Steroids and Upjohn: A Profile of Chemical Innovation
Narrative (suggested first of supporting documents to read after Nomination Form)

By the end of the 1940's various steroid compounds of the androgen, estrogen, progestogen and adrenocortical classes had been isolated from animal tissues, structurally characterized, and studied for medicinal properties. As the decade closed out a chemistry breakthrough discovery that stood out was Russell Marker working out chemical synthesis of progesterone from diosgenin extracted from Mexican yams, obviating the need for animal tissues. On the medical front, a major breakthrough that shone through was the discovery by Mayo Clinic researchers that the corticosteroids like cortisone were effective as anti-inflammatories treating debilitating diseases like rheumatoid arthritis.

At the dawning of the 1950's an overwhelming demand for cortisone arose. However, cortisone was still being manufactured almost entirely as an extract from animal adrenal glands, making the supply very low and the cost very high. Merck had a synthetic process for manufacture of cortisone, but the process involved about 37 chemical steps from cholic acid from bile, a complexity that also limited supply and came with a high cost. Other attempts at synthesizing cortisone had hit dead ends. Percy Julian was able to synthesize the related compound Reichstein's Compound S, but could not find a way to carry out a key oxygenation step needed to carry the process all the way to cortisone (See Compound S supporting document for more detail). Similarly, Russell Marker could not find a way to oxygenate progesterone to convert it to cortisone (Carl Djerassi followed up on Marker's work by working out a chemical process for converting progesterone to cortisone, but the process was too complex to be commercially feasible).

Concurrent with the growing cortisone demand and lack of supply, The Upjohn Company was in the midst of a head-first plunge into the sea of steroid chemistry. The company had been working with steroids during the 1930's and 1940's, the work of scientists George Cartland and Marvin Kuizenga being most cited during that period. The two developed processes for extraction of steroid fractions from animal adrenal glands (marketed as a product named ACE), and invented an analytical unit for adrenal hormone potency, the Cartland-Kuizenga Unit, which became the worldwide standard. In the mid-1940's in a bold future-looking move, The Upjohn Company took on expansion of their R&D organization, creating interdisciplinary steroid discovery and development teams consisting of chemists, biochemists, microbiologists, engineers and production managers. The company also expanded their manufacturing facilities dramatically – fully fourfold greater than the foreseeable demand. When the new unmet need appeared in 1949-1950 then, for chemical synthesis and mass production of cortisone, The Upjohn Company was in position to take on the challenge.

Due to this unprecedented focus on steroid chemistry, positive results were achieved relatively quickly. In 1950 the Upjohn R&D team led by Herbert Murray (a microbiologist) and Duey Peterson (a biochemist) discovered that a type of fungus that could be grown in fermenters could efficiently do the steroid chemistry that had been elusive to lab chemists around the world—selectively oxygenate progesterone to hydroxy-progesterone, which could be chemically converted to hydrocortisone and cortisone. This was a major chemistry breakthrough of the time (See Progesterone supporting document). In addition to opening the door to a relatively simple, inexpensive

and commercially scalable synthesis of cortisone, the discovery brought to life the chemistry of steroid microbiological transformations, and more generally the use of fungi (as an addition to bacteria) for chemical transformations. The team's success was also a testament to the strategy of using multi-disciplinary R&D teams, a practice that became standard for all pharmaceutical companies.

At almost the same time, a second Upjohn R&D team led by Haines discovered a bacterium that could selectively oxidize Julian's Reichstein's Compound S directly to hydrocortisone. This second major discovery confirmed the importance of using microbial transformations for performing complex steroid chemistry like selective oxidations. The discovery also meant that Upjohn had the option of having two potential synthesis routes to make cortisone (See Compound S supporting document). The progesterone route was selected to take forward based on expected availability and cost of materials.

From here, Upjohn chemists took the hydroxy-progesterone obtained from the microbial transformation of progesterone, and developed an elegant five step synthesis to end up with hydrocortisone, which in one additional step could be converted to cortisone. The process was refined, scaled-up and moved to production, and by 1953 Upjohn was marketing low-cost, high-quality cortisone and hydrocortisone (Cortef) products, which were very well received.

This alone would be a very good ending to a historic chemistry story—a team of scientists in the early 1950's apply a newly discovered mix of synthetic chemistry and microbiological biochemistry to bring a much needed medicine to patients in need. But what makes this story worthy of historic chemical landmark designation is that even more chemistry breakthroughs followed.

