Old medicines, new indications

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Drug repurposing, which is the process of finding new therapeutic uses for already known drugs and/or developing different formulations for the same drug, has several advantages over the traditional drug development process.
It is faster, has a higher success rate and the costs are lower. However, not much is known about the (dossier)requirements. Only limited guidance is available.

	Traditional drug	Repurposed drug
Approval time	10-17 years	3-12 years
Success rate	~ 10%	~ 30%
Costs	-	50-60% reduction

Aims
To define the required preclinical and clinical support for marketing authorization applications for repurposed drugs in the European Union.

Methods
Repurposed drugs authorized in the period 2000-2017 were identified and Public Assessment Reports of applications with an article 8(3) full-mixed dossier as a legal basis were selected. Next, we evaluated whether the applicants performed their own (pre)clinical studies and/or used data from the literature.

Results
40 PARs have been identified; 28 for a product with a new formulation, 7 for a product with a new indication and 5 for a product with both. For preclinical studies (Table 1), all applicants used data from the literature. For a new indication, 75% of the applicants and 91% for a new formulation performed at least one preclinical study; PK, single– and repeat dose toxicity and local tolerance studies. Only few reproductive toxicity and genotoxicity studies were performed. Whether or not these were carried out was not determined by the guideline.

For clinical studies (Table 2) almost all applicants used data from the literature and all applicants performed at least one clinical study.
Applications without own PK studies were for products with a low systemic exposure. PD studies were not necessary when there was sufficient data available from the literature. Clinical safety and efficacy studies were performed by all applicants.

Table 1: Preclinical studies

Type of preclinical study	New Indication	New formulation	Guideline non-clinical studies full-mixed MAA
Pharmacology	25%	42%	Normally not necessary
Pharmacokinetics	36%	53%	Normally not necessary
Single/repeat dose toxicity (including local tolerance)	50%	82%	Normally not necessary
Reproductive toxicity	27%	23%	Required
Genotoxicity	25%	39%	Required
Carcinogenicity	18%	10%	Normally not necessary

Table 2: Clinical studies

	Type of clinical study	% applicants performing own clinical studies	# own studies	# pivotal studies
New Indication	Pharmacokinetics	75%	1-11	NA
	Pharmacodynamics	0%	0	NA
	Safety/Efficacy	100%	1-6 (average 3-5)	1-3
New formulation	Pharmacokinetics	79%	1-15	NA
	Pharmacodynamics	21%	1-8	NA
	Safety/Efficacy	10%	1-7 (average 1-3)	1-2

Conclusions

Together, our results show that:

- for drug repurposing additional studies are always required;
- although preclinical guidance is available, the characteristics of the drug and the availability of literature determine the preclinical study program;
- clinical safety and efficacy studies are always required and often more than one.