+}$], there exists the presence of

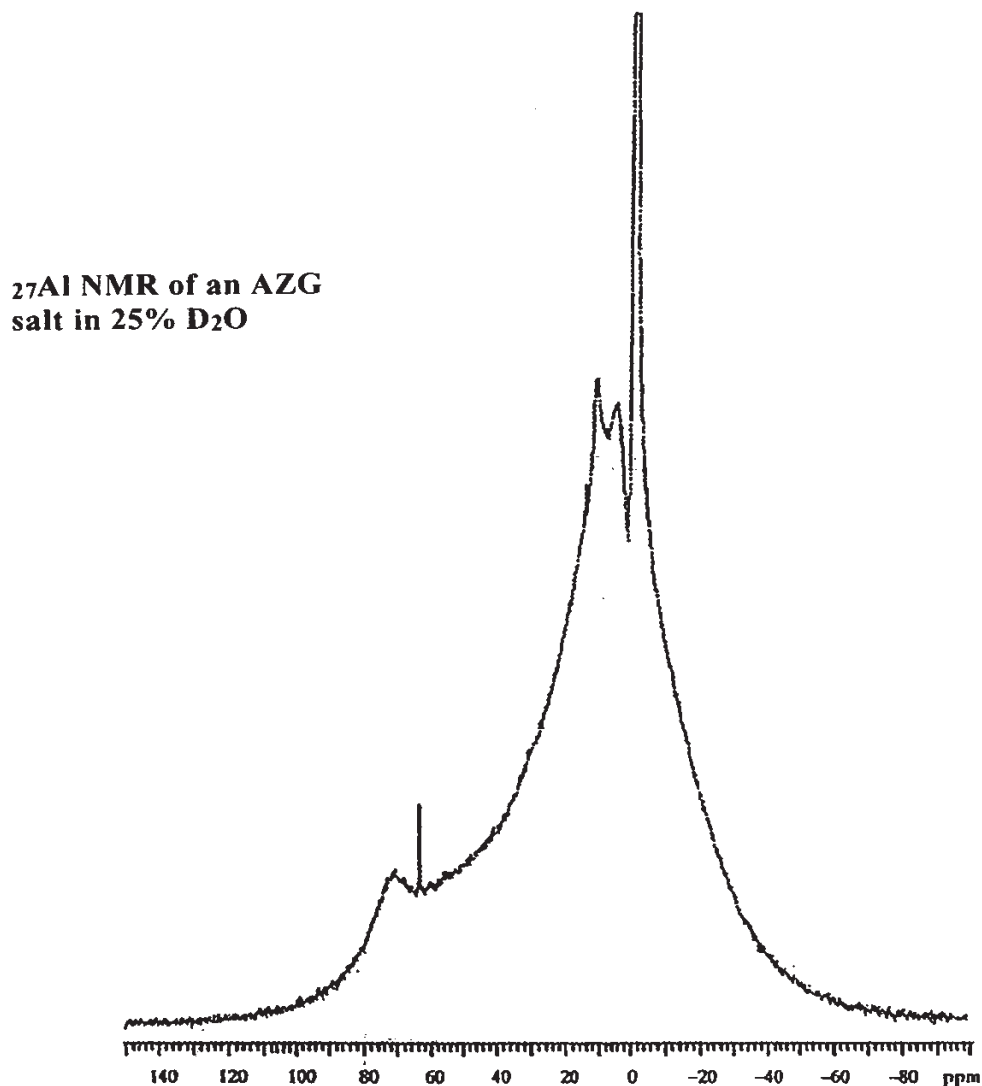


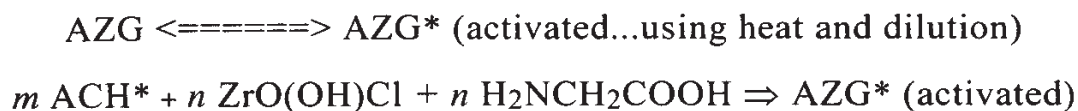
Figure 5
Typical NMR structural distribution of AZG

heteronuclear (aluminum-oxo-zirconyl type) species. Also, when glycine is used to buffer aluminum-zirconium chlorohydrate actives, the glycine is coordinated to zirconyl ions via its carboxyl group and is involved in hydrogen bonding through its protonated amino group with the oxo-aluminum part or another zirconyl cation of the AZG [91].

Further improvements in sweat reduction performance came in the form of enhanced "activated" aluminum-zirconium complexes. Two methods for the preparation of "activated" AZG salts are generally used: pre-treating ACH and adding to zirconyl hydroxychloride, or post-heat treatment of AZG. In Equation 6, post-heat treatment of a dilute AZG solution is analogous to the method of preparation of activated ACH. The "activated" AZG is offered as a spray-dried powder; in an aqueous solution the product can deactivate back to the larger poly-oxo species.

Equation 6

AAZG chemical reaction equation:



4.2 Analytical measurement techniques

Any analytical evaluation of antiperspirant actives should be based on: (1) hydrolysis chemistry and physiology of the metal oxo-halides antiperspirant active during handling and application; (2) physical state changes that can occur to the active during formulation and application (e.g., liquid to solid state); and (3) interactions of the antiperspirant active with formulation ingredients.

Antiperspirant actives are considered drugs or therapeutics in most parts of the world, and are therefore regulated for purity and compliance. The US has established analytical specifications and test methods that are outlined in the National Formulary/US Pharmacopoeia (NF/USP) [92]. Besides the specifications for aluminum, zirconium, chloride, glycine, sulfate, arsenic, heavy metals, iron, and pH, as identified in the NF/UPS, other properties can characterize and distinguish AP actives to understand the purity and physical/chemical properties: solubility, specific gravity, bulk density, particle size, size exclusion and gel

chromatography (SEC/GPC). It is best to contact a manufacturer of the antiperspirant actives for the most up-to-date detailed information.

Each test provides valuable information about an AP active:

(1) Aluminum, zirconium, chloride, and glycine tests can provide valuable information about the empirical formula of each type of antiperspirant active.

a. Aluminum and zirconium can be measured by numerous tests, but atomic adsorption spectroscopy and EDTA colorimetric titration are the most reliable and commercially feasible methods. Ash can also be employed as a simple test; but there are concerns about reliability: it cannot be used effectively when more than one metal is present (e.g., aluminum and zirconium).

b. Chloride is typically measured by potentiometric titration with silver nitrate.

c. Glycine can be analyzed by colorimetric titration with cyanide-ninhydrin reagent (caution must be placed on color intensity, susceptibility to temperature, and rate of titration) or high pressure liquid chromatography (HPLC) [93].

(2) Simple dissolution in water or alcohol provides visible information on trace contaminants and impurities.

(3) Specific gravity relates to active content in solution; for aluminum chlorohydrate, the chloride and density can accurately predict the active content.

(4) Bulk density can relate air to solid content for powders that can provide information on drying and micronizing conditions; that can effect suspendability in formulations.

(5) Heavy metals and iron content, measured typically by atomic adsorption spectroscopy, are important for two reasons; they are required by the NF/USP specifications, and relate to performance. Iron has historically been one of the factors associated with the yellowness of the AP active and clothing staining. Another metal measured is arsenic, which is not acceptable in cosmetics for toxicological reasons.

(6) Particle size is performed in several different ways; but mesh screen sieving for determination of large particles greater than 45 micron (associated with perceptible grittiness) and particles less than 10 microns (associated with respirable particles), and laser light scattering

(for a broad, accurate evaluation of particle distribution) are the best tools.

