

Incremental innovations in drug research

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Between the mid-eighties and 2006, the share of generic prescription drugs have increased from 20% to 60% in US (and also globally). Blockbuster drugs expiring (like kingpins) in serial sequence is causing feverish pressure on pharma firms to innovate. However, in the short term, almost all innovator groups (and products) are trying to extend the life of expiring, nearby expired or patent challenged expired drugs through incremental innovations.

Contributions from incremental innovations in progress of research, especially pharma research cannot be ignored. However, what is important to note about such sequential improvements are that they either contribute in increased efficacy, including safety or/and stability, but also, often lead to better cost benefit ratios. In the absence of such contribution, they cease to be incremental pharma innovations or fall short of utility requirements as well as overall patentability criteria.

Nikola Tesla, Marconi and Edison, contemporaries in radical innovations could get to their respective breakthroughs building on a compounding and cumulative impact of their own or others (during the late 19th and early 20th century's) incremental innovations. A good drug discovery chemist, for example, can arrive at a sequence which might click for a specific target based on the trend visible or noticeable in a series of sequential inventions.

Among the byproduct of the slowing down of the discovery research, the increasing attention and respect for combination therapy is dominant in the incrementality with utility. While combinational chemistry may not have delivered to meet the "Great Expectations" in drug discovery research, the "combination" dosage forms especially combined with NDDS (novel drug delivery systems) have led to very beneficial and patent-friendly incremental innovations which have become or have potential to become near blockbusters at the market place. This is the innovation range and "patent fields" for Indian pharma researchers in the next few years. India has traditionally been promoting and practicing rational drug combination therapy for last few decades, even ahead of the west.

It is said, "necessity is the mother of inventions". In spite of India not granting product patents for last 30 plus years, Indian pharma companies have been continuously and increasingly indulging in "incremental innovations" without patent protection. If so, what was the basic motivation?

Innovations come from a variety of motivations. Patent protection is one of them. India having denied product patent grants from 1970 and also having brought in 'licence of right' tag on process patents, the Indian dosage form "revolutions" in the eighties and

nineties could not have been motivated by patent protection. Indian pharma corporates and researchers were actively pursuing combination therapy in the meanwhile. In fact, India was being decried for encouraging "combination therapy". The NGOs who considered only the "western evidence" as reliable were fast to join the bandwagon of "irrational combination therapies". While admitting that all communications were not rational, a large majority of the Indian combination dosage forms were indeed innovative, rational and were truly incremental innovations.

If not patents, what motivated these inventions? These inventions were not motivated, but were necessitated by irrational and overzealous drug policies of the late seventies, eighties and nineties.

Indian domestic pharma companies were pushed to the wall through repressive and arbitrary pricing policies and controls and other regulations. The National Pharma Industry had to find innovative ways of survival by circumventing the successive DPCOs. These led to the incremental innovations, through changes in dosages, new drug delivery systems and more importantly drug combinations/combos or cocktails.

It is only after the adverse impacts of drying of the discovery pipeline was felt, that even US FDA had started having a relook at combination therapy including Fixed Dose Combinations (FDC). Today a wide range of AIDs drug cocktails are listed in the US FDA's CDER guidance or FDC etc. (see tables). A number of anti-diabetic, anti-cancer, anti-malarial, anti-hypertension and other combinations are also currently approved or under approval.

While Sec. 3(d) and the newly introduced "Explanation", denies patentability to new forms of known molecules unless they contribute to utility over its prior form, incremental improvement in physical form may not, by itself, contribute to patentability as per Sec. 3(d). However, patentability is not the final destination for incremental innovations, or sole motivation for research in incremental innovations.

Indian scenario

The current pharma scenario in India is ideal for such a motivation. In spite of the global trends and the globally acknowledged "Manmohanomics" from the early nineties, it appears that the C&F Ministry's "cheese" is still unmoved. There is a "Bear" in the "China shop", surprisingly going amok. When the bandwagon of market-oriented economy is moving forward with visible gains and widely acknowledged benefits to public interest, it is surprising that a lone Ministry seems to have missed the bus. The "threats" and "warnings" seem to be replaying of the recordings of the seventies, not even eighties and nineties. While no one is expecting anything to happen in spite of all the "sound and fury", the compulsions to have a wide basket of monitoring, if not control, could be ideal motivation for the pharma industry to seek the incremental innovation route to arm and "brand" themselves to be different from the crowd of generics which are the latest and current target of the raging "Red Bull". India is receiving acknowledgement and acceptance as a reliable economically priced pharma source.

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While emphasis (often voluntary) on cGMP and world-class quality assurance was being practiced even from the eighties (by some), currently the emphasis on quality and efficacy not so much on price. Past experiments on stringent price control have led to proliferation of spurious and substandard drugs. Currently, most high quality Indian pharma manufacturers (big or small) are generating their larger turnover and even bigger share of profits from international operations. Creating roadblocks, hurdles and controls on the domestic front will force these front ranking players to bypass or deemphasize the domestic market. After all, the interests of the stakeholders are also important and cannot be ignored in the long term. Ministers such as this, have in the past created havocs in the short term and are to blame for the morbidity and eventual mortality of one time vibrant and healthy public sector organizations like IDPL (Indian Drugs & Pharmaceuticals Ltd.), HAL (Hindustan Antibiotics Ltd.) and Haffkine Institute at Mumbai. Incremental mindset changes also would be a welcome feature while debating on incremental innovations.

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A few of the enabling characteristics of incremental pharma innovations to qualify for potential protections are:

- 1)enhanced efficacy
- 2)improved safety
- 3)lower dose and toxicity/side effects
- 4)patient regimen compliance / convenience /benefits
- 5)tailor-made solutions
- 6) device linked dosage forms, and
- 7) herbal combinations.

In spite of the larger pharma corporates declaring their "drug discovery" interests, the opportunities in incremental pharma innovations are unlikely to be missed by big and small across the cross sections of the industry. Peter Drucker's definition of a good innovation being the one which is a success in the marketplace will undoubtedly be put to test by a few of the incremental pharma innovators in the current scenario. Let us wish them the best.

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