

## ► Three paths to Novartis

*Linkage of stalwart companies of the past led to the development of the modern pharmaceutical giant.*

BY MARK S. LESNEY

In 1996, Novartis was formed through the integration of Sandoz and Ciba-Geigy— instantly making it one of the largest life sciences companies in the world. The creation of this modern business giant was the final destination of three major historical pathways, as it completed the fusion of three venerable chemical companies, each born in Basel, Switzerland, centuries ago, the oldest of which, Geigy, traces its origin to the mid-1700s. Throughout their individual histories, these companies moved in and out of cooperative agreements and collaborations with each other across the gamut of chemical production, making their ultimate union seem logical, if not inevitable.

### In the beginning . . .

In 1758, Johann Rudolf Geigy-Gemuseus (1733–1793) founded J. R. Geigy AG in Basel to sell “materials, chemicals, dyes, and drugs of all kinds.” In 1857, Johann Rudolf Geigy-Merian (1830–1917) and Johann Müller-Pack built a dyewood mill and dye extraction plant in Basel, and within two years, the Geigy Company was manufacturing the synthetic dye fuchsine, which was originally discovered by E. Verguin.

In 1914, the company changed its name to J. R. Geigy Ltd., and although it produced drugs throughout its lifetime, it was not until 1938 that it created a pharmaceutical research department. Its first major discovery was the antirheumatic drug Butazolodin (1949). This was followed by the psychotropic drug Tofranil (1958); the first long-lasting diuretic Hygrotone (1959), used to treat high blood pressure; and the antiepileptic Tegretol (1963).

Simultaneously, Geigy was doing research

across the gamut of chemical products, from the production of paints and pigments to the work of Paul Müller, who discovered the insecticidal efficacy of DDT (dichlorodiphenyltrichloroethane) in 1939. For this work, Müller received the 1948 Nobel Prize in Physiology or Medicine. And Geigy was responsible for the introduction of the pop-



Sandoz plant in New York City.

ular triazine-based herbicides Simazine and Atrazine in the mid-1950s.

The linkage of general chemicals, dyes, and drugs born in the early days of the pharmaceutical industry was the norm. This was in part because of the nature of what is referred to by modern historians as the development of “heroic medicine”—a practice of attacking disease with powerful mineral therapeutics and bloodletting that characterized professional medicine in the 18th and 19th centuries.

In the 18th century, mineral-based drugs such as calomel (mercurous chloride), tartar emetic (antimony potassium tartrate),

and potassium iodide increasingly replaced herbal remedies in the pages of the various materia medica. Such chemicals, sometimes dosed in astonishing amounts to modern perceptions, were used to treat everything from depression to syphilis, and along with copious bloodletting, probably killed as many patients as they cured.

But it was not until the 19th century that a scientifically valid relationship between chemical companies and drug production would be uncovered. In the 1850s, W. H. Perkin’s (1838–1907) attempts to produce quinine gave rise to a colored compound, which led to the synthesis of the purple dye mauvein and the development of the synthetic dyestuffs industry.

The scientific explanation of this connection came in the 1890s with the realization, following Paul Ehrlich’s (1854–1915) magic bullet concept, that synthetic dyes had the potential to be used as medicines because of their greater ability to stain attacking microbes than human cells. For example, in 1891, Erlich used methylene blue, an aniline dye, to treat malaria. The use of metallic chemotherapy similarly flowered in the first part of the 20th century with Ehrlich’s development of arsenical compounds for treating syphilis and other diseases.

### The story of Ciba

In 1859, Alexander Clavel (1805–1873) began producing fuchsine in his silk-dyeing factory in Basel, creating a separate production facility five years later. In 1873, Clavel sold the dye works to Bindschedler & Bush, a company that gained a presence throughout Europe and the United States by 1876 and became the joint-stock company Gesellschaft für Chemische Industrie Basel in 1884. The new company’s name was quickly abbreviated Ciba, but the new name did not become official until 1945.

Ciba produced its first pharmaceuticals—the antiseptic Vioform and the antirheumatic Salen—in 1900, but like

Geigy, the company maintained a diverse chemical enterprise, working on insecticides, adhesives, and textile products while maintaining the continuing development of pharmaceuticals. This last category included Coramine (1924) for improving blood circulation and Desferal (1963) to treat thalassemia.