(7) HPLC size exclusion chromatography (SEC/GPC) has become a good tool to evaluate the polymeric composition of the various hydrolytic components of an antiperspirant salt, in particular, activated AP actives. It is important to take into consideration the type of column, the mobile phase that carries the salt through the column, and the hydrolytic stability of the salt during measurement (since activated antiperspirant salts have a potential to revert to larger poly-oxo species). It is necessary to consult the antiperspirant actives' manufacturer for the best method and interpretation of the data for characterization.

Other than SEC/GPC, the above tests do not provide an accurate understanding and structural characterization of these antiperspirant active salts. Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR), and X-ray crystallography, in conjunction with SEC/GPC, can be employed to provide a more encompassing characterization [94]. Possible limitations are that: (1) these methods are complex and not easily employed in most laboratories, and (2) due to the hydrolytic nature of activated antiperspirant salts, any methodology requiring dissolution in water to determine structural morphology should be employed with caution.

Since there are numerous deodorant actives, it would be difficult to address them in this monograph, and the manufacturer should be consulted for specific tests. The most popular antimicrobial active is Triclosan. Information on detection can be obtained from the suppliers.

4.3 Antiperspirant efficacy

Since one of the key requirements for antiperspirant products is their ability to reduce sweat production, the actual performance data of antiperspirant actives are an important selection criteria.

Early published data [95] compared aluminum chloride, aluminum sulfate, ACH, and AZG. The non-hydrolyzed halides had demonstrated significant improvements in efficacy compared to the hydrolyzed states. There was a clear indication that the hydrolysis state and presence of zirconium are major factors influencing effectiveness.

In the 1978 edition of the FDA Tentative Final Monograph, average percentage sweat reduction was reported for different dosage forms. For the most part, aqueous systems displayed higher sweat reduction than anhydrous systems. As aluminum becomes more hydrolyzed (less acid-

ic), from ACH at a 2:1 Al/Cl molar ratio (aluminum chlorohydrate) to 1:1 Al/Cl molar ratio (aluminum dichlorohydrate), efficacy increases. There is insufficient data on the tetra, tri, penta, and octa versions of AZG to determine the effect of total metals to halide and Al:Zr molar ratio on the efficacy. There is some speculation that the "octa" region provides optimal efficacy. Figure 6 provides a general comparative guideline for different types of antiperspirant actives.

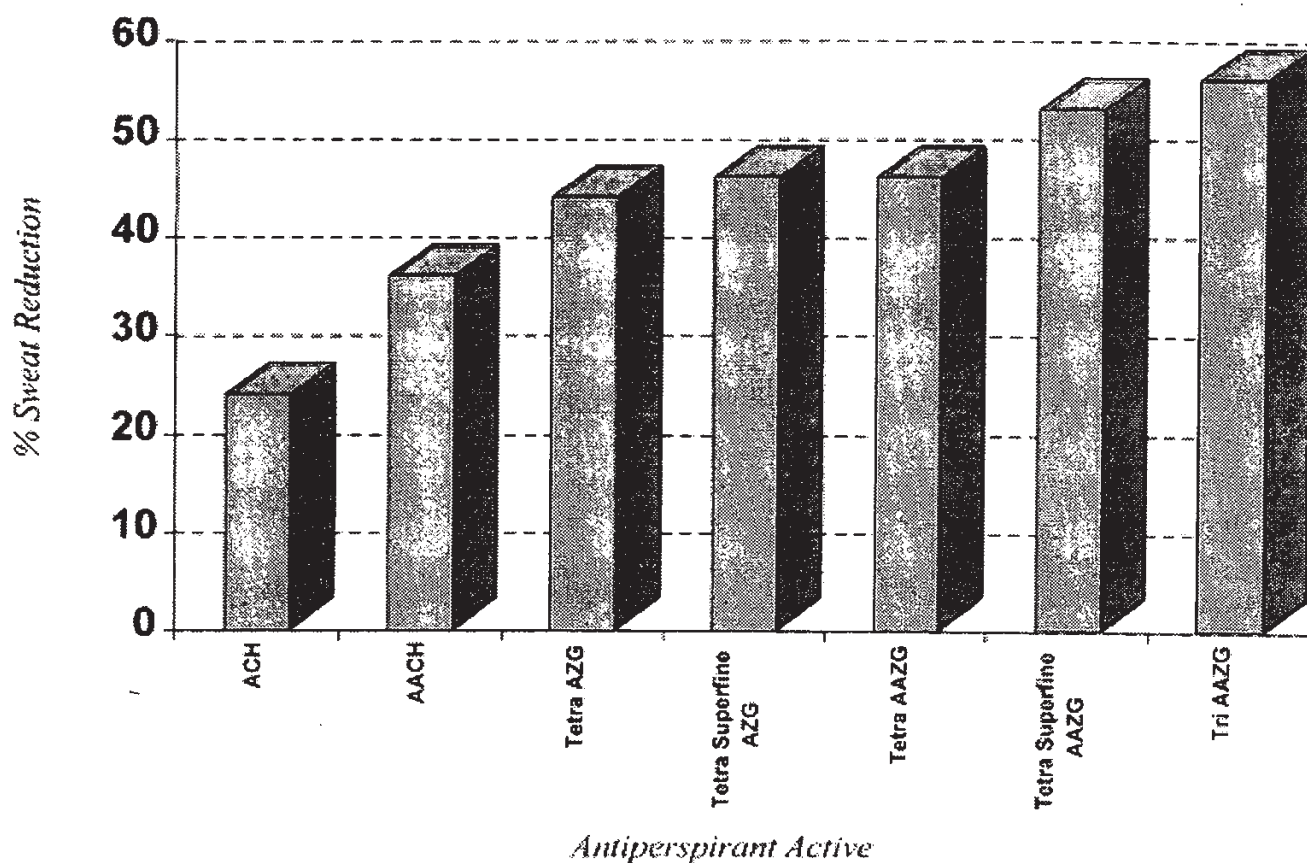


Figure 6 [96]
Efficacy comparisons of typical antiperspirant actives

5 Clinical Sweat Production Evaluation Methods: Antiperspirant Testing

5.1 Introduction and background

The FDA TFM defines minimum clinical methodology and effectiveness, and statistical protocol for treatment of data. In accordance with the TFM, to be claimed and marketed as an antiperspirant, a product must realize a response of a minimum efficacy performance of at least 20% reduction in perspiration for 50% of the target population. Furthermore, to meet minimum efficacy requirements and to substantiate product label and advertising claims, clinical testing is required for any new formulation or formulation modification. Basically, this is because formula ingredients and a product's dispensing characteristics are known to affect active ingredient efficacy.

Thus, to provide an objective measurement of a product's effectiveness for actual antiperspirancy or deodorancy, that a consumer is to realize during normal daily use, *in vivo* human clinical measurements have to be performed under specific conditions. These conditions are designed to control a complex combination of factors: climate; level of physical, thermal, and/or emotional stress; bathing habits; tactile sensual aesthetics of a formulation on an underarm; and/or interaction of normal body substances with the chemical and fragrance formulation ingredients. Furthermore, as a consumer's determination of the effectiveness and, therefore, acceptability of an underarm product is based upon factors encountered during actual use, measurement of the "subjective" clinically measured efficacy of a product under normal conditions is an important consideration in formulation development. As a result, several different types of subjective consumer test protocols are employed throughout the US and other countries to ensure cultural, geographical, climatic, and environmental relationships.

