Regulation and excipient innovation.

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Innovation, by its very nature, is a foray into the unknown, where the end product, however specifically envisaged (to generate a profit and/or improve the public good), can never be entirely predicted. It is a predominantly subliminal process on many cogitative and non-cogitative levels, one that cannot be 'called upon' or made to 'materialize' on demand, contrary to its misguided application as a Frederick Taylor type activity in many knowledge based organizations. Often, the full nature and/or possibilities of incremental or disruptive innovation only dawns after the event and may include unforeseen applications and/or impact.

Innovation proceeds faster where there is reasonable expectation of financial gain. Excipient companies have to be especially careful in allocating R&D resources to develop new excipient products when the only path to market hinges on their incorporation in a third-party pharmaceutical product. It becomes more profitable to 'innovate' and manufacture those excipient molecules that can be widely incorporated into a generalized (independent of their *in vivo* mechanisms of action) emergent stream of increasingly hydrophobic active pharmaceutical ingredients (APIs), hence the innovation focus on pharmaceutical grade surfactants, solubilizers and amphiphilic molecules. There is little incentive to invent excipients for specific pharmacological purposes such as gene promoters/delivery modifiers, endosome disruptors, cellular efflux modifiers and 'off target' receptor modifiers because there is no general 'mass market' for such extremely specialized excipients. Conventional wisdom does not recognize that excipients may possess innate pharmacological properties. It makes more financial sense to subsequently evaluate mass market surfactants, solubilizers and amphiphilic excipient molecules for specific mechanisms of action. In the absence of a separate regulatory path for new enabling excipients, the above paradigm has become so pervasive that pharmaceutical excipient definition and scope have come to be typically assumed as being synonymous with largely commoditized molecules incapable and/or devoid of any intrinsic, *in vivo* enabling, modulating or pharmacological activities.

Regulation generally includes tests, specifications and criteria to define and enforce attributes for the benefit of the public good. Regulation requires standard setting

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organizations that are perceived to be competent, impartial, representative and cognizant of the public good. However, in the fields of medicine or pharmaceuticals, where unregulated goods and services are (generally) not possible, the lack/paucity of regulation to keep pace with the innovative process, or proactively drive the innovative process in specific trajectories, can (and does) prove detrimental to the public good. It can drive innovation to less productive ends such as overreliance on compliance. A focus on compliance at the expense of innovation drives unnecessary and repetitive activities at a level of detail and minutiae which is financially burdensome on industry and adds little to making APIs more effective. Attributes should not be regulated merely because they can be (so regulated), rather, because of their criticality (see further below).

Regulation must achieve a fine balance between the public good and innovation. In the field of pharmaceutical excipients, the critical attributes of safety and identity (from manufacture to point of use, either as part of the supply chain or after incorporation into a pharmaceutical product during shelf life) should remain paramount properties with additional purview of properties important for drug delivery. The identification and control of other excipient properties that are critical to the manufacturability and the quality of pharmaceutical products can, and should be managed outside of regulatory specifications using QbD and/or supplier-pharma engagement. Grade-differentiation, amphiphilic properties of surfactant excipients, particle size and size distribution are some examples.

Modernization of testing requirements must explicitly allow for cross-validation against existing methods especially if there are no safety or identity related issues. Many people are unaware that they can use validated methods other than those of the monograph. Chemometric or dimensionality reduction methods, where results depend also on statistical and/or software/algorithm dependent parameters, present particular challenges because instrument software qualification and validation (whose magnitude and scope is vastly greater than, for example, conventional HPLC) is inextricably tied in with the measurement method itself.

The practice of frequent revisions to specifications for excipients made from natural products arising out of variable factors such as geographical location, time of harvest and species biodiversity must be re-examined. The minimum specifications that are required for safety and identity should be retained. Recently, much progress has been made in this regard especially for setting and/or modifying specifications for fats and oils. Genetically modified (GM) species will prove to be especially challenging for regulating excipients made from natural products in the future.

Ideally, as few attributes as possible should be in excipient monographs with limited, universal, harmonization-capable and cost-effective test methods. For those regulated attributes, specification limits must be as broad as possible within the confines of meeting safety and identity requirements. The impression that 'specifications are written in stone' should be replaced with the concept of 'adaptive specifications' to ensure fitness for purpose in the application.

Chemical derivatives or covalent and/or co-processed combinations and/or variants of excipients and food ingredients that significantly improve drug delivery or ADME of 'non-mass-market hydrophobic APIs should have fast-track designations allowing parallel development of excipient and pharmaceutical product. The absence of regulation for a new excipient product should not serve as a deterrent for its incorporation into a pharmaceutical product for clinical trials. Unless innovators have some assurance that a new, hitherto untested excipient will not disproportionately hinder regulatory approval of a pharmaceutical product (especially a non-mass-market API) that incorporates it, it will be

difficult to encourage innovation. FDA denial of an NDA or BLA containing the new excipient will not relegate the new excipient to financial and/or therapeutic oblivion if there is sufficient regulatory latitude to permit the evaluation of that excipient with other APIs.

For this to happen, excipients must be regulated with more attention to, and recognition of, their API pharmacology complementing *in vivo* properties rather than regarding them as inert ingredients. For those who argue that this will only add to the confusion and blur the lines of distinction between excipients and APIs, the other choice is being forever stuck with adapting structural motifs of existing solubilizers, surfactants and amphiphiles as 'new' excipient 'safe financial bets'. Proactive regulation that breaks from the current anachronistic paradigm, ready to recognize excipients, not only *for what they are*, but *what they have the capacity to be*, will see excipient innovation come into its own, hopefully with a profusion of pharmacologically enabling excipients and food chemicals. There is a plethora of such molecules to be harnessed, if innovation-friendly excipient regulation can be promulgated.

Chandigarh and Gandhinagar are two planned cities in India post-independence. Chandigarh, designed by Le-Corbusier, is epitomized by Cartesian precision, brute functionalization, and a cold detached cityscape totally alien to its denizens. The 'rock garden' is the only representative symbol of the long suppressed desire of its citizens to innovate their indigenous ethos in the midst of their forced regulated environment. On the other hand, Gandhinagar, the planned capital of the state of Gujarat, designed by Prakash Apte, deliberately incorporates in its physical layout and space, the traditional culture of the populace it is designed for. One of these cities attempts to regulate from without, the other from within. One enforces alien norms and customs and recognizes city planning *for what it is*, the other offers an adaptive physical environment suited to its users and recognizes city planning *for what it can be*. One envisages the city as a machine, the other as a foundation to be innovated on by its dwellers. Neither of these cities takes a *laissez-faire* approach to regulation in so far as adhering to basic planning norms. The difference is in the manner of genesis and hence in the method of implementation, adoption and response to those regulations.

The regulatory environment for pharmaceutical excipients is a matter of active ongoing discussion and debate among stakeholders. Regulation of pharmaceutical excipients must not become so unduly copious, unmanageable, dysfunctional, dogmatic or nuanced so as to justify the comment from Oliver Wendel Holmes quote on related content, "I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be bad for the fish and good for humanity". Regulation of excipients must also recognize their tremendous *in vivo* potential so that deliberate encouragement and discovery of new molecules along these lines may occur.

Excipients can be so much more – give them a chance!