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Generic drugs play a key role in healthcare spending policies. Generic drugs cost on average 30% less than branded drugs, saving 27 billion euros in France from 2000 to date (according to GEMME, an association which includes 13 generic medicine manufacturers).

The market for generic drugs is constantly expanding. In the United States, 80% of prescribed drugs are generic [1]. In France, generic drugs are the subject of more debate as evidenced by the questioning of their effectiveness in oncology [2] and generics accounted for 2% of drug sales in the early 1990s and 47.5% of drug sales in 2019 [3].

With the aim to encourage the use of generic drugs, Article 66 of the French law for financing health ("LFSS2019: loi de financement de la sécurité sociale") modified the conditions for substituting branded drugs by generic drugs as of January 1st, 2020 and made it mandatory for prescribers to provide a medical justification if a drug was "not substitutable" as noted on the prescription. A three-letter code next to the note of "non-substitutable" should then be added, referring to three situations. The first refers to the absence of a generic drug with a pharmaceutical form adapted to paediatric patients (*i.e.* less than six years old) in contrast to the brand-name drug (code EFG). The second situation is active pharmaceutical ingredients displaying narrow therapeutic margins (code MTE). The third code (CIF) refers to patients who are allergic to an excipient with a known action or effect (*i.e.* formal contraindication) that is included for the composition of all generic drugs but not those of branded drugs.

Brand-name and generic drugs: similarities and differences

A generic drug is manufactured with the same active pharmaceutical ingredients as an approved drug (a brand-name drug). Generics display the same qualitative and quantitative composition of active ingredients and the same pharmaceutical form, share the same route of administra-

Do generic drugs cause hypersensitivity?

Generic drugs may differ from brand-name drugs in nature and quantity of excipients. Hypersensitivity to generic drugs is a subject of growing importance given their key role in healthcare spending policies, however, a review of published data highlighted that relevant data is sparse. No scientific rationale has emerged for labelling patients allergic to all generic drugs, and hypersensitivity to generic drugs may rather be explored on a case-by-case basis. In the case of hypersensitivity without any change in medication, it is advisable to check for a switch from a brand-name to a generic drug, and if hypersensitivity to a generic drug is suspected, its composition must be checked.

Key words: generic drug, brand-name drug, hypersensitivity

tion, and demonstrate bioequivalence to brand-name drugs (in the case of drugs for oral use). However, the names of generic drugs, their presentation (*i.e.* packaging, colour, shape, taste, *etc.*), their price and their qualitative and quantitative composition regarding excipients may be different to those of brand-name drugs.

Raw materials used for generic manufacturing may be subject to criticism. One may suggest that their quality may be inferior to that of the brand-name drug. However, the American Food and Drug Administration (FDA) published reassuring data on the purity of raw materials used for generic manufacturing [4]. Furthermore, it would be illusory to suppose that brand-name manufacturers produce themselves all the raw materials used to manufacture the drugs they distribute. In fact, 80% of raw materials used in the composition of generics as well as brand-name drugs come from imports [5].

In France, generic drugs are listed in a repertoire by the National agency for security of medicines and healthcare products (ANSM: "Agence nationale de sécurité des médicaments et des produits de santé"). The purpose of this repertoire is to facilitate generic substitution. Drugs are classified into groups, each including a brand-name drug and its generic equivalents. The repertoire also includes excipients with a known action or effect used in the manufacturing of brand-name and generic drugs (*table 1*). According to LFSS2019, the "CIF" justification for generic non-substitution is based on the presence of at least one excipient with a known action or effect in all generics that is absent in the brand-name drug, which is an uncommon situation. Moreover, this implies that only excipients with a known action or effect are responsible for hypersensitivity reactions. It seems indeed more relevant to review the entire composition of excipients in order to propose, or not, generic substitution.

According to the ANSM's repertoire of generic drugs, substitution of a brand-name drug by its generic equivalents by a pharmacist is feasible without extra precautions when the generic drug does not contain any excipient with a known action or effect. Generic drugs may nevertheless contain additional inactive pharmaceutical ingredients

Table 1. List of 47 excipients with a known action or effect (ANSM).

