Supplementary Tables

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CPIC vs DPWG vs EMA/FM vs FDA comparison (condensed table)

Table S1. Comparison of FDA and EMA/FM labels with CPIC and DPWG guidelines for 58 gene-drug interactions. Pharmacogenomic information refers to information which does not require action. N.a. depicts that the drug is not registered. Based on Bank *et al.*[1]

Drug	Gene	Institution	Therapeutic recommendations	Ref.
Abacavir	*HLA-B*	CPIC	Abacavir is not recommended due to the risk of hypersensitivity reactions.	2,3
		DPWG	Contraindicated due to the risk of hypersensitivity reactions.	4,5
		EMA	**Mandatory:** *HLA-B*5701* status must always be documented prior to initiating therapy.	
		FDA	**Recommendation dealing with absolute contraindication.**	
Acenocoumarol	*VKORC1*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	5
		EMA	n.a.	
		FIDMD	n.a.	
		MEB	No information.	
		FDA	n.a.	
Allopurinol	*HLA-B*	CPIC	Contraindicated due to the risk of hypersensitivity reactions.	6
		DPWG	Consider alternative drug (febuxostat) or dose adjustment.	5
		EMA	**Recommendation**: Screening for *HLA-B*5801* should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high.	
		FDA	**Recommendation:** Immediately discontinue at first signs of skin rash or allergic reactions.	
Amitriptyline	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	7,8
		DPWG	No action required.	5
		EMA	n.a.	
		FIDMD	**Strong recommendation**: Consider specific dose adjustment.*	
		MEB	**Strong recommendation**: Consider specific dose adjustment.	
		FDA	No information.	
	CYP2D6	CPIC	Consider alternative drug or dose adjustment.	7,8
		DPWG	Consider alternative drug or dose adjustment.	4,5
		EMA	n.a.	
		FIDMD	**Strong recommendation**: Consider specific dose adjustment.*	
		MEB	**Strong recommendation**: Consider specific dose adjustment.	
		FDA	Pharmacogenomic information.	
Aripiprazole	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	5
		EMA	Pharmacogenomic information.	
		FDA	**Strong recommendation**: Specific dose adjustment.	

Atazanavir	*UGT1A1*	CPIC	Consider alternative drug.	[9]
		DPWG	No guideline.	
		EMA	No information.	
		FDA	No information.	
Atomoxetine	*CYP2D6*	CPIC	Consider dose adjustment.	[10]
		DPWG	In case of efficacy with adverse reactions, lower the dose and monitor if efficacy is maintained or consider alternative (clonidine).	[5]
		EMA	n.a.	
		FIDMD	**Recommendation:** A lower initial dose and a slower titration may be considered.	
		MEB	**Recommendation:** Consider a lower starting dose and slower up titration of the dose.	
		FDA	**Strong recommendation**: Specific dose adjustment.	
Atorvastatin	*SLCO1B1*	CPIC	No guideline.	
		DPWG	Consider alternative drug or advise patient to reach out in case of myopathy while taking Atorvastatin.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	No information.	
Azathioprine	*TPMT*	CPIC	Consider alternative drug or dose adjustment.	[11,12]
		DPWG	Consider alternative drug or dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Dose adjustment.*	
		MEB	**Recommendation**: Dose adjustment.	
		FDA	**Recommendation**: Alternative drug or dose reduction is recommended.	
	NUDT15	CPIC	Consider alternative drug or dose adjustment.	[11,12]
		DPWG	Consider alternative drug or dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Recommendation:** Dose adjustment and monitoring of blood levels.*	
		MEB	**Recommendation:** Dose adjustment.	
		FDA	**Recommendation:** Consider alternative drug.	
Capecitabine/5-fluorouracil	*DPYD*	CPIC	Select alternative drug or dose adjustment.	[13]
		DPWG	Select alternative drug or dose adjustment.	[4,5,14]
		EMA	**Mandatory**: Patients with partial DPD deficiency must be treated with extreme caution and frequent monitoring with dose adjustment according to toxicity.	
		FDA	**Recommendation**: Select alternative drug.	
Carbamazepine	*HLA-B*	CPIC	If patient is carbamazepine-naive, do not use carbamazepine.	[15]
		DPWG	Choose alternative drug.	[5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Do not use carbamazepine unless no alternative drug is available.	
		MEB	**Recommendation**: Do not use carbamazepine unless no alternative drug is available.	

		FDA	**Recommendation dealing with absolute contraindication.**	
Citalopram	*CYP2C19*	CPIC	Consider dose adjustment or alternative drug.	[16]
		DPWG	Consider dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Strong recommendation:** Specific dose adjustment.	
		MEB	**Strong recommendation**: Specific dose adjustment.	
		FDA	**Strong recommendation**: Specific dose adjustment.	
Clomipramine	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	No information.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	No information.	
	CYP2D6	CPIC	Alternative drug or dose adjustments.	[7,8]
		DPWG	Consider alternative drug or dose adjustment.	[4,5,17]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Clopidogrel	*CYP2C19*	CPIC	Consider alternative drug.	[18,19]
		DPWG	Consider alternative drug.	[4,5]
		EMA	Pharmacogenomic information.	
		FDA	**Recommendation**: Consider alternative drug.	
Codeine	*CYP2D6*	CPIC	Avoid codeine use due to potential for toxicity.	[20,21]
		DPWG	Codeine is contraindicated in CYP2D6 ultra-rapid metabolizers due to the risk of overdose.	[4,5,17]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	**Recommendation dealing with absolute contraindication.**	
		FDA	**Recommendation dealing with absolute contraindication.**	
Desipramine	*CYP2D6*	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	No guideline.	
		EMA	n.a.	
		FIDMD	n.a.	
		MEB	n.a.	
		FDA	Pharmacogenomic information.	
Doxepin	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	No action required.	[5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	Pharmacogenomic information.	
	CYP2D6	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	Consider alternative drug or dose adjustment.	[4,5]

		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	Pharmacogenomic information.	
Efavirenz	*CYP2B6*	CPIC	No guideline.	
		DPWG	In the case of adverse reactions, dose adjustment.	[5]
		EMA	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Eliglustat	*CYP2D6*	CPIC	No guideline.	
		DPWG	Eliglustat is contraindicated in CYP2D6 ultra-rapid metabolizers.	[5]
		EMA	**Recommendation dealing with absolute contraindication.**	
		FDA	**Strong recommendation**: Specific dose adjustment.	
Escitalopram	*CYP2C19*	CPIC	Consider dose adjustment or alternative drug.	[16]
		DPWG	Consider dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Strong recommendation**: Specific dose adjustment.	
		MEB	**Strong recommendation**: Specific dose adjustment.	
		FDA	Pharmacogenomic information.	
Fenprocoumon	*VKORC1*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	n.a.	
		MEB	No information.	
		FDA	n.a.	
Flecainide	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	No information.	
Flucloxacillin	*HLA-B*	CPIC	No guideline.	
		DPWG	Monitor liver function regularly. Select an alternative drug if liver enzymes or bilirubin levels increase.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	n.a.	
Fluvoxamine	*CYP2D6*	CPIC	Consider dose adjustment or alternative drug.	[16]
		DPWG	No action required.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	**Recommendation**: Be cautious.	
Halogenated volatile anesthetics (enflurane,	*RYR1/ CACNA1S*	CPIC	Contraindicated due to the risk of malignant hyperthermia, unless the benefits far outweigh the risks.	[22]
		DPWG	No guideline.	

isoflurane) or succinyl choline		EMA	n.a.	
		FIDMD	**Recommendation dealing with absolute contraindication.**	
		MEB	No information.	
		FDA	**Recommendation dealing with absolute contraindication.**	
Haloperidol	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider dose adjustment or alternative drug.	[5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Haloperidol should be used with caution if patients simultaneously receive a CYP3A4 inhibitor.	
		MEB	**Recommendation**: Be cautious in patients who are receiving a CYP3A4 inhibitor.	
		FDA	No information.	
Imipramine	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	Consider dose adjustment or alternative drug.	[4,5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	No information.	
	CYP2D6	CPIC	Alternative drug or dose adjustment.	[7,8]
		DPWG	Alternative drug or dose adjustment.	[4,5,17]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	Pharmacogenomic information.	
Irinotecan	*UGT1A1*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	**Strong recommendation**: Specific dose adjustment.*	
		MEB	**Recommendation**: Check for hematologic toxicity.	
		FDA	**Recommendation**: Initiate therapy with a reduced dose and titrate based on individual patient's tolerance.	
Ivacaftor	*CFTR*	CPIC	Indicated.	[23]
		DPWG	No guideline.	
		EMA	**Indication**.	
		FDA	**Mandatory**: A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated.**	
Lamotrigine	*HLA-B*	CPIC	No guideline.	
		DPWG	Consider alternative drug, if not available inform the patient to reach out in case of skin rash.	[5]
		EMA	n.a.	
		FIDMD	No information	
		MEB	No information.	
		FDA	No information.	
Mercaptopurine	*TPMT*	CPIC	Consider alternative drug or dose adjustment.	[11,12]
		DPWG	Select alternative drug or dose adjustment.	[4,5]
		EMA	**Recommendation**: Consider a substantial dose reduction.	
		FDA	**Strong recommendation**: Specific dose adjustment.	