Subjective testing, which supports label and marketing claims, is subjected to regulatory processes in most countries. A primary purpose of these governmental regulations is to protect the rights and safety of human volunteers who participate in clinical studies prior to initiation of these studies.

These *in vivo* test protocols are employed because (a) manufacturers are required to substantiate claims they desire to make about their products; (b) federal, state, provincial and local governments often require claim substantiation data as part of a pre-market approval process or as

a product dossier record; and (c) groups such as advertising agencies, Better Business Bureaus, and radio and television networks, often require supportive data for review in connection with advertising claims.

Regardless of the method(s) to be employed in testing a product, committees have been organized to oversee new product studies. For certain clinical research studies, approval by an ethics review committee or Institutional Review Board (IRB) may be required prior to initiation of a study.

5.1.1 Axillae sweat measurements protocols

Developing an antiperspirant product frequently proves to be an expensive undertaking, as the potential for efficacy failure can be great. In an effort to provide sweat reduction performance data in a cost effective manner, manufacturers/marketers of underarm products have developed three screening techniques to assist in forecasting product efficacy [97]: (1) visualization [colorimeter], (2) instrumentation [sensor], and (3) gravimetric. Required by the TFM, gravimetric *in vivo* clinical efficacy testing is the recognized method throughout the world, even though this type of testing remains difficult to administer and is expensive.

Of these testing methods, visualization techniques have been around the longest [98,99,100]. Visualization methods can help the subjective understanding of how many pores are firing (releasing excrement). Usually with this type of test protocol, a staining indicator is painted on a test axilla site (e.g., iodine dye in a mixture of starch powder and castor oil [101]). Subsequent to painting, a color change results when moisture is released from an eccrine pore. This change allows visual quantification estimates of sweat output. Usually, within minutes of application of a staining indicator, a sweating pattern can be observed and recorded. (Wade and Takagaki [102], and Tashiro et al. [103] also did work in this area.)

Quatralle et al. [101] employed a cellophane tape stripping procedure; first tape is applied to the axilla, then stripped off. Once removed, the tape is examined by scanning electron microscopy (SEM), transmission electron microscopy (TEM), or fluorescence spectroscopy. What is being evaluated is the horny layer, from the axilla, that was removed by the tape stripping technique. Quatralle et al. noted that Scotch® tape stripping removes stratum corneum, in turn exposing the stratum granulosum layer of viable epidermis. Evaluation allows for the determination of whether an antiperspirant product has resulted in the formation of plugs to block sweat glands. It also allows one to see how deep plugs

may be residing; they have been recorded as deep as the intraepidermal duct at the level of the stratum granulosum.

A more recent visualization method has been published [104] detailing the use of a less laborious and restrictive confocal microscopy technique that optically slices through layers of tissue a few hundred microns thick. This technique can examine gland density and gland microstructure of both functioning and quiescent glands in an *in vivo* environment. Still another recently published *in vivo* technique employs the standard hot room gravimetric method, but uses a hand-held deep field microscope and a digital imaging technique [105], to visually show volume changes per unit of time, giving sweat rates for individual eccrine sweat glands.

The instrumental, or sensor, methods have been less successful [106a,b] than visualization or gravimetric methods. Unfortunately, results of tests from these methods have not been shown to correlate well with gravimetric method results in demonstrating the effectiveness of one antiperspirant active or formulation versus another. Many sensor methods have been utilized: water loss by infrared gas analyzer [107], electrolytic cells containing a water-sensitive mixture of methanol-acetone and oxalic acid [108], and electrical types of humidity-sensor elements [109].

Gravimetric methods are employed when testing an antiperspirant product for regulatory approval. The most influential publications on gravimetric testing, which support current OTC monograph efficacy testing conditions, were those of Reller (1964 [110]), Wooding, Jass and Ugelow (1964 [111]), Majors and Wild (1974 [112]), Wooding and Finkelstein (1975 [113]), and Majors and Carabello (1975 [114]). The FDA, in 1982, established guidelines [115], setting the basic standards and conditions for evaluating antiperspirant products and for testing the effectiveness of antiperspirant drug products in finished form. As mentioned previously, these guidelines are still followed today by manufacturers and marketers of underarm products.

In addition to methods employed to meet FDA guidelines for efficacy testing of antiperspirant products, antiperspirant manufacturers and marketers often test their products for comparative efficacy potential so that they can advertise their products to consumers by way of more competitive comparison claims. Manufacturer/marketer comparative efficacy studies are identical in methodology to regulatory guidelines, with the exception that active products are directly compared to each other.

Suggested guidelines for effectiveness testing of OTC antiperspirant drug products are summarized below:

a) Objective:

- i) To qualify as an effective antiperspirant drug product in finished form.

b) Test Subjects:

- i) Selection of subjects: panelists are pre-screened before being accepted and used in clinical studies.
- ii) Representative test panelists with sweat rate differences which do not exceed 600 milligrams.
- iii) Seventeen (17) day abstinence from use of all anti-perspirant products.

c) Test Conditions:

i) Hot room:

Temperature $100^{\circ}\text{F} \pm 2^{\circ}\text{F}$ ($37.8^{\circ}\text{C} \pm 1.1^{\circ}\text{C}$).

Humidity 35 – 40% RH.

Influence factors controlled (air movement, mental or emotional stimuli, position of trunk and extremities).

ii) Ambient:

Normal daily routine during collection period.

d) Test Procedures:

- i) Treatment vs. placebo.
- ii) Balanced treatment assignment.
- iii) Normal application amounts.
- iv) Once a day treatment for 2-4 days.
- v) Hot room conditions:

Air movement

Forty-minute warm-up.

Two 20-minute weighed sweat collections.

vi) Ambient conditions:

Three to five sweat collections during normal daily routines.

Activity of panelists in hot room—they are asked to sit with both feet on the floor, uncrossed (posture can affect sweat output).

Right/left axilla: subjects are numbered; equal number of panelists from each group have applied product A or product B to right axilla; the product not

applied to right is then applied to left to eliminate the side-effect" bias.

e) Data Analysis:

- i) Nonparametric techniques.
- ii) Projection of results: 50% of population will obtain at least 20% sweat reduction.

5.2 Odor evaluation protocols: deodorant testing

5.2.1 Standard Practice of the ASTM

In 1987, the American Society for Testing and Materials (ASTM) published a Standard Practice for the Sensory Evaluation of Axillary Deodorancy, Designation: E 1207-87 [116]. This publication provides a detailed background and explanation of the evaluation of deodorant products, including all the important facets required to support adequately deodorant efficacy.

5.2.2 *In vitro* evaluations

The very complex subjective detection of the many odors present on the human body is mostly measured by *in vivo* methodologies. Unfortunately, as mentioned previously, *in vivo* methods can be expensive and time-consuming.

An alternative to *in vivo* methodology is *in vitro* methodology. *In vitro* methods provide quicker responses at a lower cost. Although *in vitro* procedures, which lead to the determination of antimicrobial activity, are useful in determining a product's or compound's potential, these procedures do not accurately quantify malodors. Thus to date, *in vitro* methods do not provide meaningful quantification of axillae malodor. However, new *in vitro* instrumentation that may better detect odor is currently under investigation [117]. An example of *in vitro* methodology, gas chromatography, identifies malodorous components, but is limited in its objective determination of odor due to the complex nature and variation of compositions of axillae malodor [118].

