Tom Layloff

Cultures and Visions; Confusion, Frustrations, and Remedies

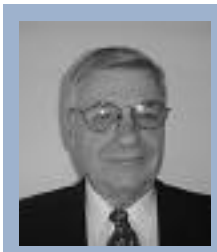
I would like to revisit the Discovery, Development, and Control (DDC) model, presented initially in the first article in this series, as it relates to science, individual vision, and culture; this model may be helpful in understanding, and, hopefully, improving people's roles and interactions in new drug* development, quality control, and regulation. In this model, the Discovery process identifies a new dimension of knowledge, the Development process explores and defines its envelope, and the Control process takes it to fruition to serve societal needs.

Each of us comes packaged with an array of attributes including Culture, Abilities, Skills, and Knowledge (CASK). Culture is probably the most important single attribute and it is instilled by family, friends, peers, role models, etc. Work ethic, art and music appreciation, scholarship, discipline, respect for societal mores, etc., are all part of the repertoire of culture that is instilled in us.** Abilities are the next most important attribute category and these are innate; they are a genetic birth gift. Abilities include coordination, which is especially important in athletic prowess; the ability to focus on tasks; intellectual development, especially comprehending mathematical concepts; physical attributes; maintaining orderly processes; etc. Skills are the next in the hierarchy of attributes. These are developed through the application of cultural drivers that marshal discipline to focus ability to achieve tasks. Playing the violin, being a basketball great like Michael Jordan or a golf great like Tiger Woods, etc.; the cultural focus on ability produces successful skills. Next is knowledge, which is acquired again through the cultural driver acting through intellectual ability to build rote knowledge blocks. These CASK attributes are elements that characterize individuals and how they interact with others and knowledge.

Taking the CASK concept into the drug Discovery, Development, and Control paradigm helps to build understanding on individual performance and perceptions. The Discovery process is a paradigm-smashing event, most often occurring by bringing together previously unrecognized relationships between old concepts and models into new truths. This domain is populated with youthful CASK individuals, especially during their adolescent years, when every well-held truth comes under scrutiny and is questioned. All cherished structures seem to come into challenge. This unrest, if properly focused on intellectual topics in a contemplative environment, often can yield spectacular insights, but only if the surrounding social/intellectual infrastructures are sufficiently self-assured to allow the challenges. The Discovery CASK in

*Although "drug" is used in the discussion, the same arguments would apply also to biologics, medical devices, etc.

**This concept is presented well in the autobiography of Nobel Laureate Rosalyn Yalow, in which she notes, "Neither (*parent*) had the advantage of a high school education but there was never a doubt that their two children would make it through college. I was an early reader, reading even before kindergarten, and since we did not have books in my home, my older brother, Alexander, was responsible for our trip every week to the Public Library to exchange books already read for new ones to be read." (Cited from www.nobel.se/medicine/laureates/1977/yalow-autobio.html.)



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some individuals often extends beyond the adolescent years, although the truly great paradigm breaks generally are made by individuals prior to their 25th year.

Upon maturing, many individuals who come down the Discovery path move into high-level Development CASK or exploring the envelope of Discovery breakthroughs. This process frequently happens in therapeutics. A Discovery event is rapidly assimilated into an intensive Development mode to explore the envelope of what has been found (i.e., the Discovery) and to identify the ways to maximize its utility. It should be noted, however, that CASK individuals who are truly in Discovery generally are not into Development; they are into paradigm-smashing events and not into exploring the bounds of intellectual envelopes. This is similar to the role of revolutionary CASK individuals in any context. An example cited in a previous article was the discovery by Prof. John Enders and his colleagues of how to culture the polio virus. Prof. Enders and his colleagues elected not to abandon their Discovery CASK to pursue the Development CASK of the polio vaccine; they instead redirected their efforts toward making new discoveries, thereby leaving the vaccine development activity to the Development CASK individuals, Drs. Jonas Salk and Albert Sabin and their colleagues. There are numerous similar therapeutic examples of this process.