	NUDT15	CPIC	Dose adjustment or alternative drug.	[11,12]
		DPWG	Select alternative drug or dose adjustment.	[4,5]
		EMA	**Recommendation:** Dose adjustment.	
		FDA	**Strong recommendation:** Specific dose adjustment.	
Metoprolol	*CYP2D6*	CPIC	No guideline.	
		DPWG	In cases of symptomatic bradycardia or when gradual lowering of heart rate is desirable, dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	Pharmacogenomic information.	
Nortriptyline	*CYP2D6*	CPIC	Consider alternative drug or dose adjustment.	[7,8]
		DPWG	Consider alternative drug or dose adjustment.	[4,5,17]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Ondansetron	*CYP2D6*	CPIC	Select alternative drug.	[24]
		DPWG	No guideline.	
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Oxcarbazepine	*HLA-B*	CPIC	No guideline.	
		DPWG	Select alternative drug; if there is no alternative available, inform the patient to reach out in case of skin rash.	[5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Use of oxcarbazepine can be considered if the benefits are expected to be greater than the risks.	
		MEB	**Recommendation**: Only use oxcarbazepine if the benefits are expected to outweigh the risks	
		FDA	**Recommendation dealing with relative contraindication.**	
Paroxetine	*CYP2D6*	CPIC	Consider alternative drug or dose adjustment.	[16]
		DPWG	Consider alternative drug.	[4,5,17]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	No information.	
		FDA	No information.	
Pegylated interferon-α	*IFNL3*	CPIC	Consider implications before initiating therapy.	[25]
		DPWG	No guideline.	
		EMA	No information.	
		FDA	No information.	
Phenytoin	*CYP2C9*	CPIC	Consider dose adjustment.	[26]
		DPWG	Consider dose adjustment.	[4,5,17]
		EMA	n.a.	

		FIDMD	**Recommendation**: Dose reduction along with monitoring of plasma concentrations may be necessary.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
	HLA-B	CPIC	No guideline.	
		DPWG	Consider an alternative drug; if there is no alternative available, inform the patient to reach out in case of skin rash.	[5]
		EMA	n.a.	
		FIDMD		Pharmacogenomic information.
		MEB	**Recommendation**: Do not use phenytoin unless the benefits outweigh the risks.	
		FDA	**Recommendation**: Avoid treatment with phenytoin as an alternative to carbamazepine in patients with *HLA-B*1502* due to the risk for hypersensitivity reactions.	
Pimozide	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	n.a.	
		MEB	**Strong recommendation:** Specific dose adjustment.	
		FDA	**Strong recommendation:** Specific dose adjustment.	
Propafenone	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider alternative drug or dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	**Recommendation**: Avoid use of CYP3A4 inhibitors.	
Rasburicase	*G6PD*	CPIC	Contraindicated due to the risk of acute hemolytic anemia.	[12]
		DPWG	No guideline.	
		EMA	**Recommendation dealing with absolute contraindication.**	
		FDA	**Recommendation dealing with absolute contraindication.**	
Ribavirin	*IFNL3*	CPIC	Consider implications before initiating therapy.	[25]
		DPWG	No guideline.	
		EMA	No information.	
		FDA	No information.	
Sertraline	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	[16]
		DPWG	Consider dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Titrate the dose based on clinical response.	
		MEB	Pharmacogenomic information.	
		FDA	No information.	

Simvastatin	*SLCO1B1*	CPIC	Consider alternative drug or dose adjustment.	[27,28]
		DPWG	Consider alternative drug or dose adjustment.	[4,5]
		EMA	Pharmacogenomic information.	
		FDA	No information.	
Tacrolimus	*CYP3A5*	CPIC	Consider dose adjustment.	[29]
		DPWG	Consider dose adjustment.	[4,5]
		EMA	No information.	
		FDA	No information.	
Tamoxifen	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider alternative drug or dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Tegafur	*DPYD*	CPIC	Consider alternative drug or dose adjustment.	[13]
		DPWG	Consider alternative drug.	[4,5,14]
		EMA	Pharmacogenomic information.	
		FDA	n.a.	
Thioguanine	*TPMT*	CPIC	Consider dose adjustment.	[11,12]
		DPWG	Select alternative drug or dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Consider dose adjustment.	
		MEB	**Recommendation**: Dose reduction is usually necessary. Monitor blood count closely.	
		FDA	**Strong recommendation**: Specific dose adjustment.	
	NUDT15	CPIC	Consider dose adjustment.	[11,12]
		DPWG	Consider alternative drug or dose adjustment.	[4,5]
		EMA	n.a.	
		FIDMD	**Recommendation**: Genotypic analysis should be considered before initiation of thiopurine therapy to determine the NUDT15 genotype.	
		MEB	**Recommendation**: Dose adjustment.	
		FDA	**Strong recommendation:** Specific dose adjustment.	
Tramadol	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider alternative drug or dose adjustment.	[5]
		EMA	n.a.	
		MEB	Pharmacogenomic information.	
		FIDMD	Pharmacogenomic information.	
		FDA	**Recommendation dealing with absolute contraindication.**	
Trimipramine	*CYP2C19*	CPIC	Consider alternative drug or dose adjustment.	[8]
		DPWG	No guideline.	
		EMA	n.a.	
		FIDMD	No information.	
		MEB	n.a.	
		FDA	No information.	
	CYP2D6	CPIC	Consider alternative drug or dose adjustment.	[8]
		DPWG	No guideline.	
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	n.a.	
		FDA	Pharmacogenomic information.	

Tropisetron	*CYP2D6*	CPIC	Consider alternative drug (granisetron).	[24]
		DPWG	No guideline.	
		EMA	n.a.	
		FIDMD	n.a.	
		MEB	No information.	
		FDA	n.a.	
Venlafaxine	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider alternative drug or dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Voriconazole	*CYP2C19*	CPIC	Choose alternative drug.	[30]
		DPWG	Dose adjustment.	[4,5,17]
		EMA	Pharmacogenomic information.	
		FDA	Pharmacogenomic information.	
Warfarin	*CYP2C9*	CPIC	Calculate dose based on validated published pharmacogenetic algorithm.	[31,32]
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	n.a.	
		FDA	**Strong recommendation**: Specific dose adjustment.	
	VKORC1	CPIC	Calculate dose based on validated published pharmacogenetic algorithm.	[31,32]
		DPWG	Consider dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	No information.	
		MEB	n.a.	
		FDA	**Strong recommendation**: Specific dose adjustment.	
Zuclopenthixol	*CYP2D6*	CPIC	No guideline.	
		DPWG	Consider alternative drug or dose adjustment.	[5]
		EMA	n.a.	
		FIDMD	Pharmacogenomic information.	
		MEB	Pharmacogenomic information.	
		FDA	n.a.	