Aprotinin	Hydrogenated glucose syrup
Arachis oil	Invert sugar
Aspartame (E951)	Lactitol
Azo colouring agents	Lactose
Balsam of Peru	Lanolin (wool fat)
Benzalkonium chloride	Latex natural rubber
Benzoic acid and benzoates	Maltitol (E965) and isomalt (E953)
Benzyl alcohol	Mannitol (E421)
Bergamot oil (containing bergapten)	Organic mercury compounds
Boric acid (and borates)	Parahydroxybenzoates and their esters
Bronopol	Phenylalanine
Butylated hydroxyanisole (E320)	Potassium
Butylated hydroxytoluene (E321)	Propylene glycol and esters of propylene glycol
Castor oil polyoxyl and castor oil polyoxyl hydrogenated	Sesame oil
Cetostearyl alcohol	Sodium
Chlorocresol	Sorbic acid and salts
Dimethyl sulphoxide	Sorbitol (E420)
Ethanol	Soya oil
Formaldehyde	Stearyl alcohol
Fructose	Sucrose
Galactose	Sulphites including metabisulphites
Glucose	Wheat starch
Glycerol	Xylitol
Heparin	

that are described in the literature as being involved in immediate hypersensitivity reactions [6]. For example, polyethylene glycol (macrogol 4000/6000) is a non-active ingredient of the brand-name drug Augmentin® (French brand name for amoxicillin/clavulanic acid for oral use), but not of its generic equivalent marketed by the manufacturer Almus®. In contrast, generic drugs of phloroglucinol contain crosopovidone and aspartam, unlike the brand-name drug, Spasfon® (table 2).

Hypersensitivity to generic drugs

Although this is a subject of concern for our patients, a literature review on hypersensitivity to generic drugs highlighted few articles and conflicting results. Published data were essentially clinical case reports and small-sample retrospective studies. Only one non-randomized prospective study on hypersensitivity has been published. Furthermore, in published papers, immediate and delayed hypersensitivity, involving immuno-allergic or toxic mechanisms, were often mixed. Publications on hypersensitivity to generics were mainly about anticancer chemotherapies. Fewer publications were related to antiepileptic drugs [7] and antibiotics. Clinical cases were reported about antihypertensive drugs, octreotide and allopurinol. Gernez *et al.* reported two cases of hypersensitivity to carboplatin after substitution of the brand-name drug, Teva®, by a generic equivalent. Mannitol contained in the generic

drug was suspected, but prick tests with mannitol were negative for both patients. The pathophysiological mechanism was not elucidated [8]. In contrast, a retrospective study conducted in 2016 in Italy did not show any significant difference between the brand-name drug of oxaliplatin and its generic equivalents. Toxicodermatitis occurred in 12.1% (33/273) of patients treated with the brand-name drug compared to 9.8% (15/154) in the generic group [9]. One case of maculopapular exanthema was described with the generic drug, docetaxel. Nevertheless, no previous sensitization to branded docetaxel (Taxol®), nor allergological test or rechallenge were reported in this study [10]. A 2017 Japanese retrospective study reported hypersensitivity reactions with the generic drug, paclitaxel, in 10% of patients. The primary objective was to determine predictive factors of hypersensitivity. Of 414 patients included in the study, 193 received the brand-name drug, Taxol®, and 195 received its generic equivalent, paclitaxel. Hypersensitivity reactions were reported for 26 patients: two in the Taxol® group and 24 in the paclitaxel group. The difference was not statistically significant. Predictive factors of hypersensitivity were young age, previous allergy and short-duration premedication. Prescription of a generic drug was not identified as a predictive factor [11]. In 2015, a retrospective study reported an increase in acute hypersensitivity reactions occurring during infusion of docetaxel generic drugs. The authors suspected that this increase might be due to a higher amount of polysorbate 80 in generic drugs compared to the brand name, Taxotere® [12]. In contrast, a significant difference between branded docetaxel and its

Table 2. Non-active ingredients of brand-name drugs and generic drug equivalents.