5.2.3 *In vivo* clinical evaluation

The nature of a clinical study is subject to variation, but proper statistical analysis of data and control of as many variables as possible should lead to an informative result [119]. The method of choice in clinical evaluation of deodorant effectiveness is *in vivo*.

Clinical evaluation of deodorant effectiveness can best be divided into two groups according to subject-odor judge interaction: direct and indirect axillary odor evaluations. Selection of the direct or indirect method of evaluating axillae is dependent upon a judge's training and the ease with which a judge can perform his/her duties most consistently [120]. Other types of evaluations of deodorant effectiveness of antimicrobial agents include removal of body flora with swabs, placing of the flora in cultured plates, and evaluation of cultured antimicrobial activity over time [121].

5.2.4 Outline of direct axillary odor evaluation method

(a) Objective:

Objective screening using the direct axillary odor evaluations may vary as follows: (i) to screen prototype samples; (ii) to lend support to a deodorancy claim; and (iii) to rank comparatively several test products.

(b) Procedure

Overall study procedure is basically the same for all objectives. Variations may exist in the number of subjects and intervals of odor assessment. Regardless of the objective, the procedure consists of three key elements:

Subject Conditioning: Approximately two weeks prior to a baseline odor study, subjects are instructed to abstain from use of any deodorant and/or antiperspirant materials.

Subject Selection: Subjects are selected for their ability to develop axillary malodor during a control period and at specific intervals following a controlled washing procedure.

Subject Rules: For subjects to participate in deodorancy studies, they must comply with the following rules:

- i) Abstain from using any deodorants, anti-perspirants, and perfumed or medicated products on the underarm areas throughout conditioning and entire testing period. The conditioning period should be at least 17 days, and the test period last typically up to 5 days.

- ii) Use control soap bars for all bathing and washing during conditioning and test periods, and abstain from washing of underarms during the test period except for supervised washing at the test location.
- iii) Abstain from wearing either on body or clothing perfumes, powders, or any other scented products (including laundry rinses, hair sprays, and after-shaves) during the entire test period.
- iv) Abstain from (a) smoking for at least one hour prior to each visit to the test location during test period, (b) drinking of alcoholic beverages or caffeinated beverages during a test period; and (c) chewing gum, eating breath mints, and gargling with mouth rinses.
- v) Female subjects should shave their underarms at least 24 hours prior to a test period and then abstain from any underarm shaving during the test period.
- vi) Abstain from swimming during the final week of the conditioning period and throughout the entire test period. Also, minimize physical exertion such as tennis and jogging during the test periods.
- vii) Agree to withdraw from the study at the start of the test period if odor scores obtained during the control period indicate that the axillae odor intensity is not within the criteria for the study.
- viii) Abstain from eating highly spiced foods (e.g., those containing onions and garlic) for 24 hours prior to beginning of the odor test evaluations.

5.2.5 Odor evaluation method

By directly sniffing a subject's axillae, three to five trained odor judges respectively evaluate axillae odor levels of test subjects.

(a) Scaling techniques

Scaling techniques are employed to chart test results. For axillae odor scaling, usually numeric category scaling or ratio scaling techniques are employed. With regards to numeric category scaling, zero (0) to ten (10) scale has been used as both an unstructured and structured scale. An unstructured scale is described by

two and sometimes three intervals (for example: 0 = no odor; 5 = moderate odor; 10 = strong, disagreeable odor). A structured scale can either be 0 to 10, or 0 to 5. The 0 to 10 scale is generally represented in the following way (descriptive terms may vary slightly, depending on the investigator):

<i>Score</i>	<i>Malodor intensity scale</i>
0	None; no odor
1	Threshold odor
2	Very slight odor
3	Slight odor
4	Slight to moderate odor
5	Moderate odor
6	Slightly strong odor
7	Moderately strong odor
8	Strong odor
9	Very strong odor
10	Extremely strong odor

The 0 to 5 scale has been standardized by using varying dilution levels of isovaleric acid to correspond to an odor level [122]. These odor levels are assigned a reference number from 0 to 5 and are represented in the following way:

<i>Score</i>	<i>Malodor intensity scale</i>
0	No odor
1	Slight odor
2	Definite odor
3	Moderate odor
4	Strong odor
5	Very strong odor

In contrast to numeric scaling, ratio scaling, or magnitude estimation, is based on assigning a ratio (or pro-

portion) of two different odor measurements that indicates the relative magnitude difference between them. To be qualified as a judge, a person is tested with regard to his/her ability to (a) make correct ratio judgments with known materials, and (b) make correct ratio judgments of various concentrations of odors. In actual odor evaluation for each subject, a judge is asked first to rate the right axilla with an intensity value and then rate the left axilla either higher or lower, at some ratio relative to the right axilla. The data is recorded similarly to the numeric scaling.

(b) Typical test schedule

A typical test schedule is listed below. The subjects go through a conditioning period prior to entering the clinic for odor evaluation. They then go through a series of washings and baseline testing. For the next four days, they are treated and evaluated to determine the effectiveness of the deodorant active.

<i>Test day</i>	<i>Test operation</i>
-14 to 1	Conditioning period
-1	AM control wash
0	AM control odor evaluation, subject selection
1	AM Treatment 1
2	AM Treatment 2
3	AM Treatment 3, PM 12 hour odor evaluation
4	AM 24 hour odor evaluation

(c) Data analysis

Parametric and/or nonparametric analysis may be used when the specific assumptions for either technique are met.

5.3 Statistical measurement tools and protocols

Several statistical protocols [123,124,125] — that is, in interpreting raw data and reporting results — are commonly employed in evaluating test data. Statistical protocols to support antiperspirant efficacy claims include: the Sign test, the Wilcoxon Sign Ranked (WSR) test, and the Student *t*-test.

Generally not considered the most desirable protocol, use of the Sign Test calls for raw data to be converted to a "yes/no", "pass/fail", or "A/B" scale. Thus, relative magnitudes have no meaning, and results are basically interpreted as having a lower sweat output for product A/underarm versus product B/underarm. This protocol relies on the forced order ranking: where the higher the number and greater the difference between products, the more one would weight the effectiveness of product A to product B.

The Wilcoxon Sign Ranked Test (WSR) — recommended in the TFM [126] — is the safest protocol to employ. Using this protocol, first data is converted to relative ranks, irrespective of positive or negative sign (based on R = ratio of log of one axilla to another). Then the sum of the positive and negative are tested against a hypothesis mean (equal to the sum of number of panelists divided by 2). With this protocol, the basic score — a Z-score — is expressed as a deviation from the mean in standard deviation units. After the mean and standard deviation are calculated for a set of scores, it is easy to convert the Z-score to a normal distribution from a Z-table.

$$Z = \frac{[(R+) - \text{mean}]}{(\text{std deviation of mean})}$$

Most antiperspirant marketing companies will use the WSR to state the worst case probability.

The strongest statistical protocol for determining probability, in which two means are compared, is the Student *t*-test. This *t*-test generates a "t"-value which is used to determine probability of rejecting the null hypothesis.

$$t = \frac{[(\text{mean of group 1}) - (\text{mean of group 2})]}{(\text{std error of difference between the means})}$$

The *t*-test assumes a parametric statistic, having populations normally distributed and variances within the groups that are the same. If assumptions are not based on normalized distributions, researchers should use non-parametric analog.