Abbreviations:
IM = intermediate metabolizer; NM = normal metabolizer; PM = poor metabolizer; RM = rapid metabolizer; UM = ultra-rapid metabolizer; ADE = adverse drug event; M = moderate; S = strong; O = Optional; IN = Insufficient evidence; 0 = data on file; 1 = published incomplete case reports; 2 = well documented case reports / case series; 3 = published controlled studies of moderate quality; 4 = published controlled studies of good quality; A = minor clinical effect; B = clinical effect : short-lived discomfort (<48 h) without permanent injury; C = clinical effect: long-standing discomfort (48-168 h) without permanent injury; D = clinical effect: long-standing effect (>168) and permanent symptom or invalidating injury; E = Increased risk of failure of lifesaving therapy / expected bone marrow depression; F = death, arrhythmia, unexpected bone marrow depression
CACNA1S = calcium voltage-gated channel subunit alpha1 S; CFTR = CF transmembrane conductance regulator; DYPD = dihydropyrimidine dehydrogenase; HLA-B = major histocompatibility complex, class I, B; G6PD = glucose-6-phosphate dehydrogenase; IFNL3 = interferon lambda 3; NUDT15 = nudix hydrolase 15; RYR1 = ryanodine receptor 1; SLCO1B1 = solute carrier organic anion transporter 1B1; TPMT = thiopurine-S-methyltransferase; UGT1A1 = UDP-Glucuronosyltransferase 1A1; VKORC1 = vitamin K epoxide reductase complex subunit 1.

* SmPCs for which depending on the formulation differences and/or missing data regarding PGx information were found.

**This information was retrieved from the section 12.1. Mechanism of Action.

CPIC = Clinical Pharmacogenetics Implementation Consortium; DPWG = Dutch Pharmacogenetics Working Group; FDA = Food and Drug Administration (U.S.A.); EMA = European Medicines Agency (Europe); MEB = Medicine's Evaluation Board (Netherlands); FIDMD = Federal Institute for Drugs and Medical Devices (Germany)

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EMA vs FDA comparison (condensed tables)

Table S2. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group A (**Alimentary tract and metabolism**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate (MoviPrep)	*G6PD*	EMA	n.a.
		FDA	**Recommendation**: MoviPrep should be used with caution in patients with G6PD deficiency.
Carglumic Acid (Carbalglu)	*NAGS*	EMA	**Indication**: Treatment of hyperammonaemia due to NAGS primary deficiency.
		FDA	**Indication**: Treatment of hyperammonaemia due to NAGS primary deficiency.
Cerliponase alfa (Brineura)	*TPP1*	EMA	**Indication**: Treatment of neuronal CLN2 disease, also known as TPP1 deficiency.
		FDA	**Indication**: Pediatric patients 3 years of age and older with late infantile neuronal CLN2, also known as TPP1 deficiency.

Chlorpropamide (Diabinese)	*G6PD*	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation**: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
Dronabinol	*CYP2C9*	EMA	n.a.
		FDA	**Recommendation**: Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function.
Elosulfase	*GALNS*	EMA	n.a.
		FDA	**Indication**: Patients with MPS IVA.
Eluxadoline (Truberzi)	*SLCO1B1*	EMA	**Recommendation**: Genetic disposition may be unknown; it is recommended that patients be monitored for impaired mental or physical abilities needed to perform potentially hazardous activities.
		FDA	No information.
Glibenclamide	*β-cell ATP-sensitive potassium channel and chromosome 6q24-related transient neonatal diabetes mellitus*	EMA	**Indication**: β-cell ATP-sensitive potassium channel and chromosome 6q24-related transient neonatal diabetes mellitus.
		FDA	No information.
	G6PD	EMA	**Recommendation**: Patients carrying a G6PD enzyme deficiency: not to be prescribed for these patients, and the use of an alternative treatment is strongly recommended, if available. If there is no alternative, the decision for each patient must consider the danger of haemolysis and the potential benefit expected from the treatment. Screening should be conducted for the occurrence of any haemolysis.
		FDA	**Recommendation**: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
Glimepiride (Amaryl)	*G6PD*	EMA	**Recommendation**: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
		FDA	**Recommendation**: Use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative.
Glipizide	*G6PD*	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation**: Caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
Metoclopramide	*CYB5R*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: Known history of methemoglobinaemia with metoclopramide or NADH CYB5R deficiency.
		MEB	**Recommendation dealing with absolute contraindication**: Contraindicated in patients with known NADH-cytochrome b5 reductase deficiency.

		FDA	Pharmacogenomic information.
	G6PD	EMA	n.a.
		FIDMD	No information.
		MEB	No information.
		FDA	**Recommendation**: In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended.
Migalastat (Galafold)	*GLA*	EMA	**Indication**: Patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.
		FDA	**Indication**: Patients with a confirmed diagnosis of Fabry disease and an amenable GLA variant based on in vitro assay data.
Pantoprazole	*CYP2C19*	EMA	No information.
		FDA	**Recommendation**: In patients who are CYP2C19 poor metabolizers no dosage adjustment is needed. For known pediatric poor metabolizers a dose reduction should be considered.
Sodium Phenylbutyrate (Ammonaps, Buphenyl)	*ASS1*, *CPS1*, *OTC*	EMA	**Indication**: Patients with urea cycle disorders, involving deficiencies of CPS, OTC or argininosuccinate synthetase.
		FDA	**Indication**: Patients with urea cycle disorders involving deficiencies of CPS, OTC or argininosuccinic acid synthetase.
Sulfasalazine	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication:** G6PD deficiency.
		MEB	**Recommendation dealing with absolute contraindication**: Contraindicated in patients with G6PD deficiency.
		FDA	**Recommendation**: Patients with G6PD deficiency should be observed closely for signs of hemolytic anemia.

Abbreviations: ASS1, argininosuccinate synthase 1; CLN2, ceroid lipofuscinosis type 2; CPS, carbamylphosphate synthetase; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); GALNS, galactosamine (N-acetly)-6-sulfatase; GLA, galactosidase alpha gene; G6PD, glucose-6-phosphate dehydrogenase; MEB, Medicines Evaluation Board (CBG-MEB); MPS IVA, Mucopolysaccharidosis type IVA; NADH, Nicotinamide adenine dinucleotide; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; SLCO1B1, solute carrier organic anion transporter family member 1B1; TPP1, tripeptidyl peptidase 1.

Table S3. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group B (***Blood and blood forming organs***). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	**Gene**	**Institution**	**Therapeutic advice**
Acetylsalicylic acid/Clopidogrel (Zentiva)	*G6PD*	EMA	**Mandatory**: This medicinal product must be administered under close medical supervision in patients with G6PD deficiency due to risk of haemolysis.
		FDA	No information.
Avatrombopag (Doptelet)	*F2, F5, PROC, PROS1, SERPINC1*	EMA	n.a.
		FDA	**Recommendation**: Consider the potential increased thrombotic risk when administering Dopetelet to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).
Caplacizumab (Cablivi)	*Hemophilia, coagulation factor deficiencies*	EMA	**Recommendation**: Due to a potential increased risk of bleeding, use of Cablivi in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies) is to be accompanied by close clinical monitoring.
		FDA	Pharmacogenomic information.
Eltrombopag (Promacta)	*F5/ SERPINC1*	EMA	**Recommendation**: Caution should be used when administering to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden).
		FDA	**Recommendation**: Potential for an increased risk of thromboembolism when administering to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease).
Lusutrombopag (Mulpleta)	*F2, F5, PROC, PROS1, SERPINC1*	EMA	**Recommendation**: Patients with congenital coagulopathy the risk for thrombosis or thromboembolism may increase. These patients should be clinically monitored when treated with lusutrombopag.
		FDA	**Recommendation**: Consider the potential increased thrombotic risk when administering to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency).

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); F2, Coagulation factor 2; F5, Coagulation factor 5; G6PD, glucose-6-phosphate dehydrogenase; MEB, Medicines Evaluation Board (CBG-MEB); PROC, protein C; PROS1, protein S; SERPINC1, serpin family C member 1.

