What the agrochemical industry can teach the pharmaceutical industry

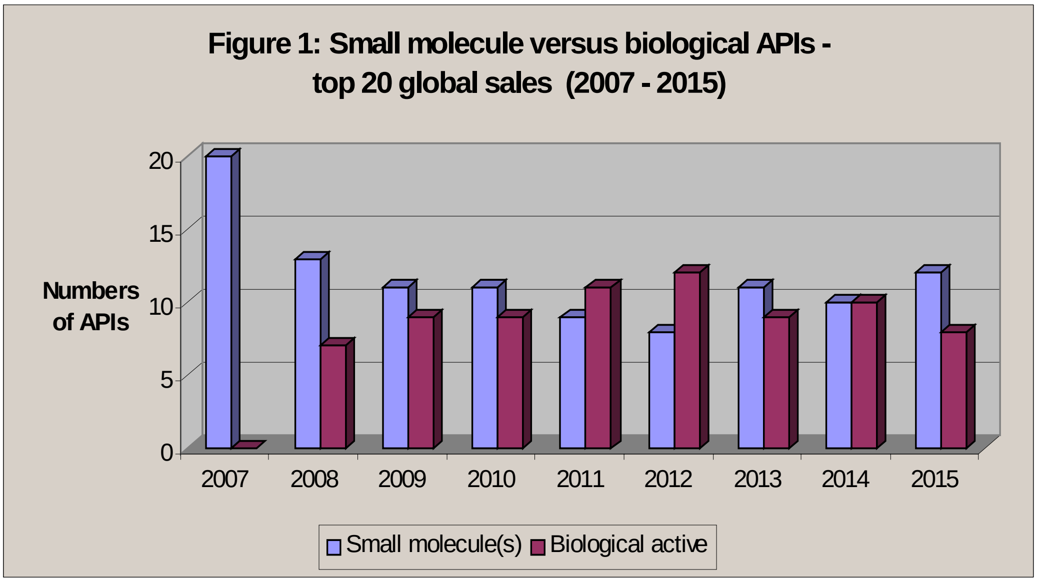
The fine chemical industry is a bioscience-based industry. Its role is to produce biologically active compounds that can be used commercially to effect an affordable contribution to the control of biological systems of interest to man. During the last 75 years this has meant that the majority of chemists moving into this industry have had a strong interest in the chemistry and synthesis of natural products and, more recently, their biosynthesis.

As the science has developed, so has the understanding of the incredible complexity of the workings of the "simple" cells that make up the majority of organisms in Nature. Researchers involved in developing new pharmaceuticals have tended to develop ever more complex candidates in order to interact with ever more complex biological targets. Cost constraints within agrochemical research have meant that candidate active ingredients have stuck to rather simpler compounds than has been the case in the pharmaceutical industry, where the majority of users do not influence the price of medicines.

During the 1980s, the costs and profits that customers of the two bioscience sectors were able to bear steadily became more divergent. This difference was reconciled by the major bioscience companies spinning out their agrochemical businesses in the 1990s – early 2000s. The global sales of these two industries in 2014 demonstrate that the contrasting economics have remained very different: USD 1.05 trillion (pharmaceuticals) and USD 69 billion (agrochemicals).

Pharmaceuticals

From around 1998 onwards, the introduction of a rapidly increasing number of "biologics" or "biological active ingredients" has meant that many new products avoid the use of chemistry altogether. Up to 2007, there were no top twenty drugs using biological ingredients, but by 2014, half the world's top twenty pharmaceuticals were biologics (see Figure1).



Source: Brychem, using several sources of global sales estimates

During the past 15 years, the pharmaceutical industry has introduced ever more complex "small molecules" and "biologics", which have lead to many more treatments costing more than USD 10,000 per patient per year. It is not the intention of this article to discuss the factors that have driven such massive price increases, but even in advanced economies, the prices of these treatments have become politically contentious. Indeed, the UK's National Health Service is unable to offer an increasing number of biologicals to its patients because the cost/benefit ratio has become unacceptable (as advised by the National Institute for Clinical Excellence). To illustrate the growth of these expensive biologics, the top 20 global best-sellers are listed in Table 1. "Small molecules" (SM), Biologics (Bio) and monoclonal antibodies (Mab) are listed.

