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Position Paper

What Role for Systematic Drug Repositioning?

Author: Dr. Andreas Persidis

CEO, Biovista Inc.

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In an ideal world we shouldn't need drug repositioning. In an ideal world we would know exactly how and why drugs work the way they do, drugs would perform exactly as advertised, drug development would be a much more deterministic process, therapies would be optimized for each patient and there would be no side effects.

In an *almost* ideal world, we might still not need drug repositioning. Large pharmaceutical corporations would *know what they know*, there would be no corporate 'silos' and the relevant development teams would also know, in a timely fashion, all that is publicly known on any given biological process, disease and therapy. They would also know all *potentially relevant* information even the *seemingly disparate*, and would factor all that in the design of their drugs from the early development stages.

But we don't live in an ideal world, not even an almost ideal one. And so for now, there seems to be a role for drug repositioning and even more so for systematic drug repositioning. But this role must, and will be, a changing role, one that evolves as the biopharma community works towards its ideal world.

The good news is that even though drug repositioning is relatively young as a distinct field of work, it has been evolving rather rapidly and is already in what might be considered its "3rd generation". Generation 1 was *serendipitous drug repositioning* (DR), a chance event that was exploited opportunistically. Generation 2 is *systematic drug repositioning* (SDR) and is what the community is at the present time mostly talking about. It is a process done on a regular basis as part of drug LCM/PLE and new therapy development, and is increasingly recognized as a valuable tool in the pharmaceutical executives' box of tools aimed at extracting maximum value from each asset.

Generation 3 is also already on the table. Generation 3 drops the "re" from repositioning to give us *systematic drug positioning* (SDP). The difference is that whereas SDR is reactive and focuses mainly on older drugs and compounds, SDP aims to be proactive, identifying all the possible applications of a promising compound from its early development stages. Interestingly, those who question the value of DR point out that the proactive search for multiple indications is already happening with new drugs, and so there is no need for repositioning. While this might be true, it fails to recognize the potential contribution of a future discovery that would change the state of knowledge and could create opportunities for a solution where in the past there was none.

More importantly, whether we say that such a systematic search for alternative indications is happening as a part of the normal drug development process or we call it SDP so that we can refer to it as a specific process *with its own specific mindset, tools and resources*, is missing the point because we all agree that it must be done and indeed it is already being done. What is much more interesting is to ask ourselves whether SDR/SDP is currently done in the best possible way, and if not, what are the challenges. We would also be well served to start thinking about how SDP might evolve further as the research and business community itself evolves towards the target of a "more ideal world", better-differentiated products and better clinical outcomes.

On the technical/scientific level there are many approaches to SDR each with its pros and cons. But as with all knowledge intensive processes, it seems that the *science* of SDR is not the only item on the critical path to success that we should be thinking hard about. The *art* of SDR, i.e. how we integrate SDR within an organization with minimum disruption to existing processes, is equally important and possibly a much tougher nut to crack. Because it has to do with people and organizational issues, with reward schemes,

daily work priorities, biases and resource limitations, internal versus external innovation, attitudes to risk taking, appropriate business models and a host of challenges that are not specific to SDR and are notoriously hard to solve. And so those of us who are involved with SDR/SDP have already got our work cut out for us.

As for the evolution of SDR/SDP we also have to ask ourselves whether it is an "interim solution", a "fix" dictated by some temporary necessity (patent cliff, R&D output etc.) that, as some people view it, is only able to extract *additional value* from the hard work of others and not really capable of creating *new value* (new knowledge) on its own. A quick answer is that "value is always valuable", whether de novo or incremental, and so once again a more interesting question is to consider what that next stage of the evolution of SDR/SDP might be, so that indeed it does not become an interim solution but a permanent and powerful tool for systematic innovation.

The answer seems clear: while we are practicing it on a regular basis and learning how to optimize SDR/SDP as a business process, we must already start thinking about "systematic drug and therapy *discovery*" (SDTD), a process that is more efficient and ideally more "deterministic" than what drug development currently is; more akin to an engineering process than a series of filters that take in 10,000 candidates as input and produce a single marketable drug as output.

This of course is the wholly grail not only of the pharmaceutical community but also of many innovation-intensive industries, and a lot of ideas and methodologies have been put forward by researchers and innovation strategists worldwide. What the SDR/SDP community must therefore start thinking about are two main questions that are *specific to the biopharma domain*:

1. What principles/techniques/methods from SDR/SDP and elsewhere can we use or adapt so as to evolve towards an SDTD capability? Just like "gamification" is not about turning applications into games or adding a game to a web site, but rather about applying *principles* from the design of on-line games to a variety of other business challenges, so SDR/SDP can serve as a resource for principles, tools and processes that could help create an SDTD capability. Clearly, this alone would be a significant value contribution to the healthcare industry.
2. What does our present understanding of biology and disease teach us in terms of designing an SDTD capability? Systematic discovery in biology can probably make use of certain "domain characteristics" that are not applicable when thinking about systematic discovery in, say, engineering. So what are these domain characteristics and how can we integrate them in the methodologies, algorithms and tools we develop and use for SDR/SDP?

The challenge of better healthcare is clear, real and present, and one that demands innovation on many levels. Clearly the SDR/SDP community is not, and must not be, the only community that works towards SDTD. But dealing, almost by definition, with the use and reuse of available knowledge on a daily basis, it is certainly well placed to contribute to this worthy goal.

Author Information

Dr. Andreas Persidis is the CEO of Biovista Inc. He is a frequent contributor to discussions on knowledge discovery and systematic innovation. He can be contacted at: andreasp@biovista.com

