Editorial

Drug Development Output from 1975 to 1996: What Proportion for Tropical Diseases?

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Notwithstanding recent advances in research and drug discovery, the drug development pipeline for tropical diseases is drying up.[1] Despite the ever-increasing demand for effective, safe, and affordable drugs, tropical diseases, by their nature and prevalence, are a low priority for private industry.

The authors analyzed the drug development process with particular emphasis on the top ranking six groups of parasitic diseases in terms of morbidity and mortality (filariasis, helminthic infections, African trypanosomiasis, leishmaniasis, malaria, and schistosomiasis). Data were retrieved through systematic search of the medical press (through MEDLINE Database, 1994 to 1997; Drugs and Pharmacology Embase, 1986 to 1997), pharmaceutical statistics (IMS International data) and the World Health Organization (WHO) reports.

Of the 1223 new chemical entities commercialized worldwide between 1975 and 1996, 379 were real therapeutic innovations.[2] Less than 1% (11 new molecules, plus two new approvals for reformulation of known chemical entities) were destined for tropical diseases, of which only a minority may be claimed by Western pharmaceutical companies as genuine products of their research, the majority being either "incidental" discoveries recovered from veterinary medicine or molecules discovered by governmental or academic institutions and only later acquired and commercialized by the Western industry. Furthermore, atovaquone development for malaria would have been endangered if its effectiveness in acquired immunodeficiency syndrome (AIDS)-related opportunistic infections had not been discovered. In addition, various artemisinin-type drugs in use do not meet international standards and are registered only in the country of origin and few other countries (Table 1).

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What prevents drug companies from conducting research and development (R&D) for tropical diseases, against the current scenario of high awareness of emerging infections and particularly malaria?

First, the cost:risk ratio of drug R&D is compounded by the low purchasing power of the endemic countries. The average cost of bringing a new chemical entity to the market, a process taking 8 to 12 years,[3] is US$160 million (although some claim more), with "only" US$16 to 54 million of this allocated to clinical development,[4] hence the advantage of "piggy-backing" on other discovery efforts. As Western drug companies expand through repeat mergers, the target in terms of sales for a development candidate grows higher, and tropical diseases drop down the priority list. Donation programs (e.g., ivermectin, atovaquone) are often preferred to dual-pricing for wealthy and indigent customers, as the latter strategy could jeopardize sales of high-priced compounds also marketed for nonparasitic indications.

Second, the protection of proprietary rights and the recovery of investments also are important issues to drug makers. With the long payback period associated with these indications, costs often are not recovered when a compound runs off patent and generic products may be introduced. A sales decline of over 50% is expected within the first few months of generic entry.[3] Moreover, unfair competition and counterfeit products are not uncommon.

Lastly, regulatory requirements have a considerable impact on the length and costs of the process and, hence, on the ultimate market price of the product. Paradoxically, increasingly demanding standards favor the larger wealthy companies, which are those least interested in tropical diseases. Nevertheless, dossiers do not necessarily undergo the same level of review the world over, sometimes because of bare-bones health budgets, and sometimes owing to a misconception of the regulatory process.

The net result is that fewer drugs adapted to the needs of the poor are anticipated. The immediate pipeline sounds rich: there are new antimalarial and antileishmanial drugs (see Table 1) in clinical phases of development or nearing registration, but few developments are need-driven. Some compounds are predictably expensive, and

