Drugs in 2017: a brief review

In 2017, as in previous years, few clinical advances were identified among the 92 new drugs analysed in our French edition. Increasingly early marketing authorisations and minimal evaluation result in patients being exposed to drugs with uncertain harm-benefit balances. Not to mention the exorbitant price of some drugs and the waste of collective resources.

***Rev Prescrire* 2018; 38 (412): 145-146**

Every month, *Prescrire* publishes an independent and methodical review of the latest developments in the pharmaceutical market: new substances, new indications, new pharmaceutical formulations. We also closely monitor adverse effects of medicines, marketing stoppages, market withdrawals or stock-outs, the environment surrounding medicines, particularly at European Union level, but not only. The information thus provided by *Prescrire* is intended to help subscribers make the best use of medicines and to identify new products that make real progress in healthcare.

Contrary to popular belief, companies do not have to prove that their medicines represent a breakthrough: among the 92 new medicines, there are many products providing no progress (45 rated as "Nothing new" in the table on p. 111). And some medicines even represent a step backwards, with 15 new products that are more dangerous than useful (rated "Not acceptable").

There have been a few more notable advances than in the previous year, with a total of 10 drugs rated "A real advance" or "Offers an advantage", including 3 drugs in oncology and 3 in infectious diseases (HIV and hepatitis C). And only 2 drugs useful in children: oral formulations of *nitisinone* and *raltegravir*.

The 2017 review is similar to that of previous years. We could comment again on the excesses and dangers of advertising for medicines, the lack of information on adverse effects, the race for new indications, on companies looking for easy innovations such as me-too medicines without progress for patients.

Instead we present some crucial points identified in 2017.

Assessment for marketing applications: often sloppy. The evaluation of medicines in marketing applications is too often botched: health authorities use faster access to "therapeutic innovation" as an excuse to grant marketing authorisation on the basis of very insufficient evaluation data, while requesting that companies continue the evaluation after marketing authorisation. Thus drug evaluation becomes in part funded by health insurers, advertising for medicines is boundless, and patients are often exposed without knowing it to drugs with little or no data on efficacy, let alone on adverse effects. And, years later, it is often reported that post-authorisation studies have been used primarily to establish prescribing habits, not to answer outstanding questions (*Prescrire Int* n° 189 pp. 3 and 25).

Cancer drugs: gross illustration of regulatory failures. 28 out of 92 new medicines analysed in 2017 were used in cancer. Some of these marketing authorisations have been granted without comparative trials, for example: *daratumab* in monotherapy for multiple myeloma after failure of several treatment lines (*Prescrire Int* n° 188); *nivolumab* in Hodgkin lymphoma after failure of an autologous stem cell transplant, as well as *brentuximab vedotin* (*Prescrire Int* n° 191); *crizotinib* (*Prescrire Int* n° 404) and *osimertinib* (*Prescrire Int* n° 183) in certain lung cancers.

Of these 28 marketing authorisations for cancer drugs, 20 were granted on the basis of a single clinical trial, often of poor methodological quality, because not comparative, or with biases linked to the absence of blinding; or on the basis of laboratory or radiological outcomes that are not necessarily correlated with a longer survival or a better quality of life.

Some advances are noteworthy, however, such as *pertuzumab* (*Prescrire Int* n° 184) in metastatic breast cancer, *nivolumab* (*Prescrire Int* n° 185) in metastatic renal cell carcinoma, and *eribulin* (*Prescrire Int* n° 187) in inoperable or metastatic liposarcoma. Most other cancer drugs are poorly assessed, and many have an unfavourable harm-benefit balance, which should have prevented them from being approved.

In summary, in oncology, there are many commercialisations in a market made very attractive by its ease of access for companies, at exorbitant prices that are disconnected from therapeutic progress or research and development costs (see p. 107-109).

Marketing withdrawals too slow. In addition to the very lax requirements for granting marketing authorisation, there is also a great deal of immobility on the part of the agencies when it comes to withdrawing or suspending the marketing authorisation of medicines whose adverse effects are disproportionate to the expected benefits.