Table S4. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group C (**Cardiovascular system**), group D (**Dermatologicals**) and group G (**Genito-urinary system and sex hormones**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Carvedilol	*CYP2D6*	EMA	n.a.
		FIDMD	**Recommendation**: In patients with slow hydroxylation of debrisoquine, plasma concentrations of carvedilol are up to 2-3 fold higher than those of fast debris quinone metabolizers. Patients known to be poor at metabolizing debrisoquine should be closely monitored at baseline.
		MEB	No information.
		FDA	Pharmacogenomic information.
Evolocumab (Repatha)	*PCSK9*	EMA	**Indication**: Patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. Patients with homozygous familial hypercholesterolaemia.
		FDA	No information.
Ranolazine (Ranexa)	*CYP2D6*	EMA	**Recommendation**: If the CYP2D6 status of the patient has been determined or is previously known to be EM, Ranexa can be used with caution in these patients when they have a combination of several of the risk factors.
		FDA	No information.
Dapsone (Aczone)	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation:** In patients with hereditary deficiency of G6PD, the risk of unwanted side effects is markedly increased, which is why the use should be avoided. In case of urgent indication, try to get by with half the recommended dose.
		MEB	n.a.
		FDA	Pharmacogenomic information.
	Nonsepcific (congenital methemoglobinemia)	EMA	n.a.
		FIDMD	No information.
		MEB	n.a.
		FDA	**Recommendation:** Avoid use of Aczone Gel, 5% in those patients with congenital or idiopathic methemoglobinemia**.**
Tretinoin (Vesanoid)	*PML-RARA*	EMA	n.a.
		FIDMD	n.a.
		MEB	No information.
		FDA	**Indication:** Patients with acute promyelocytic leukemia, French-American-British classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML-RARA.
Flibanserin	*CYP2C19*	EMA	n.a.
		FDA	**Recommendation**: Increase monitoring for adverse reactions in patients who are CYP2C19 poor metabolizers.

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration, FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); MEB, Medicines Evaluation Board (CBG-MEB); PCSK 9, proprotein convertase Subtilisin/Kexin Type 9.

Table S5. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group J (**Antiinfectives for systemic use**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Ceftriaxone	*G6PD, nonspecific (congenital methemoglobinemia*	EMA	n.a.
		FIDMD	No information.
		MEB	No information.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.
Daclatasvir (Daklinza)	*HCV genotype*	EMA	**Strong recommendation**: Specific treatment regimens depending on HCV genotype.
		FDA	**Strong recommendation**: Specific treatment regimens depending on HCV genotype.
Elbasvir/Grazoprevir (Zepatier)	*HCV genotype*	EMA	**Strong recommendation**: Depending on the genotype other treatment recommendations and not recommended in patients infected with HCV genotypes 2, 3, 5 and 6.
		FDA	**Strong recommendation**: Depending on HCV genotype, different treatment regimens.
Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide fumarate (Genvoya)	*HIV mutations*	EMA	**Indication**: Genvoya is indicated for the treatment of HIV-1 infection without any known mutations.
		FDA	Pharmacogenomic information.
Glecaprevir / pibrentasvir (Maviret)	*HCV genotype*	EMA	**Strong recommendation**: Recommended Maviret treatment durations for HCV genotype 1, 2, 3, 4, 5, or 6 infected patients with compensated liver disease (with or without cirrhosis).
		FDA	n.a.
Hydroxychloroquine (Plaquenil)	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: G6PD deficiency.
		MEB	**Recommendation**: Be cautious in patients with G6PD deficiency.
		FDA	**Recommendation**: Plaquenil should be administered with caution in patients having G6PD deficiency.
Isoniazid, Pyrazinamide, and Rifampin	*Nonspecific (NAT)*	EMA	n.a.
		FIDMD	**Recommendation** for isoniazid (single compound): monitor serum isoniazid in slow acetylators.
		MEB	**Strong recommendation for Isoniazid:** Pyridoxin prophylaxis (10-15 mg/day) should be administered in adult with isoniazid doses higher than 5 mg/kg bodyweight per day, in slow acetylators.
		FDA	Pharmacogenomic information.

Ledipasvir and Sofosbuvir (Harvoni)	*HCV genotype*	EMA	**Strong recommendation**: For HCV genotype-specific activity.
		FDA	**Strong recommendation:** For HCV genotype-specific activity.
Maraviroc (Celsentri, Selzentry)	*CCR5*	EMA	**Indication**: In combination with other antiretroviral medicinal products for patients infected with only CCR5-tropic HIV-1 detectable.
		FDA	**Indication**: In combination with other antiretroviral agents for patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.
Nalidixic Acid	*G6PD*	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation**: Caution should be observed in patients with G6PD deficiency.
Nitrofurantoin	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: G6PD deficiency.
		MEB	**Recommendation dealing with absolute contraindication:** G6PD deficiency.
		FDA	Pharmacogenomic information.
Ombitasvir, Paritaprevir, and Ritonavir (Viekirax, Technivie)	*HCV genotype*	EMA	**Strong recommendation**: Recommended regimens with different HCV genotypes. The efficacy of Viekirax has not been established in patients with HCV genotypes 2, 3, 5 and 6. Therefore Viekirax should not be used to treat patients infected with these genotypes.
		FDA (discontinued)	**Strong recommendation**: specific treatment regimen for HCV genotype 4.
Peramivir (Alpivab)	Influenza virus genotype	EMA	**Recommendation**: Available information on influenza drug susceptibility should be taken into account when deciding whether to use peramivir.
		FDA	Pharmacogenomic information.
Sofosbuvir	*HCV genotype*	EMA	**Strong recommendation**: Treatment regimen is determined based on HCV genotype.
		FDA	**Strong recommendation**: Treatment regimen is determined based on HCV genotype.
Sofosbuvir, velpatasvir and voxilaprevir (Vosevi)	*HCV genotype*	EMA	**Strong recommendation**: Treatment regimen is determined based on HCV genotype.
		FDA	**Strong recommendation**: Treatment regimen is determined based on HCV genotype.
Sulfamethoxazole and Trimethoprim	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication:** G6PD deficiency.
		MEB	**Recommendation**: Patients with G6PD deficiency should not receive co-trimoxazol, unless strictly necessary and in this case at the lowest possible dose.

		FDA	Pharmacogenomic information.
Sulfadiazine	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication:** G6PD deficiency.
		MEB	**Recommendation**: Patients with (suspected) G6PD deficiency should be monitored.
		FDA	Pharmacogenomic information.

Abbreviations: CCR5, C-C chemokine receptor type 5; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); G6PD, glucose-6-phosphate dehydrogenase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MEB, Medicines Evaluation Board (CBG-MEB); NAT, N-acetyltransferase 1.

Table S6. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to other ATC group L (**Antineoplastic and immunomodulating agents**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Abemaciclib (Verzenios)	*ESR, PGR, ERBB2 (HER2)*	EMA	**Indication**: HR-positive and HER2-negative breast cancer patients.
		FDA	**Indication**: HR-positive and HER2-negative breast cancer patients.
Ado-Trastuzumab Emtansine (Kadcyla)	*ERBB2 (HER2)*	EMA	**Indication:** HER2-positive metastatic breast cancer patients.
		FDA	**Indication:** HER2-positive metastatic breast cancer patients.
Afatinib (Giotrif, Gilotrif)	*EGFR*	EMA	**Indication**: EGFR TKI-naïve patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s).
		FDA	**Indication**: Non-resistant EGFR mutations in patients with metastatic NSCLC.
Alectinib hydrochlorid (Alecensa)	*ALK*	EMA	**Indication**: Patients with ALK-positive advanced NSCLC.
		FDA	**Indication**: Patients with ALK-positive metastatic NSCLC.
Anastrozole (Arimidex)	*ESR, PGR*	EMA	n.a.
		FIDMD	**Indication**: Treatment of HR-positive advanced breast cancer in postmenopausal women.
		MEB	**Indication**: Postmenopausal women with HR-positive breast cancer.
		FDA	**Indication**: Adjuvant treatment of postmenopausal women with HR-positive early breast cancer. First-line treatment of postmenopausal women with HR-positive or HR unknown locally advanced or metastatic breast cancer.
Arsenic trioxide (Trisenox)	*PML-RARA*	EMA	**Indication**: Trisenox is indicated for induction of remission, and consolidation in patients with relapsed/refractory acute promyelocytic leukaemia characterised by the presence of the t(15;17) translocation and/or the presence of the PML-RARA.
		FDA	**Indication:** Trisenox is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML-RARA gene expression.
Atezolizumab (Tecentriq)	*CD274 (PD-L1)*	EMA	**Indication**: Patients with locally advanced or metastatic urothelial carcinoma whose tumours have a PD-L1 expression ≥ 5%.