Brand-name drug	Excipients with a known action or effect (ANSM)	List of excipients	Generic drug	Excipients with a known action or effect (ANSM)	List of excipients
Augmentin® 500 mg/62.5 mg for adults, coated tablets	No	Crospovidone	Amoxicillin/Clavulanic acid 500 mg/62.5 mg for adults, coated tablets	No	Crospovidone
		Colloidal silica			Colloidal silica
		magnesium stearate			Magnesium stearate
		Hydroxypropyl cellulose			Microcrystalline cellulose
		Hypromellose			Hypromellose
		Titanium dioxide			Titanium dioxide
		Polyethylene glycol 4000			Povidone K25
		Polyethylene glycol 6000			Talc
Spasfon Lyoc® 160 mg, No oral lyophilisats		Mannitol	Phloroglucinol Biogaran 160 mg, orodispersible tablet	Aspartame	Triethyl citrate
		Dextran 70		Glucose	Manntol
		Sucralose			Microcrystalline cellulose
		Polyethylene glycol 15			Crospovidone
					Aspartame
					Orange flavour
					Magnesium stearate
					Glucose
Advil® 200 mg, coated tablet	Sucrose	Starch	Ibuprofene biogaran 200 mg, coated tablet	No	Starch
		Colloidal silica			Colloidal silica
		Stearic acid			Sodium carboxymethyl starch
		Sucrose			Stearic acid
		Povidone			Povidone
		Polysorbate 80			Hypromellose
		Polyethylene glycol 6000			Polyethylene glycol 400
		Calcium carbonate			Hydroxypropyl cellulose
		Talc			Titanium dioxide
		Carnauba wax			
Effergal® 500 mg, orodispersible tablet	Aspartame	Aspartame	Paracetamol Arrow 500 mg, tablet	Sodium carboxymethyl starch	Povidone
		Glucose			Microcrystalline cellulose
		Sodium			Starch
		Sodium benzoate			Sodium carboxymethyl starch
		Sorbitol			Stearic acid
		Sucrose			Magnesium stearate
		Crospovidone			
		Sodium benzoate			
		Glucose			
		Aspartame			
		Potassium acesulfame			

generic equivalents was observed in a prospective study published in 2017. Of the 258 patients included in this study, 128 patients received paclitaxel (the brand-name drug, Taxol[®], for 65 patients and its generic equivalent, paclitaxel, for 63 patients) and 130 patients received docetaxel (the brand-name drug, Taxotere[®], for 66 patients and its generic equivalent, docetaxel, for 64 patients). Premedication was similar, and chemotherapies were administered according to similar protocols. The total rate of hypersensitivity reactions was 10% in the cohort. There was no difference between the brand-name drug, Taxol[®], (13.8%) and its generic equivalent (11.1%). However, fewer toxicities were observed in the generic group (1.6%) than in the Taxotere[®] group (13.6%; $p=0.017$). The authors noticed few differences between Taxotere[®] and the generic drug. Although the size of the groups was similar, no randomization was performed (the choice of brand-name drug or generic drug was decided according to the patients' healthcare reimbursement system) [13].

Regarding antiepileptic drugs, a prospective observational study compared the efficacy and safety of oxcarbazepine generic substitution. In the study, 76 of 103 patients accepted the substitution. No cases of hypersensitivity reactions were reported. Five patients (one in the brand-name group and four in the generic group) reported side effects, such as malaise or abdominal pain, with no significant differences [7]. In another study, published in 2008, Sabroe *et al.* reported the occurrence of DRESS in a young man, eight weeks after substitution of the brand-name drug, Lamictal[®], by the generic drug, lamotrigine. The authors hypothesized that the reaction may be linked to an impurity present in the generic drug and absent in Lamictal[®], as revealed by chromatographic analysis [14].

In vitro and experimental studies highlighted higher plasma drug levels obtained after administration of branded vancomycin compared to the generic drug. This difference was also observed with teicoplanin. In addition, more adverse effects were reported with branded than with generic teicoplanin in a retrospective study including 107 patients [15].

