New drugs and indications in 2010: inadequate assessment; patients at risk

In 2010, we rated 97 new drugs or new indications in our French edition *la revue Prescrire*, only 4 of which provided a therapeutic advantage. However, 19 others (1 in 5) were approved despite having more harms than benefits.

More paediatric products were released in 2010 than in previous years, but few of them made any real difference and many had not been properly evaluated.

Drug regulatory agencies can protect patients from exposure to dangerous drugs by refusing to grant market approval or by demanding their market withdrawal. Yet they are failing to fulfil this responsibility: so-called risk management plans and modifications to the wording in the SPC are only half-measures.

Too often the authorities put companies’ short-term financial interests above patients’ well-being by granting premature marketing authorisation, by agreeing to high levels of reimbursement that fail to take added therapeutic value into account, and by allowing the development of “umbrella” ranges.

The European authorities’ questionable plans for pharmacovigilance and advertising of prescription-only drugs were restricted after public mobilisation, but they are still likely to undermine healthcare quality.

Decision-makers must make patients’ well-being their top priority.

New drugs and indications in 2010

Half of these new products and indications – 49 to be precise – provided no advantages over existing options. Some conditions, such as cancer, diabetes and hypertension, are particularly lucrative for drug companies, but patients rarely benefit.

Lack of therapeutic advance. In 2010 we found that only 4 drugs provided a therapeutic advantage (see notes c and d of the rating table below). The only drug we rated “A real advance” was imatinib (Prescrire Int n°114), a product that had already been on the market for several years and that we re-evaluated in 2010 (see note c of the rating table below). The new data showed an overall survival time of more than 4 years with imatinib in patients with inoperable or metastatic gastrointestinal stromal tumours, compared to only 1.5 years previously.

Too few data were available to determine the role of 3 other drugs in the therapeutic arsenal (see note f of the table below). One of these 3 drugs was a cell therapy product (autologous chondrocytes, in a coming issue).

Recycling. Incapable of bringing new drugs to the market that represent a real therapeutic advance, companies are recycling old drugs in the form of fixed-dose combinations or new routes of administration. The following are a few examples in the field of cardiology, in which fixed-dose combinations continue to flood the market: amlopidine + valsartan + hydrochlorothiazide (Prescrire Int n°114), alsikiren + hydrochlorothiazide (Rev Prescrire n°315), and nebivolol + hydrochlorothiazide (Rev Prescrire n°316).

One in five new products can be avoided. In Prescrire’s at-a-glance rating system, “Not acceptable” indicates that the drug has a negative risk-benefit balance in one or more of its approved indications. The proportion of drugs that we consider “Not acceptable” has been high for the past several years and was about 20% in 2010 (19 out of 97 ratings). Half of the products concerned are cytotoxic agents authorised for use in cancer or haematological disorders (see note e of the rating table below).

Two generic drugs examined in 2010 have negative risk-benefit balances: nefopam in acute, especially postoperative, pain (Rev Prescrire n°324), and oxomemazine, in cough (Rev Prescrire n°323).

Paediatrics: inadequate assessment and little progress. Since 2007 and the implementation of the European Paediatric Regulation requiring companies to evaluate their drugs in children (unless exempted), the number of drugs authorised for paediatric use has been increasing.

In 2010, certain drugs represented a slight therapeutic advance (rated as “Possibly helpful”), but their assessment was usually minimal and sometimes wholly inadequate. They included:
- darunavir (Rev Prescrire n°321) and tipranavir (Rev Prescrire n°321) for HIV-infected children;
- losartan for hypertensive children (Prescrire Int n°108);
- omeprazole in heartburn and gastroesophageal reflux, and Helicobacter pylori infection (Rev Prescrire n°319);
- the combination of peginterferon alfa-2b and ribavirin in hepatitis C (Rev Prescrire n°325);
- botulinum toxin type A for limb spasticity (Rev Prescrire n°325).

