



New products and new indications in 2016: a system that favours imitation over the pursuit of real progress

● Little therapeutic progress was made in 2016, yet many medicines with no clinical value, uncertain efficacy or an unfavourable harm-benefit balance were authorised. This is due at least in part to the current system that drives pharmaceutical research and development. The primary focus is neither on patients' needs nor on delivering genuine therapeutic advances at affordable prices.

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Each month, *Prescrire* publishes its independent, methodical, systematic reviews, analysing new drugs, new indications for drugs already on the market, and existing drugs authorised in a new pharmaceutical form or at a new dose strength. The goal is to identify the new products and indications that represent a real advance for patients.

In 2016, *Prescrire's* Editorial Staff analysed the clinical evaluation data for 92 drugs. This yearly review sums up the results of those analyses.

2016: once again, little real progress

In 2016, according to *Prescrire's* analyses, only 15 new products or new indications represented a therapeutic advance.

A few noteworthy advances, particularly in oncology. In 2016, six new products or indications constituted a noteworthy therapeutic advance. One was rated "a real advance" and five were rated "offers an advantage" (see the table on p. 138). Four of these advances were for cancer patients: the immunostimulant *nivolumab* for patients with metastatic or inoperable BRAF V600 mutation-negative melanoma (*Prescrire Int* n° 177) or with non-small cell lung cancer after failure of platinum-based chemotherapy (*Rev Prescrire* n° 397); the MEK inhibitor *trametinib*, in combination with the BRAF inhibitor *dabrafenib*, for patients with metastatic or inoperable BRAF V600 mutation-positive melanoma (*Prescrire Int* n° 177); and high-dose (40 mg) *dexamethasone*, a corticosteroid, for patients with multiple myeloma (*Rev Prescrire* n° 395).

The other two advances were for children: the antiviral *entecavir* for children with chronic hepatitis B (*Prescrire Int* n° 179), and low-dose (100 mg) *succimer*, a heavy metal chelator, for lead or mercury poisoning (*Rev Prescrire* n° 392).

Nine new products or indications represented a modest advance and were rated "possibly helpful". Examples include *temocillin*, a useful antimicrobial in some Gram-negative bacterial infections due to its narrow spectrum (*Rev Prescrire* n° 393), and two drugs now available in a form that can be useful for patients who have difficulty swallowing tablets: *riluzole* oral suspension for amyotrophic lateral sclerosis and weekly *alendronic acid* effervescent tablets for osteoporosis (*Rev Prescrire* n° 396).

Many new products and indications offer no advantages or are dangerous. Over half of the new products and indications we examined in 2016 offered no advantages in terms of efficacy, adverse effects or ease of use compared with existing treatments. Of these, 56 were rated as “nothing new”. Five others, including three cancer drugs, received our “judgement reserved” rating, because their harm-benefit balance could not be determined based on the available data supporting their authorisation or the opinion of the European Medicines Agency (EMA).

Sixteen new products or indications received our lowest rating, “not acceptable”, usually because their adverse effects are disproportionate in relation to their minimal, unproven or lack of efficacy (see table below). Even in desperate situations when no further treatment options exist, some new drugs should only be used in clinical trials. Other drugs should simply never be used: for example, *adalimumab* in hidradenitis “suppurativa” or *febuxostat* in tumour lysis syndrome (also see Drugs to avoid in 2017 in *Prescrire Int* n° 181).

Me-too drugs and “advanced targeted” therapies: smoke and mirrors

The new products and new indications analysed in 2016 are very similar in nature to those analysed in previous years.

Me-too drugs: aiming for a slice of an existing market, not progress. Many new authorisations are actually for “me-too” drugs. As the name implies, these copycat products are very similar to existing drugs from which they are meant to capture market share.

The already overcrowded market for bronchodilators used to treat chronic obstructive pulmonary disease is a typical example, with the release in 2016 of yet another long-acting beta-2 agonist, *olodaterol*, and yet another long-acting antimuscarinic, *umeclidinium* (alone or in combination with *vilanterol*) (*Prescrire Int* n° 170, *Rev Prescrire* n° 393).

The antibiotics market was also targeted in 2016, with the introduction of the glycopeptide antibiotic *dalbavancin*, a me-too of *teicoplanin*, and the oxazolidinone antibacterial *tedizolid*, a me-too of *linezolid* (*Prescrire Int* n° 171, *Rev Prescrire* n° 397).

Another example is the antineoplastic agent *sonidegib*, a me-too of *vismodegib* (*Prescrire Int* n° 178).

These me-too drugs do not represent therapeutic advances: they mainly exist because segments of the healthcare market are very attractive for pharmaceutical companies.