Table 1: Global top-selling pharmaceuticals

Company Name	**Product Name**	**Global Sales 2014 (USD million)**	**Global Sales 2015 (USD million)**	**Active Ingredient**	**Type**
AbbVie	Humira	11,844	14,012	Adalimumab	Mab
Gilead Sciences	Harvoni	3,035	13,864	Ledipasvir and Sofosbu	SMs
Novo Nordisk	Novo-brands/Levemir/New Generation	5,466	9,426	Insulin	Bio
Amgen, Pfizer Inc	Enbrel	8,707	8,697	Etanercept	Bio
Johnson & Johnson, Merck & Co	Remicade	8,097	8,310	Infliximab	Mab
Sanofi	Lantus/Toujeo	10,331	7,209	Insulin Glargine	Bio
Roche	MabThera/Rituxan	6,552	7,115	Rituximab	Mab
Roche	Avastin	6,070	6,751	Bevacizumab	Mab
Roche	Herceptin	5,564	6,603	Trastuzumab	Mab
Pfizer Inc.	Prevnar family	4,464	6,245	Pneumococcal 7-Valent	Bio
Celgene Corporation	Revlimid	4,980	5,801	Lenalidomide	SM
GlaxoSmithKline	Seretide /Advair/Serevent	8,652	5,359	Salmeterol	SM
Gilead Sciences	Sovaldi	9,375	5,276	Sofosbuvir	SM
AstraZeneca	Crestor	8,473	5,017	Rosuvastatin Calcium	SM
Pfizer Inc.	Lyrica GIP, GEP	6,002	4,839	Pregabalin	SM
Amgen	Neulasta	4,627	4,715	Pegfilgrastim	Bio
Novartis	Gleevec/Glivec	4,746	4,658	Imatinib	SM
Bayer, Johnson & Johnson	Xarelto	1,868	4,345	Rivaroxaban	SM
Teva	Copaxone	4,788	4,023	Glatiramer	biopolymer
Otsuka Holdings, BMS, Lundbeck	Abilify	6,416	3,904	Aripiprazole	SM

Sources: Pharmacompass, IMS Health, Global Data and Informa

Agrochemicals

The impact of "biologicals" upon the crop protection business has been far more muted, with around a 1.5% market share in 2014. The current top-selling agrochemicals are shown in Table 2. There are no biologicals in this list; the only major biological is an insecticidal bacterium called *Bacillus thurungiensis* (global sales in 2014 were USD 237 million), although there are a number of newer microorganisms with sales above USD 10 million.

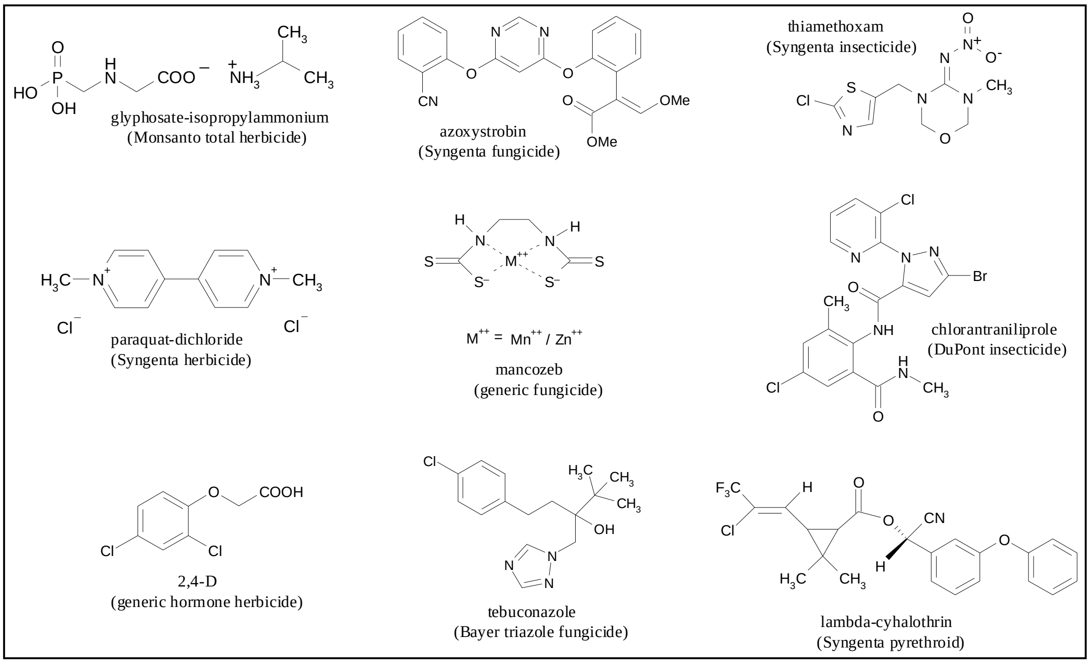
Table 2: Leading agrochemical active ingredients in 2014
(by global sales value at end-user level)