A retrospective study including 18 patients treated for at least one year with branded octreotide reported lower efficacy after generic substitution (38.8% of patients were biochemically controlled after the switch versus 77% before) [16]. The authors reported two cases of toxidermia occurring after the switch.

In 2006, a clinical case of sensitization to allopurinol after generic substitution was reported in a patient previously treated for 15 years with the brand-name drug, Zyloric[®]. Allergologic tests were all negative (for the generic drug, Zyloric[®], and the excipients). Nevertheless, reintroduction of Zyloric[®] two months later induced recurrence of maculopapular exanthema. Generic substitution seemed to be responsible for sensitization to allopurinol in this patient, although the pathophysiological mechanism was not clear [17].

Two cases of anaphylaxis to a generic formulation of omeprazole capsule were reported in the New England Journal of Medicine in 2009. IgE dot-blot assays showed that these two IgE-mediated reactions were imputable to soybean oil contained in the generic drugs [18].

A case of erythema pigmentosa caused by hydroxypropyl cellulose was reported in a patient after generic substitution

of branded sodium azulene sulfonate hydrate L-glutamine. A lymphocyte transformation test proved that this was attributable to the generic drug. However, the role of hydroxypropyl cellulose was hypothesized here based on an analysis of the composition of the two drugs [19].

In 2010, Mumoli *et al.* reported the occurrence of a maculopapular rash in an 87-year-old female patient after a switch from the brand-name drug, Lasilix[®], to a furosemide generic drug. The rash resolved after discontinuation of the generic drug and reappeared after inadvertent reintroduction. Croscarmellose sodium, contained in generic furosemide but not in Lasilix[®], seemed to be the cause [20]. Finally, a case of drug-induced leukocytoclastic vasculitis occurring in an 82-year-old female patient after introduction of an amlodipine generic drug was described in 2009 [21].

In summary, published data are mostly reassuring and to date there is no scientific rationale to support whether a patient is "allergic or intolerant to all generics". However, many patients are not convinced and treating them may be challenging. Breenan *et al.* reported a patient who was declared "allergic to generics", rejecting all generic drugs including those during the course of a life-threatening heart attack. The authors discussed ethical issues for practitioners who are caught between their collective responsibility to save healthcare costs by prescribing generic drugs, and their responsibility and the difficulty to treat patients who reject generic drugs [22].

The pathophysiological mechanisms underlying hypersensitivity reactions are not always fully elucidated and a hypersensitivity reaction to an excipient is still the most common explanation.

Hypersensitivity to excipients

Excipients are non-active compounds added to a drug to modify its dissolution, kinetic and/or absorption, to increase its stability, to influence its palatability or to add features such as consistency, taste or colour. All approved drugs contain excipients, whether they are brand-name or generic drugs. The proportion of hypersensitivity to excipients among drug hypersensitivity overall is not well described. Although seemingly relatively uncommon, hypersensitivity to excipients may lead to misdiagnoses of drug hypersensitivity [23]. Nevertheless, as discussed above, excipients may be involved in hypersensitivity to generic drugs, whether symptoms are immediate or delayed or drugs are administered orally, intravenously or topically [24]. The impact of such misdiagnoses in patients is difficult to evaluate.

The COVID-19 pandemic and mass vaccination of Sars-CoV2 highlighted issues raised by hypersensitivity to excipients, including polyethylene glycol (PEG). A recent study suggested a strong impact of PEG hypersensitivity on the quality of life of patients. Of 10 patients diagnosed as "allergic to PEG" from 2010 to 2019, eight experienced at least one anaphylactic shock and seven patients reported multiple reactions (between two and six reactions; three on average). Time from first reaction to diagnosis was 20 months on average. The authors underlined the difficulty for patients in avoiding PEG because of a lack of standardization of nomenclature, widespread use of PEG, and possible cross-reactivities [25].

Table 3. Excipients involved in immediate and/or delayed hypersensitivity reactions (based on [26, 27]).