		FDA	**Indication**: Patients with locally advanced or metastatic urothelial carcinoma whose tumors express PD-L1 covering ≥ 5%.
Belinostat (Beleodaq)	*UGT1A1*	EMA	n.a.
		FDA	**Recommendation**: Reduction of starting dose to 750 mg/m2 in patients known to be homozygous for the *UGT1A1*28* allele.
Binimetinib (Mektovi)	*BRAF V600*	EMA	**Mandatory:** Before taking binimetinib in combination with encorafenib, patients must have BRAF V600 mutation confirmed by validated test.
		FDA	**Indication**: In combination with encorafenib for the treatment of melanoma with a BRAF V600E or V600K mutation.
Blinatumomab (Blincyto)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication:** Patients with Philadelphia chromosome-negative CD19 positive relapsed or refractory B-precursor ALL.
		FDA	**Indication**: Patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.
Bosutinib (Bosulif)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication**: Patients with Philadelphia chromosome-positive chronic myelogenous leukaemia.
		FDA	**Indication**: Patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive CML.
Brigatinib (Alunbrig)	*ALK*	EMA	**Indication**: Patients with ALK-positive advanced NSCLC.
		FDA	**Indication:** Alunbrig is indicated for the treatment of patients with ALK-positive metastatic NSCLC.
Celecoxib	*CYP2C9*	EMA	**Recommendation***: Patients who are known or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution, as the risk of dose-dependent adverse effects is increased. Consider starting treatment at a reduced dose.
		FDA	**Recommendation**: Patients who are known or suspected to be poor CYP2C9 metabolizers initiate treatment with half of the lowest recommended dose. In patients with juvenile rheumatoid arthritis who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments.
Ceritinib (Zykadia)	*ALK*	EMA	**Indication**: First-line treatment of adult patients with ALK-positive advanced NSCLC.
		FDA	**Indication:** Patients with metastatic NSCLC whose tumors are ALK-positive.

Cetuximab (Erbitux)	*EGFR/RAS*	EMA	**Indication:** Patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer.
		FDA	**Indication**: Patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer.
Cobimetinib hemifumarate (Cotellic)	*BRAF V600*	EMA	**Mandatory**: Before starting this treatment, patients must have BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test.
		FDA	**Indication**: Patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.
Crizotinib (Xalkori)	*ALK / ROS1*	EMA	**Indication**: Patients with ALK-positive advanced NSCLC. Patients with ROS1-positive advanced NSCLC.
		FDA	**Indication**: Patients with metastatic NSCLC whose tumors are ALK-positive. Patients with metastatic NSCLC whose tumors are ROS1-positive.
Dabrafenib (Tafinlar)	*BRAF V600*	EMA	**Mandatory**: Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test.
		FDA	**Indication**: Monotherapy for patients with unresectable or metastatic melanoma with BRAF V600E mutation. In combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
	G6PD	EMA	No information.
		FDA	**Recommendation**: Monitor patients with G6PD deficiency for signs of hemolytic anemia.
	RAS	EMA	**Recommendation:** The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation.
		FDA	**Strong recommendation**: Permanently discontinue Tafinlar in patients who develop RAS mutation-positive non-cutaneous malignancies.
Dacomitinib (Vizimpro)	*EGFR*	EMA	**Indication**: Patients with locally advanced or metastatic NSCLC with EGFR-activating mutations.
		FDA	**Indication**: Patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations.
Dasatinib (Sprycel)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication**: Patients with Philadelphia chromosome positive (Ph+) CML, Ph+ acute lymphoblastic leukaemia and lymphoid blast CML. Paediatric patients with Ph+ CML.
		FDA	**Indication**: Patients with newly diagnosed Ph+ CML in chronic phase.

			• chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. • Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.
Denileukin Diftitox (Ontak)	*IL2RA (CD25 antigen)*	EMA	n.a.
		FDA	**Indication**: Patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the Il-2 receptor.
Durvalumab (Imfinzi)	*CD274 (PD-L1)*	EMA	**Indication:** Patients with locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells.
		FDA	Pharmacogenomic information.
Enasidenib (Idhifa)	*IDH2*	EMA	n.a.
		FDA	**Indication**: Patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation.
Encorafenib (Braftovi)	*BRAF V600*	EMA	**Mandatory**: Before taking encorafenib in combination with binimetinib, patients must have BRAF V600 mutation confirmed by a validated test.
		FDA	**Indication**: In combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
Erlotinib (Tarceva)	*EGFR*	EMA	**Indication**: Patients with locally advanced or metastatic NSCLC with EGFR activating mutations.
		FDA	**Indication**: Patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
Everolimus (Afinitor)	*ERBB2 (HER2)/ESR, PGR (HR)*	EMA	**Indication**: Afinitor is indicated for the treatment of HR-positive, HER2/neu negative advanced breast cancer.
		FDA	**Indication**: Postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane.
Exemestane (Aromasin)	*ESR, PGR (HR)*	EMA	n.a.
		FDA	**Indication**: Postmenopausal women with estrogen-receptor positive early breast cancer.
Flutamide	*G6PD*	EMA	n.a.
		FDA	**Recommendation**: In patients susceptible to aniline toxicity (e.g., persons with G6PD deficiency), monitoring of methemoglobin levels should be considered.
Fulvestrant (Faslodex)	*ERBB2*	EMA	**Indication**: In combination with palbociclib for the treatment of HR-positive, HER2-negative

	(HER2)/ESR, PGR (HR)		locally advanced or metastatic breast cancer in women.
		FDA	**Indication**: Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women.
Gefitinib (Iressa)	*EGFR*	EMA	**Indication**: Patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK.
		FDA	**Indication**: Patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
	CYP2D6	EMA	**Recommendation**: Monitoring for adverse events in poor metabolizers.
		FDA	**Recommendation**: Monitoring for adverse reactions in poor metabolizers.
Gemtuzumab ozogamicin (Mylotarg)	*CD33*	EMA	**Indication**: In combination with daunorubicin and cytarabine for previously untreated, de novo CD33-positive acute myeloid leukaemia.
		FDA	No information.
Gilteritinib (Xospata)	*FLT3*	EMA	n.a.
		FDA	**Indication**: Patients who have relapsed or refractory acute myeloid leukemia with FMS-like tyrosine kinase 3 (FLT3) mutation.
Goserelin	*ESR, PGR (HR)*	EMA	n.a.
		FIDMD	No information.
		MEB	**Indication**: Hormone receptor-positive metastasised breast cancer in pre- and perimenopausal women, combined with tamoxifen.
		FDA	Pharmacogenomic information.
Ibrutinib (Imbruvica)	*Chromosome 17p*	EMA	Pharmacogenomic information.
		FDA	**Indication**: Imbruvica is indicated for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma with 17p deletion.
Imatinib (Glivec)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication**: Patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) CML, lymphoblastic leukaemia (Ph+ ALL), relapsed or refractory Ph+ ALL.
		FDA	**Indication**: Patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase, chronic myeloid leukemia in blast crisis, accelerated phase, relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia. Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
	KIT	EMA	**Indication**: Patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors or patients who are at significant risk of relapse following