There are two evaluation protocols recommended by the FDA in the TFM [126,127]. In the first, a baseline sweat collection takes place before the axillae are treated. These data are used to calculate a baseline ratio of one axilla divided by the other. This ratio is used to adjust the post-treatment divided by untreated ratio when estimating product efficacy and sweat output reduction in that subject. The second protocol is where there is no baseline and efficacy is estimated using only post-treatment data to look at a comparison of two different actives on the same subject.

5.3.1 When baseline (pre-treated) sweat collections are obtained:

(a) The source data are individual baselines and post-treatment sweat collections, in milligrams.

(b) Antiperspirant activity is evaluated by determining shifts in ratios of sweat output by a treated axilla to output by an untreated axilla for each panelist.

(c) Data will be analyzed using the WSR test, as recommended in the August 1982 Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products. The source data for this analysis are treated-to-control ratios, adjusted for the ratio of right-to-left axillae sweating rates. These ratios are calculated using the post-treatment average of the last two collections (4th and 5th days) for each individual at each time period.

(d) The adjusted treated-to-control ratios will be calculated as follows:

$$Z = \frac{(PC)(T)}{(PT)(C)}$$

Z is the adjusted ratio; PC is the pre-treatment measure of moisture for the control axilla, PT is the pre-treatment measure for the test axilla; T is the treated measure for the test axilla; and C is the corresponding quantity for the control axilla.

(e) Study results are analyzed by comparing adjusted ratios to 0.80:1, the ratio that corresponds to a 20 percent reduction in moisture due to treatment. The hypothesis that reduction in perspiration exceeds 20 percent is tested statistically by subtracting 0.80 from Z from the sum of all test subjects and testing the resulting number with the WSR test.

(f) Hypotheses tested in the Sign Ranked test are:

H_0 : Median $Z \geq 0.80$, and

H_A : Median $Z < 0.80$

Hypothesis testing is performed at the $\alpha = 0.05$ (95% confidence interval). Rejection of the null hypothesis justifies the conclusion that at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent.

5.3.2 When no pre-treated sweat collections are obtained:

(a) The source data are individual post-treatment sweat collections, in milligrams.

(b) Antiperspirant activity is evaluated by determining shifts in ratios of sweat output by a treated axilla to output by an untreated axilla for each panelist.

(c) Data are analyzed using the WSR test, as recommended in the August 1982 Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products. Source data for this analysis are right-to-left axilla ratios adjusted for 20 percent reduction in perspiration due to treatment. Ratios are calculated using the post-treatment average B and C collections for each individual at each time period.

(d) The adjusted right-to-left ratios will be calculated as follows:

1. For subjects treated on the right axilla: $X = R/(0.8L)$
2. For subjects treated on the left axilla: $Y = (0.8R)/L$

(e) Hypotheses tested in the Sign Ranked test are:

H_0 : Median $X \geq Y$, and

H_A : Median $X < Y$

Hypothesis testing will be performed at the $\alpha = 0.05$ (95% confidence interval). Rejection of the null hypothesis will justify the conclusion that at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent.

In addition to knowing whether a product passes the FDA monograph requirements, most manufacturers wish to estimate the level of sweat reduction. For calculation of estimates of percent reduction, there are a few methods that can be utilized.

1. Direct Method [128]

With this method of analysis, no baseline measurements are used. However, post-treatment individual percentage reductions are determined for each subject. This is accomplished by calculating the percentage reductions employing the post-treatment ratio protocol:

Individual % reductions $-\ [(1 - \text{post-treatment ratio}) \times 100] =$

$$\frac{(\text{PTA}_X \text{ mg}) - (\text{PTA}_Y \text{ mg})}{(\text{PTA}_X \text{ mg})} \times 100$$

where PTA_X = post-treatment axilla X, and PTA_Y = post-treatment axilla Y

From these calculations, the mean of the individual percentage reductions is used as a point estimate of the mean percent reduction in sweating for all consumers. In turn, the confidence interval estimate is obtained from the mean percent reduction, calculated from the individual percent reductions obtained by a method used in deodorant efficacy studies.

2. Adjusted Ratio Method [129]

With this method of analysis, a pre-treatment Y-to-X ratio is determined for each subject using baseline sweat collections. The ratio for each subject is calculated by:

$$\text{Pre-treatment ratio} = \frac{\text{baseline mg of sweat from axilla Y}}{\text{baseline mg of sweat from axilla X}}$$

Likewise, following testing, post-treatment ratios are similarly calculated. That is,

$$\text{Post-treatment ratio} = \frac{\text{mg of sweat after treatment from axilla Y}}{\text{mg of sweat after treatment from axilla X}}$$

From these two calculations, adjusted-treatment ratios provide the data that are actually analyzed. For each individual, an adjusted-treatment ratio equals the individual's post-treatment ratio divided by his/her pre-treatment ratio:

$$\text{Adjusted-treatment ratio} = \frac{\text{post-treatment ratio}}{\text{pre-treatment ratio}}$$

Once these adjusted-treatment ratios are calculated, their mean is calculated; then, this is used to find a point of the mean percent reduction in sweating achieved by consumers. The mean percent reduction in sweating value is:

$$\text{Estimate of mean \% reduction in sweating} = [1 - (\text{mean of adjusted ratio})] \times 100$$

3. Wooding-Finkelstein Method [130]

For the Wooding-Finkelstein protocol, no baseline measurements are used. For each subject, the post-treatment milligrams of sweat for axilla Y and axilla X are transformed by calculating the natural logarithm of each. The means of the transformed data for axilla Y and axilla X are calculated and denoted by $Y_{\log}$ and $X_{\log}$, respectively. A point estimate of the percent reduction is calculated using the antilogs of these values as follows:

$$\text{Estimate of mean \% reduction} = \frac{(1 - \text{antilog } Y_{\log})}{\text{antilog } X_{\log}} \times 100$$

When investigators are making comparisons of two or more treatments for superiority of efficacy, the Wooding-Finkelstein protocol is frequently the method of choice.

6 Formulation Considerations and Delivery Systems

6.1 Choosing the right formulations

Today's consumers not only demand highly functional underarm products, but also expect products that are safe for both the body and the environment. To marketers, these expectations translate to a need for high-performance products that keep underarms dry and odorless, maintain the health of skin, have a "perceived" naturalness and mildness about them, and are easily applied without a perceptible residue. Underarm products may be delivered to the axillae in a variety of ways, but on a global basis, the four most important product forms are sticks/solids, roll-ons, extrudable gels/creams, and aerosols.

Whatever form a successfully formulated product takes, it should meet the following criteria:

1. Effective and uniform delivery of product to the underarm.
2. No detracting from the performance of the active, preferably enhancement.
3. Not harmful to the body or clothing.
4. Stable in its package for a reasonable shelf-life.
5. Aesthetically appealing.
6. Conforming to applicable regulations.

Deodorant actives and fragrances tend to have less formulation limitations than antiperspirants. Antiperspirant actives, being very acidic and water soluble, have distinct formulation limitations, such as: (1) water and glycol solubility that can lead to tackiness on the skin, and (2) high acidity that can cause potential skin irritation and destabilization of pH-sensitive fragrances and gellants.

Typical deodorants are in the forms of sticks/solids, aerosols, and extrudable gels. The key is to maintain minimal tackiness and no visible residue: thus the proper selection of formulation ingredients is critical. Typical ingredients found in deodorant aerosol products are volatile hydrocarbons (propellants like butane), ethanol (a quick drying solvent with antimicrobial activity), propylene glycol, and functional emollients (for aesthetics). Clear deodorant sticks rely principally on a gelling agent like sodium stearate, a diluent like propylene glycol, water, and alkoxylated ethers to improve clarity. In all deodorant forms, fragrances

and antimicrobials are then incorporated to combat odor or microbial growth.