Drug class	Excipients involved in hypersensitivity reactions
Erythropoiesis-stimulating agents	Polysorbate 80
Local anaesthetics	Sodium metabisulphite
Analgesics	Mannitol
	Povidone
Monoclonal antibodies	Polysorbate 20
	Polysorbate 80
Antibiotics	Macrogol 6000
	Polysorbate 80
Antiepileptic drugs	Carboxymethylcellulose
Non-steroidal anti-inflammatory drugs	Colloidal silica
	Macrogol 4000
	Macrogol 6000
	Yellow dyes
Antihistamines	Propylene glycol
Anxiolytics	Propylene glycol
Chemotherapies	Cremophor
	Polysorbate 80
Eye drops and ophthalmic products	Benzalkonium chloride
	Thimerosal
	Carboxymethylcellulose
	Povidone
Corticosteroids	Carboxymethylcellulose
	Benzalkonium chloride
Nasal decongestants	Lysozyme
Ultrasound gels	Imidazolidinyl urea
	Methyldibromo glutaronitrile
	Propylene glycol
	Polyethylene glycol
Insulin	Metacresol
	Zinc
	Protamine
Laxatives	Macrogol 3350, 4000
Lubricants	Propylene glycol
Wound dressings	Carboxymethylcellulose
	Colophonium
Throat lozenges	Lysozyme

Table 3. (Continued)

Drug class	Excipients involved in hypersensitivity reactions
Contrast media	Carboxymethylcellulose
	Carrageenan
	Macrogol 4000
	Povidone
	Trometamol
Mineral supplements	Sunset yellow FCF
	Casein
	Macrogol
Sclerotherapy	Benzyl alcohol
Topical medications	Ascorbyl tetraisoalmitate
	Isopropyl palmitate
	Benzyl alcohol
	Cetostearyl alcohol
	Chlorocresol
	Diocetyl sodium sulfosuccinate
	EDTA
	1,2,6-Hexanetriol
	Parabens
	Polyethylene glycol
	Propylene glycol
	Propyl gallate
	Sodium metabisulfite
	Sodium sulphite
	Sorbitan Sesquioleate
Vaccines	Formaldehyde
	Polyethylene glycol
	Aluminum
	Gelatin
	Polysorbate 80

Symptoms of immediate hypersensitivity to excipients can range from common skin urticarial reactions to very severe anaphylaxis [26, 27]. Some excipients that might be involved in hypersensitivity reactions are listed in *table 3* Table 3. The nomenclature used for excipients may differ according to country, and especially according to pharmacopoeia, when applicable. For example, the term “carboxymethylcellulose” is used in the US Pharmacopoeia, whereas the term “carmellose” refers to the same compound in the Euro-

pean Pharmacopoeia. Similarly, the term “PEG” used in the US Pharmacopoeia is referred to rather as macrogol in Europe. Thus, in France, the “summaries of product characteristics” retrieved from all drug databases indicate excipients according to the European nomenclature. Hypersensitivity to excipients can be explored with patch tests, prick tests or intradermal reactions. Laboratories such as Chemotechnique or Sigma provide some of these tests. The testing of drugs that contain excipients suspected to cause hypersensitivity may also represent an alternative strategy. Moreover, IgE-based assays are available for some excipients. However, currently, there are no clear guidelines on the methods for testing excipients during the diagnosis of hypersensitivity.

Conclusion

Generic drugs represent an important economic issue. Their prescription must be supported to safeguard our healthcare system. To date, there is no scientific rationale to support whether patients are “allergic or intolerant” to all generics. Nevertheless, the nature of excipients and their relative quantity may be different between brand-name drugs and their generic equivalents, as well as between the different generic drugs of the same branded drug. For a particular drug and in the context of hypersensitivity to an excipient, it is therefore conceivable that the brand-name drug and not the generic drug equivalent would be well tolerated. As physicians or pharmacists, we have to reassure patients who are declared “allergic or intolerant to all generics”, but we also have to remain aware of the wider context. In cases of hypersensitivity reactions without any change in medication, it is advisable to check for a switch from a brand name (or a prior generic drug) to a generic drug, and if hypersensitivity to a generic drug is suspected, its composition must be checked. ■

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