Monoclonal antibodies: too many products, rarely helpful. The number of therapeutic monoclonal antibodies (whose international non-proprietary names (INNs) end in -mab) and their indications continue to grow, especially in oncology and rheumatology. These drugs are publicised as “targeted treatments” heralding an era of “personalised medicine”. In practice, they rarely represent a major therapeutic advance, and several expose patients to unjustified risks (see notes d and e of the rating table below).

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

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<th>Prescrire’s rating</th>
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<td>1 (e)</td>
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<td>9</td>
<td>6 (b)</td>
<td>7 (b)</td>
<td>7</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>23</td>
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<td>19 (e)</td>
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<td>6</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>3</td>
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<td>3 (f)</td>
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<td>79</td>
<td>4</td>
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<td>135</td>
<td>141</td>
<td>120</td>
<td>104</td>
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</tbody>
</table>

**a** - For reasons of space, this table only shows the results for the last 10 years. The previous years’ results (1981 to 2000) can be found in Prescrire Int n°58. This table shows new products (other than generics copies) and new indications proposed by drug companies to physicians and pharmacists, for use in hospitals and/or the community; and, from 2005 onwards, line extensions (new dose strengths, new forms/presentations of existing drugs) and products for self-medication, rated in our French edition la revue Prescrire. A given product is counted several times if it was rated differently in its different indications.

**b** - Including two jointly marketed products.

**c** - Imatinib reassessed in inoperable or metastatic gastrointestinal stromal tumours (Prescrire Int n°114).

**d** - The drugs were:
- zalutumumab in malignant ascites (Prescrire Int n°109);
- cetuximab in colon cancer (Rev Prescrire n°324);
- panitumumab for neoplastic pain (Rev Prescrire n°318);
- botulinum toxin type A for limb spasticity (Rev Prescrire n°323).

**e** - The drugs were:
- fixed-dose combination of amlopidine + valsartan + hydrochlorothiazide in hypertension (Prescrire Int n°114);
- bevacizumab in metastatic breast cancer (Rev Prescrire n°317);
- capsaicin patches for neuropathic pain (Rev Prescrire n°318);
- catumaxomab in malignant ascites (Prescrire Int n°109);
- diflunisal in rheumatologic disorders (Rev Prescrire n°324);
- diltiazem in prevention of recurrent depression (Prescrire Int n°111);
- histamine in acute myeloblastic leukaemia (Rev Prescrire n°321);
- i伐bradine in stable angina (Prescrire Int n°111);
- long acting injectable olanzapine in schizophrenia (Rev Prescrire Int n°326);
- mifepristone in severe persistent asthma in children (Rev Prescrire n°324);
- mifamurtide in osteosarcoma (Rev Prescrire Int n°326);
- maraviroc in first-line treatment of HIV-infected patients (Prescrire Int n°110);
- mifepristone in rheumatologic disorders (Prescrire Int n°326);
- pazopanib in kidney cancer (Prescrire Int n°114);
- sildenafil (Prescrire Int n°109) and tadalafil (Rev Prescrire n°323).

- darunavir (Rev Prescrire n°321) and tipranavir (Rev Prescrire n°321) for HIV-infected children;
- losartan for hypertensive children (Prescrire Int n°108);
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- botulinum toxin type A for limb spasticity (Rev Prescrire n°325).

**f** - The drugs were:
- autologous chondrocytes in autologous chondrocyte grafting for knee cartilage damage (Rev Prescrire Int n°326);
- imatinib as an adjuvant to surgical excision of gastrointestinal stromal tumours (Prescrire Int n°113);
- sapropterin in tetrahydrobiopterin deficiency (Rev Prescrire n°316).

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Avoiding iatrogenic complications

Marketing authorisation is being granted prematurely for an increasing number of new drugs, before their efficacy and particularly, their adverse effects have been properly evaluated (Rev Prescrire n°326).

One would expect drug regulatory agencies to be more cautious and responsive following scandals such as the diethylstilbestrol (DES) disaster and, more recently, the benfluorex (ex-Mediator®) affair (Prescrire Int n°105, 107, 113 and Prescrire website).