			resection of Kit (CD117)-positive GIST.
		FDA	**Indication**: Patients with aggressive systemic mastocytosis without the D816V c-Kit mutation. Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. Patients following complete gross resection of Kit (CD117) positive GIST.
	FIP1L1-PDGFRA	EMA	**Indication**: Patients with advanced hypereosinophilic syndrome and/or chronic eosinophilic leukaemia with FIP1L1-PDGFR-alpha rearrangement.
		FDA	**Indication**: Patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
Inotuzumab ozogamicin (Besponsa)	*BCR-ABL1 (Ph+)*	EMA	**Indication**: Patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL.
		FDA	**Indication**: Patients with Relapsed or Refractory ALL – INO-VATE ALL Eligible patients are ≥ 18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL.
Ipilimumab (Yervoy)	*Microsatellite Instability, Mismatch Repair*	EMA	No information.
		FDA	**Indication**: In combination with nivolumab for patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient metastatic colorectal cancer.
Ivosidenib (Tibsovo)	*IDH1*	EMA	n.a.
		FDA	**Indication:** Patients with relapsed or refractory acute myeloid leukemia with a susceptible IDH1 mutation.
Lapatinib (Tyverb/Tykerb)	*ERBB2 (HER2)*	EMA	**Indication**: Patients with breast cancer, whose tumors overexpress HER2.
		FDA	**Indication**: In combination with capecitabine for patients with advanced or metastatic breast cancer whose tumors overexpress HER2.
	ESR, PGR (HR)	EMA	**Indication**: In combination with trastuzumab for patients with HR-negative metastatic disease.
		FDA	**Indication**: In combination with letrozole for the treatment of postmenopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
Larotrectinib (Vitrakvi)	*NTRK*	EMA	n.a.
		FDA	**Indication**: Patients with solid tumors that have a neurotrophic receptor tyrosine kinase gene

			fusion without a known acquired resistance mutation.
Lenalidomide (Revlimid)	*Chromosome 5q*	EMA	No information.
		FDA	**Indication**: Patients with transfusion-dependent anemia associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
Letrozole (Femara)	*ESR, PGR (HR)*	EMA	n.a.
		FDA	**Indication**: Postmenopausal women with HR-positive early breast cancer.
Lorlatinib (Lorbrena)	*ALK*	EMA	n.a.
		FDA	**Indication**: Lorbrena is indicated for the treatment of patients with ALK-positive metastatic NSCLC.
Midostaurin (Rydapt)	*FLT3 mutation*	EMA	**Mandatory**: Before taking midostaurin, AML patients must have confirmation of FLT3 mutation using a validated test.
		FDA	**Indication**: In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for patients with newly diagnosed AML who are FLT3 mutation-positive.
Mycophenolic Acid (Myfortic)	*HPRT1*	EMA	n.a.
		FDA	**Recommendation**: Avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase.
Necitumumab (Portrazza)	*EGFR*	EMA	**Indication**: In combination with gemcitabine and cisplatin chemotherapy patients with locally advanced or metastatic EGFR expressing squamous NSCLC.
		FDA	No information.
Neratinib (Nerlynx)	*ERBB2 (HER2)*	EMA	**Mandatory**: Before Nerlynx is used, your cancer must have been tested to show it is HER2-positive. You must also have previously been treated with trastuzumab.
		FDA	**Indication**: Patients with extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer.
Nilotinib (Tasigna)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication**: Patients with newly diagnosed Philadelphia chromosome positive CML in the chronic phase or chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.
		FDA	**Indication**: Patients with newly diagnosed Philadelphia chromosome positive CML (Ph+) in chronic phase or Philadelphia chromosome

			positive CML (Ph+) in chronic phase and accelerated phase.
Nivolumab (Opdivo)	*BRAF V600*	EMA	Pharmacogenomic information.
		FDA	**Indication:** Patients with BRAF V600 wild-type unresectable or metastatic melanoma or BRAF V600 mutation-positive unresectable or metastatic melanoma.
	Microsatellite Instability, Mismatch Repair	EMA	No information.
		FDA	**Indication:** Monotherapy or in combination with ipilimumab for patients 12 years and older with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer.
Olaparib (Lynparza)	*BRCA/ERBB2 (HER2)/ESR, PGR (HR)*	EMA	**Mandatory**: Patients must have confirmation of a deleterious or suspected deleterious BRCA mutation (either germline or tumour) before Lynparza treatment is initiated.
		FDA	**Indication:** Patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. Or in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
Osimertinib (Tagrisso)	*EGFR*	EMA	**Indication**: Patients with locally advanced or metastatic NSCLC with activating EGFR mutations or the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
		FDA	**Indication**: Patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.
Palbociclib (Ibrance)	*ESR, PGR (HR)/ERBB2 (HER2)*	EMA	**Indication:** Patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy.
		FDA	**Indication:** Patients of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or fulvestrant in women with disease progression following endocrine therapy.
Panitumumab (Vectibix)	*KRAS/NAS*	EMA	**Indication**: Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer.
		FDA	**Indication**: Vectibix is indicated for the treatment of patients with wild-type RAS metastatic colorectal cancer.

Peginterferon-alfa-2a	*HCV genotype*	EMA	**Strong recommendation**: Treatment duration based on HCV genotypes.
		FDA	**Strong recommendation**: Treatment duration based on HCV genotypes.
Pembrolizumab (Keytruda)	*PD-L1/EGFR/ALK*	EMA	**Indication**: First-line treatment of metastatic NSCLC in adults whose tumors express PD-L1 with a ≥ 50% tumor proportion score with no EGFR or ALK positive tumor mutations. Monotherapy for treatment of locally advanced or metastatic NSCLC in adults whose tumors express PD-L1 with a ≥ 1% TPS.
		FDA	**Indication**: Patients with metastatic NSCLC whose tumors have high PD-L1 expression with no EGFR or ALK genomic tumor aberrations.
	Microsatellite Instability, Mismatch Repair	EMA	No information.
		FDA	**Indication**: Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient.
Pertuzumab (Perjeta)	*ERBB2 (HER2)*	EMA	**Mandatory**: Patients must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry and/or a ratio of ≥ 2.0 by in situ hybridisation.
		FDA	**Indication:** Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Perjeta therapy.
Ponatinib (Iclusig)	*BCR-ABL1 (Ph chromosome)*	EMA	**Indication**: Patient with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) or who have the T315I mutation.
		FDA	**Indication**: Patients with chronic phase, accelerated phase, or blast phase CML or Philadelphia chromosome positive acute lymphoblastic leukemia. Patients with T315I-positive CML or T315I positive Ph+ ALL.
Ribociclib succinate (Kisqali)	*ESR, PGR (HR)/ERBB2 (HER2)*	EMA	**Indication**: Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant.
		FDA	**Indication**: In combination with an aromatase inhibitor or fulvestrant for the treatment of pre/perimenopausal or postmenopausal women, with HR-positive, HER2-negative advanced or metastatic breast cancer.
Rituximab (Blitzima)	*MS4A1 (CD20 antigen)*	EMA	**Indication**: Patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma.
		FDA	**Indication**: Patients with CD20-positive relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. In combination with fludarabine and cyclophosphamide, for the treatment of patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia.

Rucaparib (Rubraca)	*UGT1A1*	EMA	**Recommendation**: Caution should be used when co-administered with UGT1A1 substrates to patients with UGT1A1*28 (poor metabolizer) due to a possible increase in the exposure of SN-38.
		FDA	No information.
	BRCA	EMA	**Mandatory:** Before taking Rubraca as treatment for relapsed or progressive EOC, FTC, or PPC, patients must have confirmation of deleterious germline or somatic mutations in the breast cancer 1 or breast cancer 2 gene using a validated test.
		FDA	**Indication:** Patients with deleterious BRCA mutation (germline and/or somatic)- associated epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Strimvelis	*ADA-SCID*	EMA	**Indication**: Patients with severe combined immunodeficiency due to ADA-SCID, for whom no suitable human leukocyte antigen-matched related stem cell donor is available.
		FDA	n.a.
Talazoparib (Talzenna)	*BRCA/ERBB2 (HER2)*	EMA	n.a.
		FDA	**Indication**: Patients with deleterious or suspected deleterious germline breast cancer susceptibility gene -mutated HER2-negative locally advanced or metastatic breast cancer.
Tivozanib (Fotivda)	*VEGFR/mTOR*	EMA	**Indication:** Patients with advanced renal cell carcinoma and for adult patients who are VEGFR and mTOR pathway inhibitor-naive.
		FDA	n.a.
Toremifene (Fareston)	*ESR*	EMA	**Indication**: Fareston is not recommended for patients with estrogen receptor negative tumours.
		FDA	**Indication**: Patients with metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.
Trametinib (Mekinist)	*BRAF V600*	EMA	**Mandatory:** Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.
		FDA	**Indication**: As single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
	RAS	EMA	**Recommendation**: Consider the benefits and risks before continuing treatment with dabrafenib in patients with a non- cutaneous malignancy that has a RAS mutation.
		FDA	Pharmacogenomic information.
Trastuzumab (Herceptin)	*ERBB2 (HER2)*	EMA	**Mandatory**: HER2 testing is mandatory prior to initiation of therapy.

