Two developments have drastically changed FDA's approach to regulation of topical antimicrobial agents: the recognition of the systemic toxicity of small amounts of hexachlorophene when absorbed after topical application; and the subsequent review and recommendations concerning both safety and effectiveness of other antimicrobial ingredients as part of the FDA review of OTC drugs.

Nationally, attitudes toward topically applied antimicrobials really began to change with the introduction of hexachlorophene and other substituted bisphenols, substituted salicylanilides and carbanilides that displayed substantivity. The insolubility and substantivity of these ingredients allowed formulation in liquid and bar soaps. Whether the mechanism of persistent action is the same for all of these is unclear; these and new chemicals introduced into the United States, such as chlorhexidine, have produced new uses, approaches to effectiveness, and safety problems.

It may be useful to present a brief regulatory history of antimicrobial products, with particular reference to hand-washing agents. Topically applied antimicrobial products are used to reduce the microbial flora of the skin, prevent infection or treat infection by inhibiting, killing or removing pathogenic microorganisms on the skin. With hand-washing products the risk of infection may be reduced in the user and those individuals who are in contact with the user, such as in routine patient care and presurgery. These formulations are classified as drugs when formulations containing active antimicrobial ingredients are labeled for these uses.

The realization that topical antimicrobial applications were useful in the prevention of disease, of course, dates back to the work of Semmelweis, Koch, and Lister. The variety and uses of such products since that time are legion. Most of us are aware of the use of phenol and peroxide for such purposes. The advent of the modern synthetic antimicrobial agents for use in hand-washing and surgical-scrub products dates to the introduction of iodophores and hexachlorophene products post-World War II and in the early 1950's respectively. Prior to these products, the major one applied for surgical operating use was tincture of green soap and alcohol. During these
early years, not much attention was paid to these products by FDA when the drug regulations were being legislated and revised. Events have changed the agency’s attitude toward them.

The introduction of new antimicrobial-containing soaps and surgical scrubs promoted the development of multiple sterile basin, hand-washing tests to determine the effectiveness of removal and/or killing of bacterial cells on the skin. During the period from 1962–1972 the major test of effectiveness for these products was the conventional hand-washing test, including Price, Cade, and Quinn procedures.

When the Over-The-Counter Drug Review was initiated by FDA in 1972 the NAS–NRC review of pre-1962 prescription drugs for effectiveness was completed and the implementation of the NRC recommendations was underway, the agency turned its energies to the review of the great profusion of products and labeling claims in the OTC drug market.

The accumulating evidence concerning the systemic toxicity of topically applied hexachlorophene was just becoming obvious. The uncertainties and problems faced by the agency led the directors of the OTC review to place the Antimicrobial Panel in a high priority position: the Antimicrobial Panel was the second panel convened (June, 1972). The record of the panels’ deliberations and decision are well known and their final report published in the Federal Register and in the public and scientific press.

The coincidence of the recognition of hexachlorophene toxicity and the OTC review initiated many changes in the toxicity and effectiveness testing of topically applied antimicrobial products designed for daily use. At the same time as the OTC review was proceeding, within FDA, the necessity for guidelines for the testing of these same products, particularly surgical scrubs, became obvious. Development of the needed guidelines was started soon thereafter. The recommendations of the panel on hexachlorophene and subsequent FDA regulatory decisions initiated the submission of approximately 20 New Drug Applications (NDA’s) for hexachlorophene products for hand-washing and surgical scrub indications. These two indications were the only permissible ones remaining and their sale was placed under prescription (Rx) status. Two lines of development—changes in internal testing guidelines at FDA and the development of definitions and testing procedures by the OTC Panel—ultimately resulted in the panel’s report published Sept. 13, 1974. Many of these testing procedures have been incorporated into requirements for NDA’s for antimicrobial agents not reviewed by the OTC Panel.

At the time the OTC review was initiated, only ingredients in products marketed for a material time and to a material extent in the United States were included in the review. Any other antimicrobial agent which a sponsor wishes to market for hand-washing, surgical scrub or first aid indications is regarded as a new drug and must now have an NDA.

Although there are a number of new products under investigation with an Investigational New Drug Exemption (IND), only one NDA for a new drug entity has been submitted and approved since the panel’s review. This