Improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system

The objective of the project is to improve the preclinical predictivity of adverse effects of pharmaceuticals on the central and peripheral nervous systems through increasing our knowledge on mechanisms of neurotoxicity and improving the experimental toolbox. The results would be an integrated prediction/evaluation approach that would include a combination of in silico, in vitro and in vivo models, including safety biomarkers (for peripheral neuropathies). This toolbox would increase the preclinical prediction of adverse effects of drugs throughout all aspects: identification of hazards, characterisation of mechanisms of toxicity, prediction of clinical consequences and possible follow-up in trials with safety biomarkers, and integrated risk-assessment approach for proper decision-making process.

Neurotoxicity (used in the context of this document as “any adverse effect on the central nervous system (CNS) or peripheral nervous system (PNS)”) is poorly predicted by preclinical studies performed on pharmaceuticals during research and development (R&D) process. As a consequence, adverse effects on nervous system are not uncommon during clinical development and post-marketing. This lack of predictability might have two types of consequences:

- for human volunteers/patients, this can lead to a risk of adverse effects during clinical trials or even after marketing;
- for the pharmaceutical industry, this can lead to substantial neurotoxicity-related attrition rates, generally at late stages (clinical phase 2 or 3); according to sources, the figures for this type of attrition are variable, but typically in the range of 5-25%.

Therefore, a better preclinical prediction of adverse effects on nervous system would benefit to human volunteers/patients (by safer drugs) and pharmaceutical industry (by increased productivity).

There is a clear need for a project to deliver on: (i) increased knowledge on mechanisms of neurotoxicity (e.g. establish adverse outcome pathway for each type of neurotoxicity); (ii) better understanding of factors that favour neurotoxicity (pharmacological targets and pathways, physico-chemical properties, pharmacokinetics); (iii) implementing new-found knowledge to improve the current preclinical toolbox, through a combination of high throughput, predictive in silico, in vitro and in vivo models, including safety biomarkers, where appropriate (iiii) combine these tools in an integrated risk assessment approach for better decision-points throughout R&D process, and better protection of human volunteers and patients.

At the level of R&D, regulatory, clinical and healthcare practice the impact would be (i) safer drugs for human volunteers/patients (ii) shortened development timelines, through reduced attrition, reduced testing, and shortened development plans:

- improved subjects/patients safety during clinical trials and after marketing authorisation;
- reduced attrition, especially at late stages of R&D (during clinical trials), for safety reasons related to neurotoxic effects;
- reduced post-marketing events necessitating labelling changes;
- reduced post-marketing events resulting in drug withdrawal;
- greater R&D productivity/shorter timelines;
- lower development costs.

In terms of ethics/animal welfare/3Rs, innovation and integration of new knowledge the impact would be:

- replacement: whenever possible animal models would be replaced by in silico/in vitro models, provided they have at least the same level of prediction;
- refinement and reduction: relevant biomarkers or any other appropriate endpoints would enrich current in vivo animal experiment and help (i) earlier detection and longitudinal follow-up of toxicities before inappropriate animal suffering (ii) decision-making process.

In terms of improving European citizens' health and wellbeing (volunteers and patients), the impact would be:

- lower risk of neurotoxic events during clinical trials, whatever the clinical indication (relating to nervous system or not);
- improved monitoring and risk minimisation procedures during clinical trials;
- drugs with a better risk/benefit ratio.
- In terms of industrial competitiveness the applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

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