As the therapeutic intervention target becomes better defined, it moves through the Development domain toward the Control environment, where the processes are well structured and defined. As the material moves closer to manufacture, the product process definitions and assessment technologies are firmed into test and therapeutic limits. The robustness of the process array is evaluated and validated and the substance moves into production with everything controlled and locked into standard operating procedures (SOPs) so the product can be consistently manufactured. The quality systems come strongly into play here—document what you do and do what you document. In the Control environment, the control of variable elements is maximized—no surprises; everything works the way it has been validated to perform. This actually happens most of the time with simple organic molecules where there are a minimum number of relatively robust critical control points.

The individuals who are employed in these different segments most often come with preformed visions of their roles and performance domains, visions constructed from their culture, education, and experiences. From a management perspective, it is important to recognize an individual's CASK because these characteristics determine where they can be most effectively placed in these scientific processes. Individuals in the Discovery CASK, or even those who simply envision themselves there, generally do not perform well in the Development mode; their vision of themselves in an appropriate activity is seeking new truths and not exploring the envelope of known truths. Similarly, individuals with a Development CASK generally have difficulty accepting the uncertainties of the Discovery mode, and neither Discovery CASK individuals nor Development CASK individuals are enthusiastic performing in strictly defined environments. The individuals from the Control CASK are most comfortable in environments of predictability and control; everything is orderly and well defined. Individuals in the Control CASK prefer not to wrestle with the envelope exploration of the Development CASK or the intellectually jarring uncertainties of the Discovery CASK. They thrive on a well-regimented work environment. Many engineering scientists have CASK orientations, which result in their self-selection into the Development–Control CASK roles, whereas theoretical physicists and mathematicians frequently have CASK orientations that self-select them into Discovery–Development roles.

The Discovery CASK most often occurs in a university environment. The faculty frequently envision themselves as being into Discovery and, although they generally are past their peak of paradigm smashing, they are open to its uncertainties and do not feel threatened by the undergraduate, graduate, and postdoctoral students who form the most fertile area for these intellectual breaks. A good professor encourages the intellectual foment and can recognize and accept the new outcomes and challenges. The Development CASK most often occurs in research institutes and industries, while the Control CASK is almost the exclusive domain of the industry* and its regulators.

It is interesting that vision conflicts may erupt between the various DDC segments. To help avoid these conflicts, new product industries frequently locate their discovery operations separate from their development units, which in turn are separated from the production and control operations. Some industries co-locate their discovery operations in an academic research environment by identifying a professor who is exploring an area of interest that they can subsequently fund to enhance those efforts or by leasing a part of an academic institution's physical plant as a location for their discovery programs. This co-location is sought in the hope that the Discovery CASK staff will interact and be stimulated by the academic intellectual turmoil and foment and thereby be more productive. This type of co-location avoids much of the vision conflicts with the Development and Control CASKs. Discovery activity also occurs well in small, economically distinct firms or start-up companies that exist only to do discovery. Here, the Discovery CASK is sole occupant of the premises, and the rush to smash paradigms into new order sometimes borders on intellectual chaos.

Typically, there is no definitive product until late into the development cycle, at which point the therapeutic entity is confirmed. Product regulation in terms of safety and efficacy begins here. Discovery and early development are distant from marketed product and therefore outside the regulatory box. Society's interest in the potentially marketed product begins late in the development process (i.e., Does it work? Is it safe?) and in the controls that ensure consistency (i.e., Am I getting what I should be getting?).

Returning to the DDC paradigm, it is interesting to note that virtually all individuals who enter a doctoral

*It should be noted that some Discovery institutions, in order to generate additional income, have founded Development and Control activities as a part of their mission repertoire. This focus, however, comes at the expense of Discovery.

program in the sciences* must, at a minimum, envision themselves in the Development CASK if not in the Discovery CASK. This vision in many instances results in self-exclusion from functioning well in the Control CASK, and these degreed individuals generally are not good candidates for staffing control activities. Two-year and many four-year colleges are strongly oriented to the late development and control employment market** and do an excellent job of training and orienting students whose CASK predisposes them to late development and control work environments.