		FDA	**Indication**: Detection of HER2 protein overexpression is necessary for selection of patients.
	ESR, PGR (HR)	EMA	**Indication**: In combination with an aromatase inhibitor for the treatment of postmenopausal patients with HR-positive MBC.
		FDA	Pharmacogenomic information.
Vandetanib (Caprelsa)	*RET*	EMA	**Recommendation**: For patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.
		FDA	No information.
Vemurafenib (Zelboraf)	*BRAF V600*	EMA	**Mandatory**: Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumor status confirmed.
		FDA	**Indication**: Confirm the presence of BRAF V600E mutation in melanoma tumor specimens prior to initiation of treatment.
	RAS	EMA	**Recommendation:** Consider benefits and risks before administering vemurafenib to patients with a prior or concurrent cancer associated with RAS mutation.
		FDA	Pharmacogenomic information.
Venetoclax (Venclyxto/Venclexta)	*Chromosome 17p del/TP53 mutation*	EMA	**Indication**: Patients with chronic lymphocytic leukemia in the presence of 17p deletion or TP53 mutation or in the absence of 17p deletion or TP53 mutation in adult patients.
		FDA	**Indication**: Patients with chronic lymphocytic leukemia or small lymphocytic lymphoma, with or without 17p deletion.
Vincristine (Marqibo)	*BCR-ABL1 (Ph+)*	EMA	n.a.
		FIDMD	No information.
		MEB	No information.
		FDA	**Indication**: Marqibo is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) ALL.

*Drug withdrawn but SmPC still available.

Abbreviations: ADA-SCID, adenosine deaminase deficiency – severe combined immunodeficiency; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukemia; BRAF, B-Raf proto-oncogene; BCR-ABL1, BCR-ABL1: breakpoint cluster region - abelson murine leukemia viral oncogene homolog 1; CD274, cluster of differentiation 274; CML, chronic myelogenous leukaemia;EGFR , epidermal growth factor receptor; EMA, European Medicines Agency; ERBB2, erb-b2 receptor tyrosine kinase 2; ESR, estrogen receptor gene, FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); FLT3, FMS-like tyrosine kinase 3; FIP1L1-PDGFR, FIP1L1-PDGFR: Factor interacting with PAPOLA and CPSF1 - Platelet-derived growth factor receptor; HCV, hepatits C virus; HER2, human epidermal growth factor receptor 2; HLA-A, major histocompatibility complex, class I, A; HR, hormone receptor; IDH2, isocitrate dehydrogenase-2; IL2RA, Interleukin 2 Receptor Subunit alpha; JRA, juvenile rheumatoid arthritis; KIT, KIT proto-oncogene; KRAS, KRAS proto-oncogene; MEB, Medicines Evaluation Board (CBG-MEB); MS4A1, membrane spanning 4-domains A1; mTOR, mechanistic target of rapamycin; MYCN, MYCN proto-oncogene; NRAS, NRAS proto-oncogene; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1, PGR, progesterone receptor gene; Ph chromosome, Philadelphia

chromosome; PML-RARA, Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha; RAS, RAS proto-oncogen;RET, Rearranged during Transfection; ROS1, ROS proto-oncogene 1; TPMT, thiopurine-S-methyltransferase; UGT1A1, UDP-glucuronosyltransferase 1A1; VEGFR, vascular endothelial growth factor receptor.

Table S7. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group M (**Musculo-skeletal system**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Ataluren	*Dystrophin*	EMA	**Indication**: Patients must have a nonsense mutation in the dystrophin gene as part of their underlying disease state, as determined by genetic testing.
		FDA	n.a.
Carisoprodol (Soma)	*CYP2C19*	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation**: Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration to these patients.
Eteplirsen (Exondys 51)	*DMD*	EMA	n.a.
		FDA	**Indication**: Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
Flurbiprofen	*CYP2C9*	EMA	n.a.
		FIDMD	n.a.
		MEB	No information.
		FDA	**Recommendation**: Reduce the dose of flurbiprofen in patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates.
Lesinurad (Zurampic)	*CYP2C9*	EMA	**Recommendation**: Patients known or suspected to be CYP2C9 poor metabolizers should be treated with caution.
		FDA	**Recommendation**: Use with caution in CYP2C9 poor metabolizers.
Mivacurium (Mivacron)	*BCHE*	EMA	n.a.
		FDA	**Recommendation**: Should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.
Pegloticase (Krystexxa)	*G6PD*	EMA	n.a
		FDA	**Recommendation**: Screen patients at risk for G6PD deficiency prior to starting Krystexxa. Do not administer Krystexxa to patients with G6PD deficiency.
Piroxicam	*CYP2C9*	EMA	n.a.
		FIDMD	n.a.
		MEB	No information.
		FDA	**Recommendation**: Consider dose reduction in patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates.

Abbreviations: BCHE, Butyrylcholinesterase; DMD, Duchenne muscular dystrophy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); G6PD, glucose-6-phosphate dehydrogenase; MEB, Medicines Evaluation Board (CBG-MEB).

Table S8. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group N (**Nervous system**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Amifampridine (Firdapse)	*NAT2*	EMA	Pharmacogenomic information.
		FDA	**Strong recommendation**: Initiate in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage (15 mg/day), monitor for adverse reactions and consider dosage modification.
Articaine and epinephrine	*G6PD/Nonspecific (congenital methemoglobinemia)*	EMA	n.a.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.
Brexpiprazole (Rexulti)	*CYP2D6*	EMA	**Strong recommendation**: Dosing modifications to half the recommended doses is required for patients with known CYP2D6 poor metaboliser status. A quarter of the recommended dose is required while taking strong or moderate CYP3A4 inhibitors.
		FDA	**Strong recommendation**: Dosage adjustment is recommended in known CYP2D6 poor metabolizers. Administer half the usual dose in CYP2D6 poor metabolizers, and a quarter of the usual dose if CYP3A4 inhibitors received concomitantly.
Brivaracetam (Briviact)	*CYP2C19*	EMA	Pharmacogenomic information.
		FDA	**Recommendation**: CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction.
Cevimeline	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction.
Chloroprocaine	*G6PD/nonspecific (congenital methemoglobinemia)*	EMA	n.a.
		FDA	**Recommendation:** If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.
Clobazam	*CYP2C19*	EMA	n.a.
		FDA	**Strong recommendation**: In patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight as tolerated.

Clozapine	*CYP2D6*	EMA	n.a.
		FIDMD	No information.
		MEB	No information.
		FDA	**Recommendation**: Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers.
Deutetrabenazine (Austedo)	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: In patients who are poor CYP2D6 metabolizers, the total daily dosage should not exceed 36 mg (maximum single dose of 18 mg).
Dextromethorphan and Quinidine (Nuedexta)	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: In patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with Nuedexta.
Fosphenytoin (Cerebyx)	*HLA-B*	EMA	n.a.
		FDA	**Recommendation**: Consideration should be given to avoiding Cerebyx as an alternative for carbamazepine in patients positive for *HLA-B*1502.*
Galantamine	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.
Iloperidone (Fanapt)	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: Fanapt dose should be reduced by one-half for poor metabolizers of CYP2D6.
Inotersen (Tegsedi)	*TTR*	EMA	**Indication**: Treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis.
		FDA	**Indication***: Tegsedi is indicated for the treatment of the polyneuropathy of hereditary transthyretinmediated amyloidosis in adults.
Lidocaine and Tetracaine	*Nonspecific (Congenital Methemoglobinemia) /G6PD*	EMA	n.a.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.
Lofexidine	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers.
Mepivacaine	*Nonspecific (Congenital Methemoglobinemia) /G6PD*	EMA	n.a.
		FIDMD	No information.
		MEB	No information.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for