Antiperspirants are formulated to provide dry-feeling aesthetics upon application and effective delivery of actives. Cyclomethicones (volatile [poly]dimethylcyclorosiloxanes) are widely used because they volatilize easily without causing cooling (low heat of evaporation), stinging or staining. They also have a low surface tension that results in good spreading of the product onto the skin, and formation of a thin, lubricious film that reduces tackiness of the active during delivery and dry down.

Also useful in antiperspirants are non-volatile emollients, such as fatty esters and ethers, fatty alcohols, fatty acids and alkoxylates, dimethicone, phenyl trimethicone, alkylmethyl siloxanes, and hydrocarbons. Each of these may perform one or more functions, including detackification, feel modification, adhesion of active powders to the skin, lubrication of the skin, lubrication of packaging components, modification of the gellant, improved wash-off characteristics, and reduction of residual whitening. Because these ingredients remain on the skin, they must be carefully selected and formulated, ensuring that product efficacy is maintained, with no greasiness or tackiness remaining.

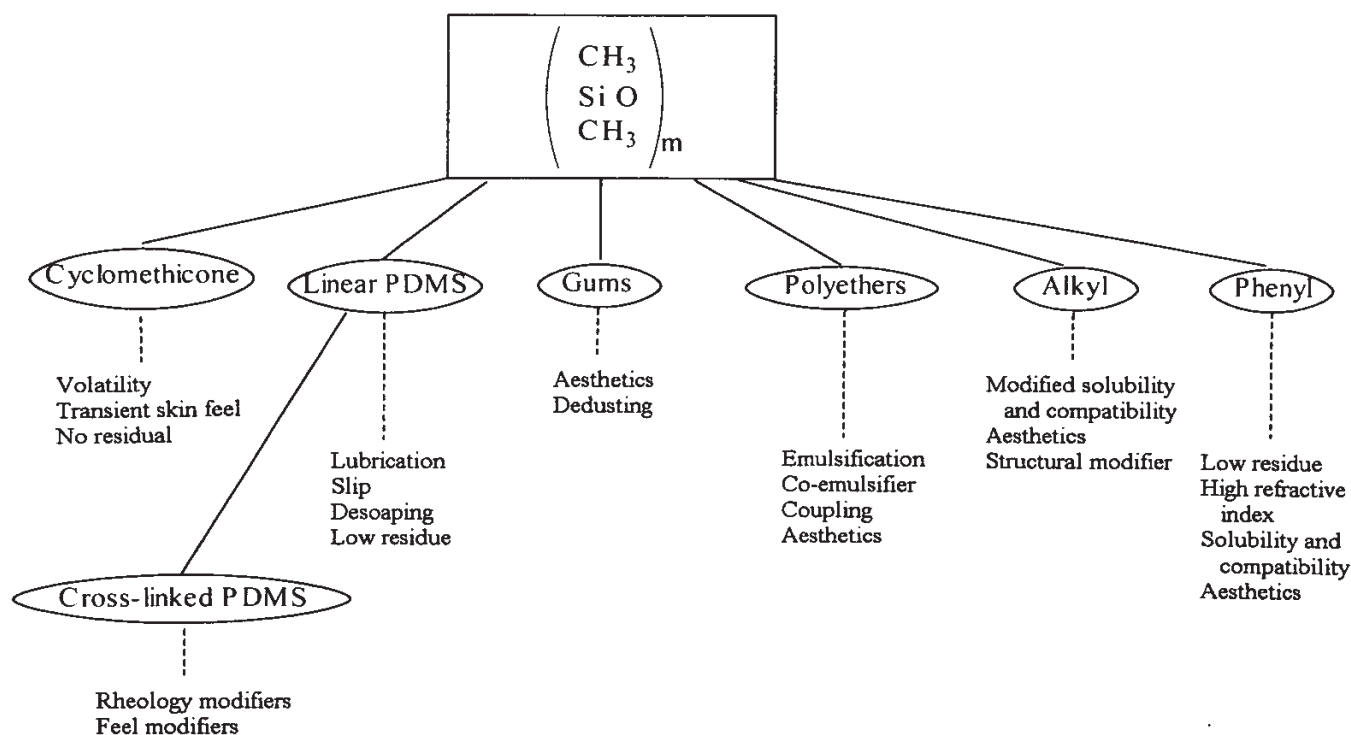


Figure 7
Key benefits of the siloxane molecule

Since silicones play an important role in most underarm formulations, figure 7 is included to outline some of their key benefits. Types of ingredients for antiperspirant/deodorant systems can be broken down into key classifications of function [131]:

1. Emulsifiers/Suspending Agents

Typically act to emulsify oil in water or water in cyclomethicone. Ingredients included in these formulations are: glycerol monostearate, fatty alcohol/acid alkoxylates, organofunctional clays, polyethers and their esters, and dimethicone copolyol.

2. Gellants and Viscosity Enhancers

Will act to solidify or modify the product's rheology, affecting the way products are delivered across the axillae. Ingredients included in these formulations are: cetyl/stearyl alcohol, synthetic waxes, fatty alcohols/acids (e.g., 12-hydroxystearic acid), polyethylene wax, stearamide/cocamide MEA (for deodorants), silica, hydrogenated castor oil, aluminum starch, dibenzyl monosorbitol acetal (for antiperspirants), and sodium stearate (for non-acidic systems).

3. Propellants and Solvents/Carriers

Most often are used to deliver the formula from its container onto an axilla (providing a steady vapor pressure sufficient to force all the contents out). Ingredients included in these formulations are: butane, isobutane, propane, ethanol, hydrofluorocarbon, dimethyl ether, compressed gas, water, and ethanol.

4. Emollients and Feel Modifiers

Used to provide an elegant, aesthetic lubrication to container parts, improve mildness (i.e., less irritating), minimize residue (whitening) on axillae and clothing, and improve dispersibility of suspended actives by wetting the surface. Ingredients included in these formulations are: cyclomethicone, dimethicone, phenyl trimethicone, glycol/glycol ethers, and fatty acid esters (e.g., isobutyl stearate, isostearyl isostearate, octyl isonononate, diisopropyl adipate).

5. Miscellaneous Additives

A broad class of ingredients that can deliver many different benefits, such as: adding or hiding color, modifying background odors or enhancing fragrancing of skin, improving mildness (pH), and improving the dispersibility of powder. The list can include talc, silica, titanium dioxide, fragrance/masking agents, antioxidants, preservatives, sorbitol, glycine, and urea.

6.2 Examples of different delivery systems

Antiperspirants and deodorants can be delivered in many different systems. For deodorants, the two most popular applicator forms globally are aerosol and stick. For antiperspirants, many different forms have been popularized globally. Figure 8 schematically represents the various delivery forms.

