Research and Development of innovative products in the Americas: a case for empowerment.

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Neglected diseases keep on affecting scores of populations in developing countries. The lack of new and more (innovative) effective products weakens the response of national authorities and other involved stakeholders. The World Health Assembly adopted the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA) through resolution WHA61.21. Pan American Health Organization's (PAHO) Directing Council endorsed the regional implementation of the GSPA in the Americas through resolution CD48.15: *Public Health, Innovation and Intellectual Property: A Regional Perspective*.

On a background of a high regional capacity to produce and deliver generic pharmaceutical products (drugs, vaccines, diagnostics and devices) the Americas has also the potential to play an important role in alleviating the lack of innovative products not only to address their own diseases that lack such products but also to contribute to the needs of diseases prevalent in other regions of the world.

The discovery and development process for innovative products is substantially different for that of generic pharmaceutical products and can be described as a "pipeline" that integrates the following activities:

- Basic biomedical, social and economic research to generate knowledge on diseases.
- Generation of product discovery and development tools. This activity "translates" basic knowledge in tools, e.g.: assays, modelling tools for generation of chemical or biological information, biomarkers of efficacy and toxicology, biostatistics, etc.
- Product discovery
    - Target identification (use of genomic information)
    - Chemical or biological lead identification, this requires development of in vitro and in vivo disease relevant screening systems and generation and modification of chemical or biological entities, either through design or through prospecting biodiversity.
    - Chemical or biological lead optimization; this comprises biological, chemical and animal pharmacology research to generate suitable "drugable" molecules to be progressed into product development.
- Product development, a process that addresses:
    - Human clinical efficacy, safety and pharmacology
    - Animal toxicology
    - Chemical or biotechnological production scale up
    - Pharmaceutical (formulation, adjuvant) development
- Product regulatory framework, a process that ensures the quality of the products and processes that the R&D sponsors generate
    - Guidelines and normatizisation of the R&D process
    - Awards the product marketing authorization to the product sponsors
    - Normatizes and monitors product post approval activities
        - Pharmacovigilance
        - Batch release quality

The analysis of the availability in the Americas of the competencies or capacities that constitute the elements of this "pipeline" reveals that on the regional level they all are available (in most instances compliant with internationally accepted standards). The quantity and quality of basic biomedical research addressing many diseases prevalent in the region is very high. Similarly the competencies required to address the different elements of the R&D" pipeline" are available. In the literature one finds many references to in vitro or in vivo disease models for neglected diseases that could be readily available for the use for product discovery. The clinical research capacity to investigate products according to the state of the art (GCP & ethics) is high in the region and can be reflected by the number of clinical centers that participate in research activities evaluating products that are being developed by the for profit innovative pharmaceutical industry. Similarly, one can find plenty of evidence from the many generic pharmaceutical industries operating in the region for quality (GMP) production capacity for active ingredients or final product. There is also evidence that demonstrates capacity to conduct (GLP) toxicology or pharmacology activities required to assess new molecular entities. However, in most cases these competencies are spread across the countries and very few of them can claim to have **all** the competencies to fully address the R&D pipeline for innovative products within their territorry. Even in the countries where this is the case the capacities are limited to address particular type of products and within these only very few particular diseases. The output of the particular capacities mostly remain as publications and very seldom progress into a product R&D "pipeline". In other instances these capacities contribute as service to product R&D initiatives lead by institutions or organizations (public or private) based in the north. Furthermore, the lack of national innovative product R&D "pipeline" can be reflected by the fact that very few national medicine regulatory authorities have the capacity to address innovative products emerging within their territories.

In many instances it has been argued that engagement in innovative product R&D by institutions (public or private) specially to address neglected diseases is not feasible because it requires high investment with relatively low chance of success (rate of attrition 1 in 100). It is further argued that the market incentives are not sufficient to stimulate investment. These arguments become even more compelling when raised by national small pharmaceutical companies who are very vulnerable to the high risk associated with innovative product R&D projects. However, this perception has been challenged by the concept developed by Product R&D public private partnership organizations (PPP's). These organizations have been successful in raising public funds to institute product R&D "pipelines". They are virtual product R&D organizations that manage product portfolios and activities mostly conducted by "collaborators" in endemic developing countries where the final product sponsor usually is a pharma in the north. While some PPP's have already proven to be able to deliver products, most of them by their nature limit the product portfolio to their financial capacity to manage a product pipeline, therefore, limiting the number of products that can be taken up at a given time. Another aspect that may limit their portfolio is the their difficulties to access local know-how (e.g.: biodiversity and traditional knowledge). While recognizing that PPP's are an important model to address the existing gap in innovative products affecting particular health problems in developing countries, new product R&D paradigms enhancing South-South cooperation must be considered.

In the region of the Americas one possibility could be the creation of frameworks where product R&D "pipelines" could be established at a regional basis through bilateral or multilateral agreements between countries taking advantage of the competencies that exist in the countries of the region. Such framework could create incentives for the national public sectors to invest more in public research institutions with R&D capability given that these institutions would be incorporated into production of innovative public health goods. Furthermore, for the national private or public pharmaceutical sector the possibility to source particular R&D activities to other institutions/organizations would reduce the necessity to invest in infrastructure and personnel, therefore, spreading the inherent "risk" (and investment) associated with product R&D process. It could also represent a viable mechanism to address the therapeutic needs for diseases that are geographically limited and therefore, will never be high in the scale of the global burden of diseases. The creation of such frameworks could stimulate bilateral or multilateral R&D agreements (within regional economic development frameworks) to generate public goods between institutions from different countries. These initiatives differently from PPP's would not require a supra national managerial R&D structures, rather would depend on their own product R&D management teams and would be closely linked to the public health systems.

Organizations such as PAHO or TDR/WHO could play key role in mapping the existing regional capabilities and act as brokers for the establishment of joint ventures for product R&D or for capacity strengthening activities among institutions in diverse countries of the region and promoting South-South cooperation. It also could play role to strengthen the regulatory capacity and harmonizing regulatory requirements among participating countries to address innovative products. It also could help fund rising for such multi country/multi institution initiatives within the multiple funding opportunities from diverse sources that are currently available for large framework projects.

In conclusion it is imperative that at a regional level countries develop new models for management and conduction of R&D for innovative products so to develop functional synergies to address efficiently and sustainably the generation of new products for health problems of the region.