Agrochemical active	**Activity**	**Originator/Major Seller**	**Sales 2014 USD million**
glyphosate	herbicide	Monsanto	6,575
azoxystrobin	fungicide	Syngenta	1,935
thiamethoxam	insecticide	Syngenta	1,740
imidacloprid	insecticide	Bayer CropScience	1,735
pyraclostrobin	fungicide	BASF	1,590
chlorantraniliprole	insecticide	DuPont	1,350
mancozeb	fungicide	Generic	1,090
abamectin	insecticide	Syngenta	1,085
trifloxystrobin	fungicide	BASF	1,030
mesotrione	herbicide	Syngenta	890
paraquat-dichloride	herbicide	Syngenta	825
fipronil	insecticide	Bayer CropScience	785
prothioconazole	fungicide	Bayer Cropscience	750
chlorothalonil	fungicide	Syngenta	740
clothianidin	insecticide	Bayer CropScience	675
lambda-cyhalothrin	insecticide	Syngenta	640
glufosinate-ammonium	herbicide	Bayer CropScience	615
chlorpyriphos	insecticide	Dow Agrosciences	563
2,4-D	herbicide	Dow Agrosciences	548
tebuconazole	fungicide	Bayer CropScience	537

Source: Crop Protection Actives (Agranova)

In Figure 2, the structures of some of the top twenty global selling agrochemicals are presented. Just one is based upon a bacterial extract: abamectin, which is available at a modest USD 78/kg. The price of the highlighted active ingredients range from USD 3.2/kg (2,4-D) – USD 245/kg (chlorantraniliprole).

Figure 2: Structures of selected leading commercial agrochemicals (2014)