Market withdrawal: an effective measure, especially when timely. Drug regulatory agencies often appear reluctant to withdraw drugs with negative risk-benefit balances, allowing sales to continue unabated and needlessly exposing patients to a risk of adverse effects.

The return of topical ketoprofen to the market after initial withdrawal at the demand of the French drug agency (Afsaps) illustrates how drug companies’ financial interests are often put ahead of patient safety (Prescrire Int n°109, 112, 113).

In 2010, only a small proportion of drugs with a negative risk-benefit balance were taken off the market, several years after their dangers were first identified. They included bufexamac, a topical non-steroidal anti-inflammatory drug, because of potentially serious cutaneous disorders (eczema) (Rev Prescrire n°321, 325); carboestane and acetylcytstine (mucolytic agents) in infants, because of respiratory adverse effects (Rev Prescrire n°320, 324); rosiglitazone (an antidiabetic), because of cardiovascular adverse effects (Rev Prescrire n°325, 326); and sibutramine (an appetite suppressant), also because of cardiovascular adverse effects (Prescrire Int n°107).

Refusal to grant marketing authorisation: another effective means of protecting patients. Patients were protected from exposure to unnecessary risks of certain drugs last year, after the EU Committee for Medicinal Products for Human Use (CHMP) refused to grant market approval or issued an unfavourable opinion, leading the authorities (or the drug companies) to take them off the market.

NSAIDs, anti-diabetics, psychotropics, etc. Several non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, especially cox-2 inhibitors:
– topical ketoprofen gel because of cutaneous disorders (Rev Prescrire Int n°109, 112). The French regulator (Afsaps) decided to withdraw these gels in late 2009, but in mid-2010, CHMP recommended that they be allowed to remain on the market;
– nimesulide because of potentially life-threatening liver damage (Rev Prescrire n°323);
– celecoxib (Celebrex® in rheumatology, and Onsenal® in familial adenomatous polyposis) and etoricoxib because of an excess of cardiovascular and cutaneous disorders (see www.english.prescrire.org and Prescrire Int n°108);
– parecoxib because of life-threatening skin reactions (Prescrire Int n°109).

And also:
– meprobamate because of the high risk of adverse effects with this psychotropic drug, too often misused as a “recreation-al” drug (see www.english.prescrire.org);
– nicorandil because of its unresolved efficacy in angina pectoris and the risk of serious ulceration (gastrointestinal, vaginal, etc.) (Prescrire Int n°110);
– quinine for cramps, because of the risk of potentially life-threatening haematological effects (Rev Prescrire n°326);
– pioglitazone, an antidiabetic drug with adverse effects that outweigh its efficacy (Rev Prescrire n°325 and www.english.prescrire.org);
– ropinivore in restless legs syndrome: this dopamine agonist has known adverse effects but no proven efficacy in this setting. In 2010, the French authorities recommended that it no longer be reimbursed (Rev Prescrire n°325);
– telithromycin, a macrolide carrying a risk of cardiac, hepatic and visual disorders (Prescrire Int n°106 and www.english.prescrire.org);
– trimetazidine, because of a negative risk-benefit balance in angina pectoris, dizziness, tinnitus and visual disorders, and especially a risk of extrapyramidal syndrome and thrombo-cytopenia (Prescrire Int n°106 and www.english.prescrire.org).

On 21 December 2010, the fixed-dose combination containing dextropropoxyphene and paracetamol was still on the market, but it is slated for European market withdrawal in 2011 (on 1 March 2011 in France) (Rev Prescrire n°323 and www.english.prescrire.org).

Cost of inadequate regulation. In view of these few examples, how can decision-makers and health authorities be trusted, when they allow patients to be exposed to harmful drugs, letting society pick up the tab for hospitalisation, sick leave, and agree to provide reimbursement for vastly over-priced drugs.

For example, the direct cost of prescriptions for glitazones in France was about 50 million euros in 2007, for the national health insurance system alone (Rev Prescrire n°317).

There is a cost for inadequate regulation. Decision-makers can start to get a grip on health spending by refusing to provide reimbursement for drugs with a negative risk-benefit balance.