At the beginning of 2017, in France, a drinkable solution containing vitamin D (Uvestérol° D - *Rev Prescrire* n° 400 and n° 401) was withdrawn from the market by the French Health Products Agency

Prescrire's ratings of new products and indications over the past 10 years (a)										
Prescrire's ratings	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Bravo	0	0	0	0	0	0	1	0	0	0
A real advance	0	0	1	0	1	0	2	3	1	1 (**b**)
Offers an advantage	6	3	3	3	3	6	5	5	5	9 (**c**)
Possibly helpful	25	14	22	13	14	12	15	15	9	18
Nothing new	57	62	49	53	42	48	35	43	56	45
Not acceptable	23	19	19	16	15	15	19	15	16	15 (**d**)
Judgement reserved	9	6	3	7	7	9	10	6	5	4 (**e**)
Total	**120**	**104**	**97**	**92**	**82**	**90**	**87**	**87**	**92**	**92**

a- This table includes new products (except generics) and new indications as well as our updated reviews (A second look).

b- *Asfotase alfa* in hypophosphatasia (Prescrire Int n° 187).

c- The drugs were:
– *emtricitabine* + *tenofovir disoproxil* in the prevention of HIV transmission (Prescrire Int n° 187);
– *eribulin* in inoperable refractory or relapsed liposarcoma (Prescrire Int n° 187);
– *methotrexate* SC in prefilled pens (Rev Prescrire n° 404);
– *methotrexate* injection in ectopic pregnancies (Prescrire Int n° 190);
– oral *nitisinone* in type 1 tyrosinemia (Rev Prescrire n° 410);
– *nivolumab* in metastatic renal cancers, in 2nd line after failure of a tyrosine kinase inhibitor (Prescrire Int n° 185);
– *pertuzumab* in metastatic breast cancer (Prescrire Int n° 184);
– *raltegravir* granules for oral suspension in infants infected with HIV (Prescrire Int n° 185);
– *sofosbuvir* + *velpatasvir* in hepatitis C (Prescrire Int n° 192).

d- The drugs were:
– *adalimumab* in hidradenitis suppurative in adolescents (Prescrire Int n° 181);
– *ataluren* in Duchenne muscular dystrophy (Prescrire Int n° 189);
– *bevacizumab* 1st line in lung cancers (Prescrire Int n° 188);
– *brentuximab vedotin* in Hodgkin lymphoma (Prescrire Int n° 191);
– *equine estrogens* + *bazedoxifene* in menopausal symptoms (Prescrire Int n° 184);
– *everolimus* in non functioning neuroendocrine tumours (Rev Prescrire n° 405);
– *fentanyl* iontophoretic in pain (Rev Prescrire n° 409);
– *guanfacine* for attention deficit with hyperactivity (Prescrire Int n° 186);
– *nivolumab* in Hodgkin lymphoma after failure of an autologous stem cell transplant and *brentuximab vedotin* (Prescrire Int n° 191);
– *palbociclib* in inoperable or metastatic breast cancers (Rev Prescrire n° 410);
– *pertuzumab* before breast cancer surgery (Prescrire Int n° 184);
– *reslizumab* in asthma (Rev Prescrire n° 410);
– *selexipag* in pulmonary arterial hypertension (Prescrire Int n° 186);
– *tolvaptan* in autosomal dominant polycystic kidney disease (Prescrire Int n° 187);
– *vandetanib* in medullary thyroid cancer in children (Rev Prescrire n° 408).

e- The drugs were:
– *ivacaftor* in cystic fibrosis (Prescrire Int n° 188);
– *ivacaftor* + *lumacaftor* in cystic fibrosis (Prescrire Int n° 188);
– *pembrolizumab* monotherapy in metastatic or inoperable lung cancers (Rev Prescrire n° 407);
– *teduglutide* in short bowel syndrome in children (Rev Prescrire n° 404).

(ANSM) after the death of an infant, while there had been reports of serious accidents for about twenty years. And in July 2017, the French Agency withdrew the marketing authorisation, granted back in the 1970s, for Proctolog° (*trimebutine* + *ruscogenin*) rectal cream and suppositories, due to an unfavourable harm-benefit balance in haemorrhoidal conditions and anal fissures (*Rev Prescrire* n° 407).

But too many other medicines remain on the market, some of which have been on the market for several decades, while their harm-benefit balance is clearly unfavourable (see pp. 107-109).

In short. Not enough regulation on the part of health authorities, increasingly accelerated marketing authorisations, minimal drug evaluation: healthcare professionals have a central role to play in choosing drugs that have a demonstrated benefit and in limiting patients' exposure to drugs that are poorly assessed, provide no tangible therapeutic value or are more dangerous than useful.

It is a question of resisting the massive overmedication of society, with its major consequences for victims of adverse effects or drug addiction. Overmedication which is also a waste of collective resources, amplified by the exorbitant cost of certain medicines (*Prescrire Int* n° 406).

Individually, one may feel helpless in the face of such a large and complex phenomenon, especially in the absence of collective and concerted responses. There are, however, important ways of resisting and acting with full awareness, starting with freeing oneself from the influence of interests that are not those of patients, and also by talking with patients about the limitations of the drug treatments they are offered or may have heard about.