Table 1. Characteristics of Drug Development Output

Indication	*Molecular Entities*	*Year First Marketed or Approved*	*Pharmaceutical Development Context*	*Pricing and Marketing Strategy*
Marketing approval of new molecular entities: 1975–1997				
Malaria	Artemether * (intramuscular)	1997	Chinese academy discovery. Public-private collaboration (WHO-TDR / Rhône-Poulenc-Rorer Co.). RPR / Kunmig Co. (China) agreement	Preferential price for public sector. Artemether from other manufacturers cheaper
	Atovaquone / proguanil	1997	Wellcome antimalarial research (now GlaxoWellcome Co.). Atovaquone first approved for *Pneumocystis carinii* infection in HIV/ AIDS	Very expensive (high cost of goods). Currently partial drug donation programme
	Halofantrine	1989	US DoD discovery (WRAIR). Public-private collaboration (WHO / WRAIR / SmithKline Beecham Co.). US Orphan Drug status	Expensive: producer price
	Mefloquine	1987	US DoD discovery (WRAIR). Public-private collaboration (WHO / WRAIR / Hoffman LaRoche). US Orphan Drug status	Expensive, but cheaper generic products exist
Human African trypanosomiasis (HAT)	Eflornithine (DFMO)	1990	Marion Merrell Dow (now Hoechst Marion Roussel Co.). US orphan product designation and approval for the treatment of HAT (*T. b. gambiense*)	Very expensive. Product originally abandoned by HMR. WHO efforts to restart and to reduce price considered
Chagas' disease	Benznidazole	1981	Veterinary originally (Roche Co.)	Producer price
	Nifurtimox	1984	Veterinary R&D originally (Bayer Co.)	Producer price
Schistosomiasis	Oxamniquine	1981	Veterinary R&D originally (Pfizer Co.)	Producer price
	Praziquantel	1980	Veterinary R&D originally (Bayer Co.). Public-private collaboration (WHO / Bayer)	Producer price and generic products
Helminthic infections	Albendazole	1987	Veterinary R&D originally (SmithKline Beecham Co.)	Drug donation under consideration
Onchocerciasis	Ivermectin	1989	Veterinary R&D originally (Merck Co.). Public-private collaboration (WHO / Merck)	Mectizan-donation programme
New approvals for already-marketed drug products in a new use or a reformulation				
Human African trypanosomiasis	Pentamidine isethionate	1950 / 1984	Rhône-Poulenc Co.: galenic reformulation (mesylate to isethionate). US Orphan Drug status and new approval only for *P. carinii* infection	Drug donation for HAT (through WHO)
Leishmaniasis	Amphotericin B lipid complex	1962 / 1996	Vestar (now NeXstar Co.): galenic reformulation of amphotericin B in liposomes. US Orphan Drug status and approval for treatment of invasive fungal infections	Extremely expensive Efforts to cut price inconclusive as yet
Possible future additions				
Malaria	Artemether / benflumetol	1998 ?	Ciba Geigy (now Novartis Co.)	Probably expensive Strategy unknown
	Pyronaridine	2000 ?	Chinese academy discovery marketed only in China, International development by WHO-TDR, currently no industrial partner	Unknown
	Artesunate rectal	1999 ?	Chinese academy discovery; international development for limited indication by WHO-TDR and Mepha Co.	
	Etaquine	?	US DoD discovery (WRAIR). Public-private collaboration (WRAIR / SmithKline Beecham Co.)	
	Chlorproguanil / dapsone	2000?	Combination of known antimalarials. Public-private collaboration (WHO-TDR / SmithKline Beecham Co.)	
	Arteether	1998 ?	Public-private collaboration (Gov. of the Netherlands/ Artecef / WHO-TDR / WRAIR)	
	Artelinate	?	US DoD (WRAIR)	
Leishmaniasis	Paromomycin (aminosidine)	1999 ?	Re-discovery of old aminoglycoside by Farmitalia-Carlo Erba (now Pharmacia-Upjohn Co.) developed by WHO-TDR, currently no industrial partner. US Orphan Drug designation (1994) for the treatment of visceral leishmaniasis	
	WR6026	?	US DoD discovery (WRAIR). Public-private collaboration (WRAIR / SmithKline Beecham Co.)	
	Miltefosine	?	Product under development as anticancer agent. Public-private collaboration (WHO-TDR / Asta Medica Co.)	

*There are other sources and formulations of artemether and other artemisinin-type compounds (artemisinin, artesunate, dihydroartemisinin, arteether in various formulations) that have received marketing approval in country of origin (mostly China and Vietnam) and few neighboring countries, or are under development.
WRAIR = Walter Reed Army Institute of Research; WHO / TDR = World Health Organization / Special Programme for Research and Training in Tropical Diseases.

no further candidate for development is expected in the short term.

This and prior analyses call for a broader debate on global drug development strategies for tropical diseases. The present profit-driven system is obviously unable to keep pace with current and evolving needs, and so far the public sector (with few exceptions) has been unable to provide the optimal environment for such activities.

There is clearly room for new approaches. Increased representation of disease-endemic countries in the process is needed. The antimalarial drug market in particular offers opportunities poorly covered by Western drug companies. What is not appealing to the Western drug industry may well be suited to small-to-medium sized start-up companies, particularly in advanced developing countries. Opportunities exist: basic research in academia generates leads that are not exploited and candidate agents that are not developed. The Special Programme for Research and Training in Tropical Diseases (TDR) stimulates projects along these lines, providing training opportunities for scientists from advanced developing countries, facilitating technology transfer to the public and private sectors, and strengthening research and infrastructure. The public and private sectors should explore the facilitation of interaction, alternative routes of marketing and distribution (purchase funds), and optimizing the regulatory process. The momentum around malaria with the newly established Roll Back Malaria Initiative of the WHO could, hopefully, break new ground.

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