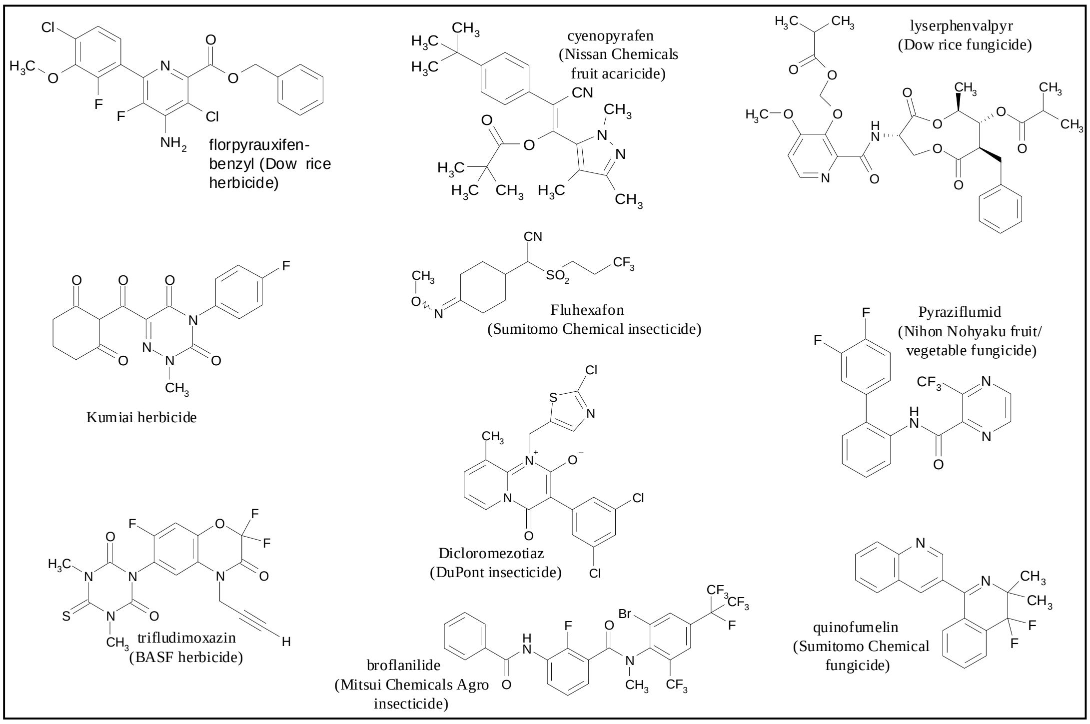
As stated above, with the customer base making the decision whether or not to purchase their products, price restraint has always been a major factor in the development of novel agrochemicals. This has meant that research into new agrochemicals has always been more disciplined by the ultimate cost of the new compound. Co-ordination between research and process development remains a key factor for success and the upshot has been that molecular targets have generally been simpler compounds that are very often “flat” (without chiral centres), if at all possible.

In spite of these cost constraints, the industry has had great success in controlling three main biological targets: weeds, insects and fungi. In Figure 3, the structures of some of the leading agrochemical candidates are presented. These are, undoubtedly, more complex than the structures of the current market leaders, but in order for success to be ensured, their final costs of production (at a reasonable scale) will need to be < USD 250/kg. It is striking that poly-substituted aromatic and heterocyclic rings predominate in these compounds, which suggests that more could be done with such “unnatural“ molecular targets in pharmaceutical research as well. It has to be said that thenewer “nib” class of anticancer drugs do fall into this chemical class. Happily, the skills of process chemists are not yet redundant in the pharmaceutical industry.

Conclusions

One wonders whether the pharmaceutical industry might be offering significantly cheaper treatments, had society imposed greater constraints upon the acceptable prices of their final products. It is a fact that process chemists working within the pharmaceutical discovery R&D departments are never invited to compare the ultimate costs of drug candidates of similar levels of potency. The decision on which the preferred candidate will be remains entirely with medicinal chemists and, in the case of biologics, chemists are not even involved.

Figure 3: Structures of leading developmental agrochemical active ingredients (2015)



There are, of course, factors operating outside the pharmaceutical industry that may eventually force the industry to take costs into consideration at an early stage of development. In a recent Financial Times' article on Duchenne muscular dystrophy (Monday 23rd May 2016), the *average* annual price of two classes treatments in the USA were quoted (source: Evaluate Pharma): USD 23,331 for non-orphan drugs and USD 111,820 for orphan drugs. The article posed even more interesting (indeed shocking) questions about the pressure on the USFDA to approve drugs of unproven efficacy.

It remains the case that the move towards the use of biopharmaceuticals, driven as much by the desire to ring-fence profits post-patent expiry as by pharmacology, has led to an unfortunate and dramatic escalation in prices, which is surely unsustainable. Is their any sign of hope? Presentations at a recent SCI process development conference suggest that, in some companies at least, efficient processes for making small molecules are being used to offer ground-breaking advances in medicine. Using the ingenuity of chemists and good process development, rather than simply making the molecules of Nature, must make more sense in a world in which the majority of people cannot afford more than USD 500/year for their medicines.

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31st May 2016

Selected further reading

Newman and Cragg, - Natural Products as sources of new drugs 1981-2014, Journal of Natural Products 2016 (available online at pubs.acs.org/jnp)

B Clifford Gerwick & Thomas C Sparks, Natural products for pest control: an analysis of their role, value and future, Pest Management Science, 2014, *70*,1169–118