Cancer drugs: “targeted” therapies, but with many targets. Twenty-three of the new products or indications we reviewed in 2016 were for treatment of cancer, a field in which patients expect major benefits from their treatment. But the evaluation data show that many of these drugs do not significantly prolong survival or increase the proportion of patients cured compared with other available treatments.

Some of these new cancer drugs were granted marketing authorisation on the basis of such limited data that it is impossible to determine their harm-benefit balance. This is the case for *ibrutinib* in mantle cell lymphoma and chronic lymphocytic leukaemia (*Prescrire Int* n° 170), *denosumab* in giant cell tumour of bone (*Rev Prescrire* n° 388), and *lenvatinib* in differentiated thyroid carcinoma (in a coming issue).

Many cancer drugs belong to the group of so-called “targeted” therapies, i.e. drugs that interfere with specific molecules responsible for the proliferation of cancer cells, the formation of new blood vessels, etc. In reality, these drugs have complex and multiple effects, and are not specific for cancer cells, thus leading to numerous adverse effects (*Rev Prescrire* n° 382).

For example, *nintedanib*, an inhibitor of multiple tyrosine kinases, is authorised in pulmonary fibrosis for its inhibitory effect on the tyrosine kinase activity associated with FGF (fibroblast growth factor) receptors, and in non-small cell lung cancer for its anti-angiogenic activity due to its inhibitory effect on the tyrosine kinase activity associated with vascular endothelial growth factor (VEGF) receptors. In reality however, regardless of the clinical situation, *nintedanib* has many serious adverse effects mainly related to its anti-angiogenic effect, including venous thromboembolism, bleeding, hypertension, gastrointestinal perforation and impaired wound healing (*Prescrire Int* n° 173).

Other antineoplastic agents are portrayed as highly specific inhibitors of particular enzymes, yet they provoke adverse effects that affect many organs, for example: the JAK1 and JAK2 inhibitor *ruxolitinib*, the ALK inhibitor *ceritinib*, the MEK inhibitors *cobimetinib* and *trametinib*, and the Bruton’s tyrosine kinase inhibitor *ibrutinib* (*Prescrire Int* n° 174, 175, 177).

Monoclonal antibodies: in a wide variety of situations. Monoclonal antibodies are also presented as targeted therapies. At first, they were mainly used in oncology, but drug companies have subsequently developed monoclonal antibodies for a wide variety of situations. In 2016, 17 of the new authorisations we examined were for monoclonal antibodies, for example: *evolocumab* and *alirocumab* in hypercholesterolaemia (*Prescrire Int* n° 174); *idarucizumab* as a *dabigatran* antidote (*Prescrire Int* n° 176); *mepolizumab* for the treatment of asthma (*Prescrire Int* n° 179); and *secukinumab* in psoriasis, psoriatic arthritis and ankylosing spondylitis (*Prescrire Int* n° 180).

These antibodies are often portrayed as major innovations. But here again, a pragmatic review of the evidence shows that these very expensive drugs generally offer no proven therapeutic advantages for patients compared with existing treatments.

Insufficient evaluation before authorisation

Analysis of the data on which marketing authorisations are granted shows that often these data are insufficient to properly determine the harm-benefit

balance of the new product or new indication compared with existing treatments. Yet the EMA continues to seek to relax pre-authorisation requirements.

Adaptive pathways: a dangerous development for patients. In 2014, the EMA launched a pilot project for a marketing authorisation procedure called adaptive pathways. The aim of this new approach to drug evaluation is to accelerate the market introduction of new drugs on the basis of limited evaluation data, in order to foster patients' early access to certain drugs. This plan has been widely criticised because of the high risk of unnecessarily exposing patients to the serious adverse effects of a drug with no proven efficacy. No advantages for patients emerged from the EMA's report on the adaptive pathways pilot project, published in 2016 (*Prescrire Int* n° 174; *Rev Prescrire* n° 398).

As well as being dangerous, adaptive pathways are unnecessary because regulatory mechanisms already exist in the European Union for providing early access to drugs intended for situations that are life-threatening in the short term and in which no further treatment options remain. These mechanisms are: marketing authorisation "under exceptional circumstances", "conditional" marketing authorisation, and "compassionate use" procedures.

Inadequate clinical evaluation. Even without adaptive pathways, the EMA already has a long track record of approving marketing authorisation applications without demanding adequate supporting data, on condition that the company conducts

post-authorisation trials. Yet companies are often slow to complete these trials or never complete them.

One new drug analysed in 2016, *olaparib* for ovarian cancer, was authorised on the basis of a phase II clinical trial, i.e. after a purely exploratory trial of its efficacy in a limited number of patients. Using a radiological endpoint, *olaparib* delayed disease progression by a few months on average, but there is no evidence that this surrogate endpoint correlates with improvement of symptoms or prolonged survival (*Prescrire Int* n° 178; *Rev Prescrire* n° 396).