			symptoms and signs of methemoglobinemia is recommended.
Patisiran (Onpattro)	*TTR*	EMA	**Indication**: Onpattro is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.
		FDA	
Ropivacaine	*G6PD/Nonspecific (congenital methemoglobinemia)*	EMA	n.a.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.
Sevoflurane	*Nonspecific (Genetic Susceptibility to Malignant Hyperthermia)*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication:** sevoflurane is contraindicated in patients with known or suspected genetic predisposition to malignant hyperthermia.
		MEB	**Recommendation dealing with absolute contraindication**: Patients with known or suspected genetic susceptibility to malignant hyperthermia.
		FDA	Pharmacogenomic information.
Tetrabenazine (Xenazine	*CYP2D6*	EMA	n.a.
		FDA	**Strong recommendation**: Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of Xenazine above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. In poor CYP2D6, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg.
Thioridazine	*CYP2D6*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: cytochrome P450 2D6 isoenzyme deficiency.
		MEB	n.a.
		FDA	**Recommendation dealing with absolute contraindication**: Contraindicated in patients, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6.
Valbenazine (Ingrezza)	*CYP2D6*	EMA	n.a.
		FDA	**Recommendation**: Consider reducing Ingrezza dose based on tolerability for known CYP2D6 poor metabolizers.
Valproic Acid (Depakene)	*POLG*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication:** Valproate should not be used in patients with mitochondrial disease caused by mutations in the mitochondrial enzyme POLG encoding nuclear gene, such as Alpers-Huttenlocher syndrome, as well as in children

			below the age of two who are suspected of having a POLG-related disease.
		MEB	**Recommendation dealing with absolute contraindication:** in patients with known mutations in POLG.
		FDA	**Recommendation dealing with absolute contraindication**: Contraindicated in patients known to have mitochondrial disorders caused by POLG mutations.
	Nonspecific (Urea Cycle Disorders)	EMA	n.a.
		FIDMD	No information.
		MEB	**Recommendation dealing with absolute contraindication**: in patients with urea cycle disorders.
		FDA	**Recommendation dealing with absolute contraindication**: Depakene is contraindicated in patients with known urea cycle disorders.
Vortioxetine (Brintellix, Trintellix)	*CYP2D6*	EMA	**Recommendation**: CYP2D6 poor and ultra-rapid metabolizer: As for all patients, depending on individual patient response, a dose adjustment may be considered.
		FDA	**Strong recommendation**: the maximum recommended dose of Trintellix is 10 mg/day in known CYP2D6 poor metabolizers.

*: The SmPC from FDA was checked manually, the retrieved information however is not mentioned in the PGx table.

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); G6PD, glucose-6-phosphate dehydrogenase; hATTR amyloidosis, hereditary transthyretin amyloidosis; HLA-B, major histocompatibility complex, class I, B; MEB, Medicines Evaluation Board (CBG-MEB); NAT, N-acetyltransferase; POLG, polymerase gamma; TTR, transthyretin.

Table S9. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to other ATC group P (**Antiparasitic products, insecticides and repellents**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Chloroquine	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: G6PD deficiency.
		MEB	n.a.
		FDA	**Recommendation**: The drug should be administered with caution to patients having G6PD deficiency.
Primaquine	*G6PD*	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation dealing with absolute contraindication:** Severe G6PD deficiency.
	CYB5R	EMA	n.a.
		FIDMD	n.a.
		MEB	n.a.
		FDA	**Recommendation**: Patient with previous idiosyncratic reaction to primaquine phosphate; patient with family or personal history of hemolytic anemia or NADH methemoglobin reductase deficiency: should be observed closely. Discontinue immediately in all patients if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.
Quinine Sulfate	*G6PD*	EMA	n.a.
		FIDMD	**Recommendation dealing with absolute contraindication**: G6PD deficiency.
		MEB	n.a.
		FDA	**Recommendation dealing with absolute contraindication:** G6PD deficiency.
Tafenoquine (Arakoda)	G6PD	EMA	n.a.
		FDA	**Mandatory:** Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing Arakoda.

Abbreviations: CYB5R, cytochrom-b5 reductase; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM);); G6PD, glucose-6-phosphate dehydrogenase; MEB, Medicines Evaluation Board (CBG-MEB); NADH, nicotinamide adenine dinucleotide.

Table S10. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group R (**Respiratory system**). Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Ivacaftor, Lumacaftor/Ivacaftor,Tezacaftor (Orkambi, Symkevi)	*CFTR*	EMA	**Indication**: Patients with CF who are homozygous for the F508del mutation in the CFTR gene.
		FDA	**Indication:** Patients with CF who are homozygous for the F508del mutation in the CFTR gene.
Oxymetazoline and Tetracaine	*G6PD/nonspecific (congenital methemoglobinemia)*	EMA	n.a.
		FDA	**Recommendation**: If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; EMA, European Medicines Agency; FDA, Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase.

Table S11. Comparison of drug labeling in EMA/FM and FDA for drugs belonging to ATC group V (Various) and other ATC groups with less than three drugs. Shortened table, gene-drug interactions that only contain non-actionable labels were excluded.

Drug	Gene	Institution	Therapeutic advice
Lutetium Lu 177 dotatate (Lutathera)	*Somatostatin receptor*	EMA	**Indication**: Patients with unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours in adults.
		FDA	**Indication**: Lutathera is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic.
Methylene Blue	*G6PD*	EMA	n.a.
		FDA	**Recommendation dealing with contraindication**: G6PD deficiency.
Methylthioninium chloride	*G6PD*	EMA	**Recommendation dealing with contraindication**: G6PD deficiency.
		FDA	n.a.
	NADPH	EMA	**Recommendation dealing with contraindication**: Deficiency in NADPH reductase.
		FDA	n.a.
Sodium Nitrite	*G6PD*	EMA	n.a.
		FDA	**Recommendation**: Patients with G6PD deficiency are at increased risk of a hemolytic crisis, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit.
	nonspecific (methemoglobinemia)	EMA	n.a.
		FDA	**Recommendation:** Monitor methemoglobin levels and administer oxygen during treatment whenever possible.
Succinylcholine	*BCHE*	EMA	n.a.
		FIDMD	n.a.
		MEB	**Recommendation**: Take special care in the presence of cholinesterase deficiency or defects.
		FDA	**Strong recommendation**: Should be used with caution, if at all, in patients known/suspected to be homozygous for the atypical plasma cholinesterase gene.
Voretigene neparvovec (Luxturna)	*RPE65*	EMA	**Indication**: Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.
		FDA	**Indication**: Luxturna is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic

			RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

Abbreviations: BCHE, Butyrylcholinesterase; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIDMD, Federal Institute for Drugs and Medical Devices (BfArM); , G6PD,glucose-6-phosphate dehydrogenase; MEB, Medicines Evaluation Board (CBG-MEB); NADPH, nicotinamide adenine dinucleotide phosphate; RPE65, retinal pigment epithelium-specific protein 65kDa.

Table S12. Gene-drug interactions that only contain an actionable label by either the EMA/FM or FDA.

Agency	**Drugs**
EMA/FM	Acetylsalicylic acid, carvedilol, caplacizumab, durvalumab, dapsone – G6PD, eluxadoline, elvitegravir, evolocumab, gemtuzumab ozogamicin, glibenclamide – beta-cell, goserelin, isoniazid/pyrazinamide/rifampin, metoclopramide – CYB5R, necitumumab, nitrofurantoin peramivir, ranolazine, rucaparib, sevoflurane, sulfadiazine, sulfamethoxazole, trametinib – RAS, trastuzumab – HR, vandetanib, vemurafenib
FDA	Amifampridine, brivaracetam, ceftriaxone, clozapine, dabrafenib, dapsone – congenital methemoglobinemia, ibrutinib, ipilimumab, lenalidomide, mepivacaine, metoclopramide – G6PD, nivolumab – BRAF, nivolumab – MSI-MR, pantoprazole, pembrolizumab – MSI-MR, piroxicam, tretinoin, vincristine