Having a process in hand for making cortisone from progesterone, Upjohn focused on the source of progesterone. In 1953, the progesterone was being supplied by Russell Marker's company Syntex, and was synthesized from diosgenin extracted from Mexican yams. Upjohn chemists Milton Herr, Heyl, Centolella and team had developed a four-step process converting stigmasterol from soybeans to progesterone in 1950, and by 1955 they had refined the process so that Upjohn was able to start making its own progesterone. Soon stigmasterol from soybeans replaced diosgenin from Mexican yams as the primary plant-based starting material for steroid synthesis being conducted by most western pharmaceutical companies. This was also an environmental blessing since the isolation of diosgenin required several processing steps which produced significant toxic waste.

To go with the switch to stigmasterol as a starting material, Upjohn scientist J. Ward Greiner and team developed an innovative leaching and counter-current process for recovering the approximately 20% stigmasterol from the soy sterols mixture produced as a distillative by-product of soybean oil purification, truly producing a classic example of using a sustainable source for a chemical starting material. Greiner's process for recovery of stigmasterol also recovered the remaining 80% of the sterols, the majority of which was a related compound sitosterol (See Extraction supporting document). The technology for fermenting sterols with saturated sidechains like sitosterol into a starting material for steroid synthesis was not known at the time.Rather than discarding it, the company, in a conservationist move, started stockpiling the very stable, water insoluble recovered sterols. This stockpile grew for over ten years until a use was found for it.

During the late 1950's with corticosteroid production well in hand, Upjohn began reaping the benefits of research toward discovery of next generation analogs of cortisone. Using the established approach of combining synthetic chemistry and microbial biochemistry, a number of new compounds were discovered and marketed, including prednisolone, methyl-prednisolone (Medrol), fluoroprednisolone (Alphadrol) and Oxylone, which showed better efficacy and safety profiles for various anti-inflammation indications than cortisone. Keeping manufacturing needs in mind, the chemistry processes used, whenever possible, intermediate compounds from the main line cortisone process. This strategy, the use of common intermediates, became standard for the pharmaceutical industry (See Manufacturing supporting document for useful graphic). The next generation discovery work also branched to include discovery of progesterone analogs including acetoxyprogesterone and melengesterol acetate for contraception applications in the veterinary area, and medroxyprogesterone acetate (Provera) as a human contraceptive. As Detroit Michigan became Hitsville USA in the music world, Kalamazoo Michigan became Hitsville USA in the steroid medicine world due to Upjohn's long-term innovative approach to medicinal chemistry and manufacturing.

In the 1970's, already having a rapidly growing steroid medicine portfolio, another major microbiological transformation discovery was made at Upjohn (See Sitosterol supporting document). Scientist Merle Wovcha and team discovered a bacterium that not only degraded the 17-sidechains of nearly all of the soy sterols, including sitosterol, but also oxidized the 11-position. The resulting compound (9α-hydroxyandrostendione) could, with additional innovative chemical development, be converted in fewer steps to both existing and new products. With this breakthrough the recovered sterol stockpile that had been growing for over ten years became a valuable starting material in its own right. With this discovery Upjohn was now not only sourcing starting materials from a sustainable source, it had found a way to utilize multiple materials from a single source, sustainability and conservation practices that were to become key principles of green chemistry. The discovery also opened up a whole new area for D-ring chemical exploration involving converting androstenedione compounds into corticoids, particularly the application of novel silicon (SNAP) chemistry to introduce the corticoid sidechain.

During the 1980's the work continued including the discovery of additional analogs, new fermentation technology for efficiently converting multiple commercially available phytosterol mixtures into an array of maximally useful intermediates, and improving production synthetic chemistry and microbiology biochemical step efficiencies and costs. By 1990, having strung together an unparalleled series of chemistry and manufacturing discoveries and developments, Upjohn had become the premier steroid medicine producer in the world. The company had a portfolio of over 30 medicinal steroid products and supplied steroid intermediates to a number of other pharmaceutical companies for synthesis of additional steroid medicines,

The significance of this chemical landmark achievement continues to be felt today. The Kalamazoo production facility, now as part of Pfizer Inc., continues manufacturing steroid medicines and intermediates for global markets. The Kalamazoo steroid manufacturing site was lauded in a 2017 Investor's Business Daily article as an example of how U.S. manufacturing can be made efficient and low cost enough to compete in today's global economy. This is a testament to the historic importance of The Upjohn Company's 1950-1990 steroid chemistry work