Ceritinib in non-small cell lung cancer (*Prescrire Int* n° 174) and *ibrutinib* in Waldenström's macroglobulinaemia (*Prescrire Int* n° 175) were granted marketing authorisation on the basis of non-comparative trials that did not adequately evaluate their efficacy. Yet the EMA was aware that comparative trials were underway when it was examining their marketing authorisation applications.

Drugs for psoriasis and in rheumatology were commonly authorised without trials comparing them with standard care. This happened with *golimumab* (*Rev Prescrire* n° 393) and *ustekinumab* (*Rev Prescrire* n° 396), for example.

One exception was *secukinumab*, which was evaluated in psoriasis versus *etanercept*, versus *ustekinumab* and versus placebo (*Prescrire Int* n° 180). This relevant comparison was useful in determining the specific situations in which its harm-benefit balance appears favourable.

Prescrire's ratings of new products and indications over the last 10 years (a)

Prescrire's ratings	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Bravo	1	0	0	0	0	0	0	1	0	0
A real advance	2	0	0	1	0	1	0	2	3	1 (b)
Offers an advantage	14	6	3	3	3	3	6	5	5	5 (c)
Possibly helpful	27	25	14	22	13	14	12	15	15	9
Nothing new	79	57	62	49	53	42	48	35	43	56
Not acceptable	15	23	19	19	16	15	15	19	15	16 (d)
Judgement reserved	3	9	6	3	7	7	9	10	6	5 (e)
Total	141	120	104	97	92	82	90	87	87	92

a- Readers interested in the results for 1981 to 2006 can find them in *Rev Prescrire* n° 213 p. 59 and 280 p. 142. This table includes new products (other than generics) and new indications, as well as products re-examined after longer follow-up.

b- The only drug rated "a real advance" in 2016 was *nivolumab* in metastatic or inoperable BRAF V600 mutation-negative melanoma (*Prescrire Int* n° 177).

c- The drugs rated "offers an advantage" in 2016 were:

- *dexamethasone* 40 mg in multiple myeloma (*Rev Prescrire* n° 395);
- *entecavir* in chronic hepatitis B in children (*Prescrire Int* n° 179);
- *nivolumab* in certain types of metastatic or inoperable lung cancer (*Rev Prescrire* n° 397);
- *succimer* 100 mg in lead or mercury poisoning (*Rev Prescrire* n° 392);
- *trametinib* in metastatic or inoperable BRAF V600 mutation-positive melanoma (*Prescrire Int* n° 177).

d- The drugs rated "not acceptable" in 2016 were:

- *adalimumab* in hidradenitis suppurativa (*Prescrire Int* n° 181);
- *capsaicin* in painful diabetic neuropathy (*Prescrire Int* n° 180);
- *ceritinib* in certain types of non-small cell lung cancer (*Prescrire Int* n° 174);
- *ciclosporin* eye drops in dry eye disease (*Prescrire Int* n° 181);
- the *estradiol* + *dydrogesterone* 0.5 mg/2.5 mg combination in postmenopausal hormone replacement therapy (*Rev Prescrire* n° 388);
- *febuxostat* in hyperuricaemia associated with tumour lysis syndrome (*Prescrire Int* n° 173);

- *idebenone* in Leber's hereditary optic neuropathy (*Prescrire Int* n° 179);
- the *insulin degludec* + *liraglutide* combination in type 2 diabetes (see page 121);
- *mepolizumab* in severe refractory asthma (*Prescrire Int* n° 179);
- *nintedanib* in certain types of inoperable non-small cell lung cancer (*Rev Prescrire* n° 389);
- *nintedanib* in idiopathic pulmonary fibrosis (*Prescrire Int* n° 173);
- *olaparib* in certain types of ovarian cancer (*Prescrire Int* n° 178);
- *panobinostat* in multiple myeloma (*Prescrire Int* n° 176);
- *prucalopride* in chronic constipation in men (*Prescrire Int* n° 175);
- the *simvastatin* + *fenofibrate* combination in hypercholesterolaemia and hypertriglyceridaemia (*Prescrire Int* n° 173);
- *tigecycline* in serious infections in children (*Prescrire Int* n° 173).

e- The drugs rated "judgement reserved" in 2016 were:

- *denosumab* in giant cell tumour of bone (*Rev Prescrire* n° 388);
- *empagliflozin*, alone or combined with *metformin* in type 2 diabetes (*Prescrire Int* n° 172);
- *ibrutinib* in chronic lymphocytic leukaemia and mantle cell lymphoma (*Prescrire Int* n° 170);
- *lenvatinib* in differentiated thyroid carcinoma (*Rev Prescrire* n° 398);
- the RTS,S/AS01E malaria vaccine for immunisation of children against malaria and hepatitis B (*Prescrire Int* n° 178).