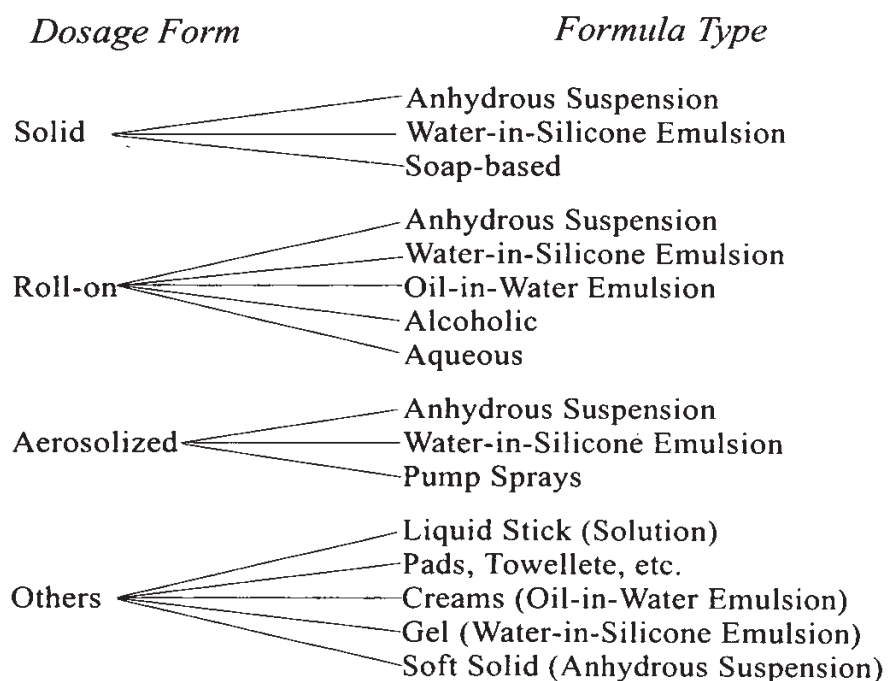


Figure 8
Antiperspirant delivery systems

To choose the right form, a formulating chemist needs to balance the cost of a product versus its performance, maximizing these against consumer acceptance and affordability. Market preference may sometimes dictate which application forms are acceptable. Cost is always a key factor and can be affected by: (1) the type of actives used (higher efficacy actives are typically more expensive), (2) the formulation (water is the least expensive ingredient in the formula), and (3) packaging. Figure 9 provides a comparison of different types of delivery systems and generic composition for each.

Gel	Stick	Soft Solid	Roll-on	Aerosol
				
16% Cyclics 1% Dimethicone Copolyol 50% AP Salts in Water 15% Propylene Glycol 17% Water	40-50% Cyclics 20-25% AP Salts (no water) 15-25% Waxes 0-10% Others	60% Cyclics 25% AP Salts (no water) 11% Organic Emulsifier 4% Organic Thickener	35-75% Cyclics 20-25% AP Salts (no water) 2-4% Bentone 0-50% Water 0-10% Other	8-15% Silicones 8-15% AP Salts (no water) 2% Bentone 75-85% Propellant

Figure 9
Common antiperspirant products

6.2.1 Aerosols: deodorants/antiperspirants

Aerosols are very complex applicators because of the need to balance aerosol can construction, value design, and vapor pressure in order to deliver either an antiperspirant or deodorant effectively. Romanowski and Schueller [132] provide a good review of aerosol design and basic formulation requirements.

For deodorants, aerosols are very popular for underarm delivery both of a fragrance and an antimicrobial active. For the most part, deodorant aerosols are simple formulation systems consisting of a deodorant active (typically triclosan, balsam, zinc ricinoleate, ACH) and/or fragrance dissolved/suspended in a propellant and delivered in a spray form. Other ingredients are added to provide enhanced aesthetics on the skin.

Formulas 1 and 2 are examples of a deodorant aerosol and pump spray, respectively.

Formula 1
Deodorant Spray

	Wt %
Dimethicone	3.0
C12-15 Alkyl Benzoate	3.5
Triclosan	0.2
Fragrance	q.s.
Hydrocarbon propellant: Isobutane/propane (80/20)	93.4

Formula 2
Pump Spray Deodorant [133]

	Wt %
Cyclopentasiloxane	36.5
SD Alcohol, 190° proof	35.2
Distilled Water	2.6
Triclosan	0.2
C12-15 Alkyl Benzoate	7.0
Poloxamer 105 Benzoate	2.0
1,3 Butylene Glycol	1.0
PPG-3 Myristyl Ether	15.5
Fragrance	q.s.

For antiperspirant aerosol systems, hydrocarbon propellants are recommended. Antiperspirant actives are insoluble in hydrocarbons, thus there is a need to suspend an antiperspirant active properly to prevent (1) uneven discharge of an active throughout the useful life of the aerosol, and/or (2) valve clogage. Proper selection of an antiperspirant active's particle size (micronize or controlled particle size) is required to minimize valve clogage, respirable particles, or compactation. Fatty acid esters and silicones help lubricate the valve, while organofunctional clays are capable of minimizing compactation by maintaining a fluffy, easily redispersible suspension.

Due to both real and emotive environmental and inhalable issues, aerosols have been declining in popularity worldwide — most significantly in the US. Since the fluorocarbon ban in Europe followed years after that in the US, European manufactures/marketers have been able (1) to provide acceptable aerosol replacements based on hydrocarbons, and (2) to educate consumers regarding both the "ozone friendliness" of hydrocarbons and the inhalation safety of aerosols. Using information gleaned from the US's aerosol experience, Europe has been able to maintain better consumer acceptance of aerosol delivery systems, although there are indications that this may be changing similarly to the United States.

Environmental concerns about volatile organic compound (VOC) content (particular to the US) is a formulating issue as much as a regulatory issue. Because of the VOC issue, formulations have gone from typically 8-12% cyclomethicone to almost 20% with a resultant hydrocarbon propellant reduction from 75% to 60-65%. Also, there is a noted trend to more concentrated formulations with lower vapor pressure, in smaller containers, yet with delivery of a high level of actives. Thus, less total amount is dispensed.

New antiperspirant aerosols are just being introduced that employ Propellant 152A (DuPont) for reduced VOC [134]. Notable benefits are small container with equal weight and less overspray. As it was a trend in the early 1970s to switch from chlorofluorocarbon to hydrocarbon propellants, so may these new VOC-exempt fluorohydrocarbons and highly concentrated systems be an indication of the next global stepwise change.

Most aerosol formulations start with a concentrate based on incorporation with a suspending agent (e.g., hectorite clays) containing an emollient (e.g., cyclomethicone), and a polar activating agent of the clay platelets (e.g., ethanol or propylene carbonate). Shearing is employed to open the clay platelets and then an active powder is added and properly mixed to uniformity, then screened to remove any agglomerates. This mixture is then placed in an aerosol can and a propellant is added.

Formula 3

Aerosol Antiperspirant

	Wt %
Aluminum Chlorohydrate Powder	10.0
Cyclopentasiloxane	15.0
Isopropyl Myristate	5.0
PPG-3 Myristyl Ether	2.0
Quaternium 18 Hectorite	0.8
Propylene Carbonate	0.75
Fragrance	q.s.
Hydrocarbon Propellant	q.s.

6.2.2 Sticks: antiperspirants

This product form dominates the US market, with some global growth potential. Three stick formulations are possible: compressed powders, solution/emulsion gellants, and anhydrous powder suspensions. Of these, the anhydrous type is currently the only commercial example.

These systems rely on the synergy between stearyl alcohol and cyclo-methicone which forms a unique, mechanically rigid matrix that allows for easy gliding upon application [135,136]. To improve the matrix integrity and reduce whitening, other additives to match the refractive index of the antiperspirant salt are incorporated: natural and synthetic waxes, phenyl trimethicone, alkylmethyl siloxane waxes, dimethicone, and fatty acid esters [137,138].