Drugs to avoid

The following is a list of certain drugs analysed in Prescrire in 2010 that have more potential harms than benefits and that should be avoided pending the decision by the authorities (or the drug companies) to take them off the market.

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Medicines agencies too often under the influence of drug companies

Delaying the decision on market withdrawal (Rev Prescrire n°323 and www.english.prescrire.org).

Parecoxib was withdrawn from the Swiss market and rejected by the US Food and Drug Administration (FDA), yet it is still authorised in the European Union (Rev Prescrire Int n°109).

Maraviroc has been authorised for first-line treatment of HIV infection in the United States, but not in the European Union, where the authorities justifiably consider that the assessment is inadequate (Rev Prescrire Int n°110).

Agencies still grant marketing authorisation despite inadequate data. Accelerated marketing authorisation based on partial data may be justified when patients have no other treatment options and might reap a major benefit. But drug regulatory agencies increasingly approve new drugs on the basis of scant data, without demanding a comparison with an existing reference treatment. It sometimes seems that marketing authorisation is granted as a consolation prize for companies that have submitted multiple applications in various indications.

Tolvaptan was authorised for the syndrome of inappropriate antidiuretic hormone secretion, with no proof of efficacy, although the company had initially applied for an indication in heart failure (Rev Prescrire Int n°109).

Gefitinib was authorised for some lung cancers on the basis of a minimal analysis showing no increase in survival (Rev Prescrire Int n°107).

After unfavourable opinions issued by the FDA and EMA based on data presented in 2005, the EMA finally authorised dronedarone in atrial fibrillation, despite the lack of convincing data (Rev Prescrire Int n°108).

Trials of raltegravir in first-line treatment of HIV-infected patients were not designed to show a benefit versus effective anti-retroviral combinations (Rev Prescrire Int n°110).

The assessment report on vinflunine in bladder cancer states that the CHMP authorised this drug on the basis of a majority decision with many dissenters (Rev Prescrire Int n°112).

Opacity: bad habits die hard. Once again in 2010, Prescrire deplored regulatory agencies’ lack of transparency.

In particular, the EMA refused to provide us with data used for the reassessment of topical ketoprofen gels. We filed a complaint with the European ombudsman (see www.english.prescrire.org).

Some of the documents obtained by Prescrire had been extensively blacked out, masking information of public interest. For example, sales figures and the number of reports of severe allergic reactions to phloroglucinol were blacked out by the French agency (Rev Prescrire n°316). Certain pages of the report on excessive weight loss linked to exenatide were blacked out by the EMA, simply to protect the company’s commercial interests (Rev Prescrire Int n°321).

In the United States, the FDA’s complacency towards a drug company that had failed to publish unfavourable clinical data on quetiapine, a neuroleptic, was revealed during legal proceedings initiated by the patients concerned (Rev Prescrire Int n°112).

Conflicts of interest: too many experts with ties to drug companies. The French agency contracts outside experts to assess marketing applications. In late 2009, it published a review of how conflicts of interest were handled within the agency. This report revealed that regulatory obligations were not fully respected; in particular, more than half of the experts were not required to leave meetings in which they had a major conflict of interest (Rev Prescrire Int n°108). These findings highlight the need for independent experts.

In 2010, the pharmaceutical industry was still heavily involved at every step of drug evaluation. And the fact that drug regulatory agencies are largely funded by drug companies (to the tune of 80% in the case of the EMA) rules out the likelihood of objective assessment (Rev Prescrire n°319). European citizens must fight for the independence of drug regulatory agencies from the pharmaceutical industry.

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Inadequate “risk management” plans. “Risk management” plans and “risk minimisation” measures are frequently inadequate. They are often delegated to drug companies by drug regulatory agencies, and they mainly serve to justify premature marketing authorisation with a commitment to conduct large post-marketing trials (Rev Prescrire n°319).