One of Geigy's key behind-the-scenes achievements was providing the first "real job" to a researcher who would later receive the 1998 Nobel Prize in Physiology or Medicine—Louis J. Ignarro (1941– ). He shared the prize with two others for his work on the signaling role of nitrous oxide. Ignarro became head of the biochemical and anti-inflammatory program of Geigy Pharmaceuticals in 1968 and helped to develop the nonsteroidal anti-inflammatory drug diclofenac.

In 1970, Geigy and Ciba merged to form Ciba-Geigy Ltd. The merger was perhaps inevitable given the continuing interaction between these companies throughout their shared history in Basel.

### The Sandoz saga

The youngest of the three major enterprises that would form Novartis was born in 1886, when Alfred Kern (1850–1928) and Eduard Sandoz (1853–1928) established the Kern & Sandoz chemical company. Its earliest products, not unexpectedly, were dyes—specifically alizarin blue and auramine. This development was followed in 1895 by the company's first pharmaceutical product, antipyrine, a fever-reducing compound, although Sandoz would not begin concerted pharmaceutical research until 1917 with the creation of a pharmaceutical department under the direction of Arthur Stoll (1887–1971). Stoll became noted for isolating ergotamine from the corn fungus ergot, which was introduced under the trade name Gynergen in 1921.

Perhaps one of the most noteworthy results of Sandoz's study of the ergot alkaloids in Stoll's group was Albert Hoffman's synthesis of the diethylamide of D-lysergic acid, or LSD-25. In 1943, while investigating its role as a stimulating factor for the central nervous system, Hoffman accidentally experienced the first LSD "trip", which launched further research into its mind-affecting properties and unwittingly made

possible the popular abuses of the drug.

Also in 1943, like its sister companies, Sandoz found a place in the agricultural chemicals business with the pesticide Copper Sandoz.

In the 1950s, Sandoz introduced the neuroleptic drug Melleril, and in the 1960s, it became a worldwide force in antibiotic production. Further diversification of the company came from mergers with food companies, including Ovaltine (1967), Wasa (1982), and Gerber (1994).



CIBA administration building in Summit, NJ.

### Now for Novartis

In 1996, Ciba-Geigy and Sandoz united to form Novartis. As is often the case in such major mergers of old and valued players in a field, the names of the original companies may disappear from main corporate mastheads, but they frequently survive in the names of subsidiaries or in particular product lines (these associations being either too famous or too marginalized to require changing). Such is the case within Novartis, as both the Sandoz and Ciba names have been recycled. In 2003, Sandoz returned as the new name uniting all of the former Novartis Generics companies worldwide—the division responsible for the development and marketing of generic drugs. The Ciba name remains in Ciba Vision—a division dedicated to eye health care that was originally set up as a separate business unit in 1987.

Typical of the trend in the 1990s to separate life sciences and pharmaceuticals from standard chemical production, Ciba

Specialty Chemicals was spun out as an independent unit one year after the merger that formed Novartis. In a few years, even the concept of a broad "life sciences" company became suspect, as many companies became more dedicated to pharmaceuticals and spun off their agricultural biology interests to consolidate profits and distance themselves from consumer backlash against genetically modified foods—as witness the formation of Syngenta in 2000 from the agribusiness components of Novartis and Zeneca, and the spin-off of Monsanto's agribusiness sector after its merger with Pharmacia.

Poor performance of the general chemical sector as compared to pharmaceuticals and biotechnology in the 1990s promoted divestiture of these traditional mainstays. In addition, the need for companies such as Ciba and Sandoz to merge proved typical of the broader trend for industry restructuring in pharma, as clinical trials and R&D costs skyrocketed and profit losses loomed inevitable from the coming lapse of key patents. According to industry analysts at Burrill & Co., such mergers provide access to powerful product portfolios; yield cost savings by eliminating overlapping products, functions, and overhead; and give combined companies the ability to augment existing businesses or enter new therapeutics areas. By the end of the century, the formation of Novartis could be seen as simply one of many, with the formation of AstraZeneca, GlaxoSmithKline, and Aventis (from Rhône-Poulenc and Hoechst).

Perhaps the story of Ciba, Geigy, and Sandoz and the birth of Novartis can be seen as a fable with a singular moral—that the day of the all-ambitious, all-chemicals-to-all-people companies, with their commitment to selling "materials, chemicals, dyes, and drugs of all kinds," is history.

### Further reading

Burrill, S. G. *Biotech 2000*; Burrill & Co. LLC: San Francisco, 2000.  
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