The manufacture of antiperspirant sticks is complex in that cooling temperature and controlled cooling rate are critical to a stick's final appearance (crystallization and cavitation on the stick's surface). Also, as antiperspirant powders have a tendency to settle [139], there is a need to (1) control the temperature, cooling rates, and viscosity of the molten wax suspension stick, and (2) incorporate wetting agents for improved suspension properties.

Formulas 4 and 5 are examples of antiperspirant suspension sticks.

Formula 4

Antiperspirant Suspensoid Stick [140]

	Wt %
Cyclopentasiloxane	55.0
Stearyl Alcohol	20.0
PPG-14 Butyl Ether	2.0
Hydrogenated Castor Oil	1.0
Talc, 325 Mesh	2.0
Aluminum Zirconium Tetrachlorohydrate GLY Superfine Powder	20.0

Formula 5

Reduced Residue Stick [141]

	Wt %
Cyclopentasiloxane	50.5
Stearyl Alcohol	20.0
PPG-3 Myristyl Ether	5.0
PEG-8 Distearate	2.0
Talc, 325 Mesh	1.0
Silica, M-5	1.5
Aluminum Zirconium Tetrachlorohydrate GLY (AZP-908 SUF)	20.0

There is an emerging trend toward clear antiperspirant sticks, with dibenzyl monosorbitol acetal as the gellant. Since most gellants are low pH sensitive, there has been a significant hurdle to incorporate traditional gellants that would be destabilized. Patents using dibenzyl mono-

sorbitol acetal have provided at least one approach to overcoming this limitation [142].

6.2.3 Sticks: deodorants

Deodorant sticks are based on sodium stearate/propylene glycol systems. The correct grade of sodium stearate, water, propylene glycol and/or ethanol, and controlled cooling rate all influence clarity. Most deodorant sticks are translucent to clear, influenced by the addition of additives such as alkoxylated ether and water-soluble dimethicone copolyols.

Below are two examples of deodorant sticks:

Formula 6 *Deodorant Stick*

	Wt %
Sodium Stearate (C1)	7.0
PPG-15 Stearyl Alcohol	20.0
Propylene Glycol	52.0
SDA 40, Anhydrous	15.0
Deionized Water	5.0
Triclosan	0.2
Fragrance	q.s.

Formula 7 *Clear Deodorant Stick [143]*

	Wt %
Sodium Stearate (C1)	8.0
Propylene Glycol	7.5
PEG-4	7.4
Cyclopentasiloxane	40.0
Isostearyl Alcohol	19.5
PPG-10 Cetyl Ether	10.0
SDA 40, Anhydrous	7.4
Triclosan	0.2

Since sodium stearate is low-pH sensitive, this system is not applicable to acidic antiperspirants. A recent patent by Katsoulis et al. [144] demonstrates that encapsulation of the active can provide formulation capability for sodium stearate systems.

6.2.4 Roll-ons

For the most part, roll-ons are used only for antiperspirants. They can be delivered in four distinctly different ways: solution (hydro-alcoholic or aqueous), anhydrous cyclomethicone suspensions, oil-in-water emulsions, and water-in-cyclomethicone emulsions. Each country has its preference, as outlined earlier. Other than the anhydrous systems, all typically employ actives in an aqueous medium that also contains emollients and other aesthetic skin-feel enhancers.

Aqueous-based systems contain water, at least 50 percent, and require a emulsifier and/or thickening agent. The emulsifier is defined by the type of emulsion (oil-in-water systems typically use PEG and glycerol ethers; and water-in-cyclomethicone systems typically use dimethicone polyether types with low calculated HLBs). Water-in-cyclomethicone systems (refer to Formula 10) are noted for their ability to produce clear systems by matching refractive indices of the continuous cyclomethicone phase and the discontinuous aqueous phase of the emulsion.

A number of examples for each type of system follow:

Formula 8 *O/W Emulsion Roll-on*

	Wt %
Water	48.0
Magnesium Aluminum Silicate	1.5
Lanolin Alcohol	0.5
PEG-40 Stearate	2.0
Cetyl Alcohol	1.5
Lanolin	2.0
Glycerin	2.0
Mineral Oil	3.0
Phenyl Trimethicone	3.0
Aluminum Chlorohydrate (50% aq)	36.5

Formula 9 *Anhydrous Suspension*

	Wt %
Cyclotetrasiloxane	71.7
Dimethicone	5.0
Quaternium 18 Hectorite	0.8
SDA 40, Anhydrous	2.5
Aluminum Zirconium Trichlorohydrate GLY Powder	20.0

Formula 10
W/Si Clear Emulsion [145]

	Wt %
Cyclotetrasiloxane	7.0
Cyclopentasiloxane (and) Dimethicone Copolyol	10.0
Water	17.0
Propylene Glycol	16.0
Aluminum Chlorohydrate (50% aq)	50.0

6.2.5 Extrudables

There is a trend in the United States to provide an antiperspirant in the form of a thick cream or gel in an extrudable dispenser that looks similar to antiperspirant stick containers. Products of this type come in systems based on anhydrous suspensions, similar to anhydrous roll-ons or water-in-cyclomethicone emulsions, with high aqueous internal phases that provide viscosities of as high as $0.15 \text{ m}^2\text{s}^{-1}$ (150 000 cSt). Rheology of resultant formulations is critical in delivering a product that does not run from its dispenser during high shear extrusion, yet rubs into the body with ease and elegance. Some of the features that highlight consumer acceptance of these systems are: (a) non-whitening; (b) dry feel; and (c) ease of application. Below are examples of each system.

Formula 11
Clear Gel [145]

	Wt %
Cyclopentasiloxane	7.0
Cyclopentasiloxane (and) Dimethicone Copolyol	10.0
Water	9.0
Propylene Glycol	16.0
Aluminum Zirconium Tetrachlorohydrate GLY (35% aq)	58.0

Formula 12
Soft Solid

	Wt %
Cyclopentasiloxane	56.5
Dimethicone	15
Polyethylene	5
12 Hydroxystearic Acid	1.0
Aluminum Zirconium Trichlorohydrate GLY (Superfine Powder)	22.5

7 Trends and Conclusions

The underarm product market has been changing over the last few years. From a US perspective, the antiperspirant market has been shifting to differentiated delivery forms — in particular extrudable gels (opaque and clear) and clear sticks. Formulations used in the deodorant market have not been changing, but deodorant packaging is paralleling the antiperspirant market packaging; especially as regards the use of clear containers. Thus antiperspirant and deodorant products look alike, which blurs the consumer's ability to distinguish between the two.

As aerosol and roll-ons are being replaced by extrudables, one is forced to wonder whether high-performance pump sprays will enter the market as new differentiated delivery forms, and as an alternative low-VOC product. Inhalation issues surrounding cyclomethicone will have to be monitored closely.

The rest of the world has always been different from the United States and the various regions of the world also differ from one another. From a global perspective, antiperspirants and deodorants have varying degrees of popularity. As markets become globalized, the question arises whether there will be a shift in the underarm product market to a universal acceptance of antiperspirant/deodorant use.

Currently, there is a push towards the use of extrudables globally, with mixed results. However, since sticks and extrudables provide aesthetics and ease of use to consumers, there is no reason why they should not become popular throughout the world.

Regardless, successful products will need to provide mildness, ease of application, soft light-weight after-feel on the axillae, and good control of odor without the observation of wetness.

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