Heterogeneous “umbrella” ranges: caution

In France, the self-medication market continued to grow in 2010, but most new products had little if any efficacy and did have noteworthy adverse effects. In addition, the fancy brand names and packaging concocted by manufacturers and allowed by drug agencies are unlikely to promote rational use. Pharmacists must carefully select the self-medication products they sell to their clients.

New self-medication products: amorolfine and omeprazole sometimes useful. In 2010, five drugs became available without a prescription: amorolfine (Rev Prescrire n°319), levocabastine (Rev Prescrire n°320), omeprazole (Rev Prescrire n°326), tixocortol (Rev Prescrire n°320) and trimebutine (Rev Prescrire n°326).

Some provide a small benefit:
– amorolfine (Rev Prescrire n°321) is only applied once a week for fungal nail infections, instead of once a day as with ciclopirox;
– omeprazole (Rev Prescrire n°326) is the standard proton pump inhibitor for gastroesophageal reflux.

In contrast, tixocortol, a steroid, should not be used for sore throat (Rev Prescrire n°320).

Fancy brand names and “umbrel-la” ranges: misinformation and danger. Patient safety can be improved by highlighting the INN on drug labelling or including it in the brand name, thus reducing the risk of overdose with drugs present in several self-medication products, such as paracetamol and ibuprofen. This can also help to avoid confusion between similar brand names (Rev Prescrire n°318, 325).

In practice, the INN is rarely highlighted, particularly in self-medication products. “Umbrella” ranges, in which several products with a different composition or regulatory status share a common stem as part of their brand name, are proliferating. This creates a risk of confusion between drugs belonging to the same product line. This is especially the case for products sold to treat coughs and colds. For example, the following “umbrella” ranges were extended in France in 2010: Clarix° (Rev Prescrire n°318), Codotussyl° (Rev Prescrire n°317), Dolirhume° (Rev Prescrire n°318) and Humex° (Rev Prescrire n°317).

Advertising: drug companies continue to spin their web

In late 2009, after reviewing the activities of medical sales reps, the French National Authority for Health (Haute autorité de santé, HAS) stressed the ineffectiveness of the medical sales charter, and admitted that it was incapable of regulating this activity (Rev Prescrire n°109). Although late in coming, this is a welcome realisation. In the meantime, however, drug companies continue to engage in advertising practices that put patients at risk.

Direct-to-consumer (DTC) advertising: prescription drugs: danger. The European Commission’s plans to allow companies to advertise prescription-only drugs directly to the public were once again debated by the European Parliament in late 2010 (see www.english.prescrire.org). The draft text was largely amended but still leaves the door open for some possible drug company advertising of prescription drugs to the public.

Marketing costs: nearly one-quarter of drug companies’ total spending. Patients and healthcare professionals need reliable and comparative information on illnesses and their management. Drug companies, for which each illness represents a market niche, are not in a good position to meet this need (Rev Prescrire n°324, 326). Yet marketing costs represent about 23% of drug companies’ spending, according to a survey conducted by the European Commission (Rev Prescrire n°315).

Drug promotion can take various forms, from training courses “under the influence” of the private sector (Rev Prescrire n°319), to the use of high-tech gimmickry to hide the dearth of real innovation (Rev Prescrire n°316), and advertising disguised as scientific information (Rev Prescrire n°323). Some healthcare professionals contribute indirectly to drug companies’ marketing strategies by providing information on prescriptions and sales, sometimes in return for small gifts (Rev Prescrire n°315).

Illicit advertising aimed at healthcare professionals. Doctors, pharmacists and even nurses are all targeted by drug companies seeking to increase sales of their products (Rev Prescrire n°108).
Finding solutions, along with patients

Faced with ongoing deregulation, with companies overstepping their roles, and with decision makers and health authorities who still fail to make patients’ interests their top priority, it is up to healthcare professionals to assure quality of care and maintain patient trust.