Drugs and pregnancy: be cautious and inform women

When drugs are first introduced to the market, so little is known about their adverse effects that they are best used with caution until more information has been acquired. This is especially important when treating pregnant women, because both the mother and her unborn child could be harmed. A number of public health disasters serve as reminders of the reality of this danger, such as the harms caused by *diethylstilbestrol* (DES) over several generations, or the malformations and autism caused by *valproic acid* (*Prescrire Int* n° 177).

It is vital that women of reproductive age are informed of the uncertainties, harms, and precautionary measures required with drugs, so that they can protect themselves and their children effectively from teratogenic drugs such as the retinoids *isotretinoin* and *acitretin* and the immunosuppressant *mycophenolic acid* (*Rev Prescrire* n° 388, 393).

Health authorities are also responsible for ensuring that patient leaflets are as informative as possible as regards the dangers drugs pose to the unborn child, and measures to take in order to avoid these risks. This information is lacking, for example, from most patient leaflets for nonsteroidal anti-inflammatory drugs (NSAIDs) and topical retinoids, yet the definite or suspected harms of these drugs have been known for a long time (*Rev Prescrire* n° 397, 398).

High prices: unaffordable cancer drugs

On the pretext that “innovation” is necessarily expensive, pharmaceutical companies market some drugs at exorbitant prices that are not based on the cost of research and development, nor on the therapeutic advance they represent for patients (see pp. 130-135). In the United States, the launch price of 58 cancer drugs increased by about 12% per year between 1995 and 2013, yet the newer drugs did not notably prolong survival compared with older drugs (*Prescrire Int* n° 172).

In France, the new cancer drugs reviewed in *Prescrire* in 2016 cost about 6000 euros per patient per month, regardless of their harm-benefit balance or the therapeutic advance they represent for patients. Notable examples include: *ibrutinib*, rated “judgement reserved” in mantle cell lymphoma and chronic lymphocytic leukaemia, and “nothing new” in Waldenström’s macroglobulinaemia, which costs 6000 euros to 8100 euros per month; *ceritinib*, rated “not acceptable” in non-small cell lung cancer, which costs 6690 euros per month; *nivolumab*, rated “a real advance” in metastatic or inoperable BRAFV600 mutation-negative melanoma, and “offers an advantage” in metastatic or inoperable lung cancer, which costs about 6000 euros per month in France as part of the temporary compassionate use (ATU) programme; *cobimetinib*, rated “nothing new” in metastatic melanoma, which costs 6300 euros per month; *ramucirumab*, rated “nothing

new” in metastatic colorectal cancer, which costs about 6000 euros per month; *pembrolizumab*, rated “nothing new” in metastatic or inoperable melanoma, which costs 6400 euros per month; *crizotinib*, rated “nothing new” as first-line therapy for certain types of lung cancer, which costs 5500 euros per month; and *lenvatinib*, rated “judgement reserved” in differentiated thyroid carcinoma, which costs about 6000 euros per month (*Prescrire Int* n° 170, 174, 175, 177; *Rev Prescrire* n° 397, 398).

Need for a new system that meets patients' needs

The flaws of the pharmaceutical market are perpetuated year after year: high drug prices that bear no relation to the actual cost of their development and production, financial speculation and the pursuit of short-term profit, and undemanding regulatory agencies. Taken together, they form a system that does not promote pharmaceutical research geared towards real therapeutic advances (see pp. 130-135).

Drug evaluation is increasingly postponed until after authorisation, creating a situation in which patients are used as guinea pigs and national health insurance systems are used to finance drug evaluation. It also creates a conflict of interest for pharmaceutical companies, because the results of these post-authorisation trials are liable to tarnish the image of their drugs.

The new products and indications authorised in 2016 provided a tangible benefit for very few patients. Pharmaceutical companies seem more concerned with profits than with human health and do not hesitate to halt production of well-established but insufficiently profitable drugs, even those that are useful in some situations, such as *spectinomycin* (*Rev Prescrire* n° 397) and *probenecid* (*Rev Prescrire* n° 398).

Improvements in healthcare and patient safety do not seem to be the main priorities of drug regulatory agencies either.

From the development of me-too drugs, to the granting of marketing authorisations for products without requiring proof that they represent a therapeutic advance, the current system that drives pharmaceutical research and development encourages an entire sector to invest more in imitation and capturing market share from existing drugs, rather than the pursuit of real therapeutic progress.

It is high time we adopted a new system to guide the economics of pharmaceutical development, one that encourages drug companies and governments to orient research and development towards delivering affordable treatments that meet society's most pressing health needs.

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