An example of how these CASK features can have impact is shown from my experience as an FDA laboratory director. For a number of years, the FDA has had a methods validation package (MVP) evaluation program. The New Drug Application process requires the submission of proposed methods to be used to assess product quality. The FDA, through laboratory validation, determines if they are suitable for their intended use. These methods typically originate in the bowels of the product discovery process and are evolved to some degree in the product development process before they finally are submitted to the FDA as the control methods for the specific product. The FDA's role in this process is to determine whether or not the defined assessment techniques are suitable to consistently assess the product quality. Experience showed that if the MVP evaluation was submitted to reviewers who could be characterized as falling in the Control CASK, an evaluation was promptly conducted to determine if the method performed as claimed and a "yes/no" answer was quickly reached. If the evaluation was assigned to an individual falling in the Development CASK, the evaluation typically began by asking whether this was the best technology to perform the assessment and whether the assessment method could be more efficient. In other words, if the MVP was sent to the Development CASK, you received development and only with added push a control focus. A further problem in this process is that different individuals in the Development CASK frequently come to different conclusions as to what should be done. The focus of one individual may relate to one area, while a second individual may focus on an entirely different aspect of the test methods. This inherent variation in the assessment by Development CASK individuals can be frustrating when one expects a consistent performance and response from a given set of data or information. If you send the same MVP evaluation to five different Development CASK staff persons, you may get five different answers, none of which directly address the "yes/no" question. As noted previously, it is difficult to inculcate a strong Control CASK vision into Development CASK individuals. To a certain degree, training and structured SOPs can help provide some assistance in attaining consistency, but the envelope exploration model occasionally erupts, thereby creating uncertainty in the processes.

It should be noted that the FDA field investigators have an academic degree in a scientific discipline for entry into this employment area and after hiring are extensively trained in the Control CASK and adherence to structured requirements. Development CASK individuals or development activities that may occasionally drift into the control environment frequently result in conflict and misunderstandings. Development individuals see changes as perfectly reasonable, whereas these activities may be an anathema to the Control aficionados. This conflict situation commonly occurs on preapproval inspections (PAI)* where the reviewing scientist (Development CASK) and field investigator (Control CASK) come to investigate whether or not a manufacturing facility is ready for product launch. Since the manufacturing has not yet been launched, there may still be some development changes that the Development CASK individuals may tend to overlook while at the same time appalling the Control CASK individual.

The bottom line on this DDCCASK business is to understand the baggage that each individual brings to the table in order to avoid uncertainty and frustration. A manager must first critically assess his/her own baggage in order to identify his/her CASK leanings so they may be understood and kept in control while dealing with individuals from other CASKs. This is true for managing a popular restaurant chain, a start-up pharmaceutical discovery firm, or a top university research mathematics department. A leading university research mathematics professor would likely have major conflicts and misunderstandings while attempting to manage a restaurant even if all individuals had good will and intent; the CASK conflicts would overshadow successful operations. In order to keep your organization's internal and external operations running smoothly, recognize these individual CASK differences in establishing interactions and assignments. Assign Development CASK personnel to development activities and Control CASK individuals to control activities to help ensure smoother communications and more predictable responses. This is also important when dealing in a regulatory environment; recognize the CASKs of the individuals in the process so you may appropriately order your information and communication activities for maximum effectiveness.

*This would include the Ph.D., D.Sc., and the research-based M.D. degrees.

**I estimate that 90% of the employment opportunities are in the product development and control functions.

*As with all FDA issues, a flagrant procedural violation gives rise to a new regulatory initiative. In the PAI instance, a firm had submitted and had received approval to market products for which it had no production capabilities at its own site or under potential contract.

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