Training and education. Quality healthcare requires continuing education for healthcare professionals and reliable information for patients. This implies:

– basic education for all healthcare professionals in the principles of critical appraisal (Rev Prescrire n°320), so that they are in a position to analyse clinical assessment data on individual drugs, instead of relying solely on others’ judgement (Rev Prescrire n°321); it is particularly important to be able to distinguish surrogate endpoints from robust outcomes that take adverse effects into account (Rev Prescrire n°320);
– searching SPCs for important “buried” information such as clinical trial data and adverse effects (Rev Prescrire n°319);
– being able to recognise a drug’s pharmacological class, notably by using international nonproprietary names (INNs), in order to avoid exposing patients to known adverse effects (Prescrire Int n°108);
– reminding patients not to believe everything they read or hear in the media. Reports of research results in the lay media can be misleading; many researchers have a tendency to exaggerate the significance of their findings, both for financial reasons and for personal status (Rev Prescrire n°320);
– acknowledging one’s errors, as part of a constructive attitude towards improving professional practice (Prescrire Int n°109).

Mobilise! The positive impact that healthcare professionals and patients can have on healthcare quality was illustrated by several events in 2010:

– a French physician succeeded in bringing the severe adverse effects of benfluorex (ex-Mediator®) to the public’s attention (Rev Prescrire n°325 and www.english.prescrire.org), and a national health insurer (Cnamts) commissioned a study of its adverse effects (issue 316 p. 114), both of which led to benfluorex being withdrawn from the French market;
– patient groups successfully lobbied for market reinstatement of 100-mg capsules of efavirenz that are adapted to the treatment of certain HIV-infected young children (Rev Prescrire n°320).

Resist “medicalisation of life”. Disease-mongering continued unabated in 2010, especially in the field of mental health (Rev Prescrire n°321 and www.english.prescrire.org). Thus, in draft version V of the Diagnostic and Statistical Manual (DSM), to be published in 2012, certain diagnostic criteria are bizarre and diagnostic thresholds for some illnesses have been lowered (Rev Prescrire n°323). In 2010, the indications for sertraline were extended to cover various anxiety disorders (panic disorder, social anxiety disorder, post-traumatic stress disorder) (Rev Prescrire n°316).

Companies are trying to get their products authorised for use in earlier stages of the disease concerned. For example, glatiramer is now authorised for suspected recent-onset multiple sclerosis (Prescrire Int n°108). This medicalisation serves companies’ interests by expanding the market for their drugs, at the expense of patient safety and well-being.

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Some of the advertisements banned by the French regulator (Afssaps) in 2010 are particularly informative:

– misleading comparison and overstated results for Alimia® (pemetrexed) and Loramyce® (miconazole) (Rev Prescrire n°318);
– minimisation of the risks of Botox® (botulinum toxin A) (Rev Prescrire n°318);
– overstated claims concerning the indications for Calciprat vitamine D3® and Caltrate vitamine D3® (calcium + vitamin D3), Gardasil® (papillomavirus vaccin 6, 11, 16, 18), Lacteol® (Lactobacillus acidophilus) and Solacy® (vitamin A + L cystine + sulphur + yeast) (Rev Prescrire n°318; 323; 326);
– misleading information on the indications for Inoler® (ferrous succinate) (Rev Prescrire n°318);
– unfounded criticism of generic versions of Omexel® (tamulosin) (Rev Prescrire n°318);
– overly positive presentation of Exforge® (amlodipine + valsartan) and Tareg® (valsartan) by opinion leaders (Rev Prescrire n°323).

In the United States, legal action taken against the company markingquetiapine (Seroquel®) revealed the extent to which some firms are willing to go to promote their products: off-label promotion, financial incentives for physicians to write or even simply sign articles on off-label uses. The company was forced to refund public health insurers for the costs of unwarranted prescriptions (Prescrire Int n°112).

Patients first!

In 2010, as in previous years, there was a dearth of real therapeutic advance as well as continued failings of policy makers and healthcare authorities, such as approval of poorly evaluated drugs with negative risk-benefit balances, or failure to withdraw them from the market.

Unable to rely on regulatory agencies and healthcare authorities, it is up to healthcare professionals to select drugs that truly benefit their patients and avoid needlessly exposing them to the risk of adverse effects.

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