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COMMENTARY

Take Care of the Fast-in-Human Study

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INTRODUCTION

Drug developers often evaluate products with an unprecedented mechanism of action, under pressure to bring products to patients fast. The recent tragedy with a fatty-acid amide hydrolase inhibitor raises questions on balancing good science and good business while safeguarding safety and ethical standards. Was the issue with processing information rather than data package? Full disclosure and root cause analysis are called for. Recommendations are made to ensure integration of preclinical learning with the clinical plan.

COMMENTARY

Early in 2016, the drug-developing community was jolted by the unanticipated brain injury in healthy subjects in a study of the fatty acid amide hydroxylase (FAAH) inhibitor BIA-102474. This event has been the subject of various discussions and comments.[1–5] However, in this Commentary the event is discussed in the light of the drug developer's challenge of balancing good science with good business when under pressure, while safeguarding safety and maintaining ethical standards.

All of us active in the discipline of development of novel medicinal products are very privileged and challenged. We are privileged by having the opportunity of working at the forefront of new pathophysiological insight in disease, clinically evaluating novel products that modulate disease pathways in ways never explored before, or, if we are just behind that initial wave of innovation, by learning from recent experience with a predecessor novel molecule.

We are challenged by doing our work in an environment which, if in the setting of industry-sponsored clinical development, is under the relentless pressure of "not-a-day-to-lose." Assuming an 8-year patent protected window for recovering R&D costs and making a fair profit, the debated USD 1 B costs figure per clinical development success implies that the costs of a lost day exceeds a year's salary of a well-paid clinical development leader. Clearly, the ever-present time pressure requires the successful drug developer to balance good science with good business, without compromising safety or ethical standards

The no-time-to-lose pressure can impose a "bar chart-driven" approach to clinical development, as if it were a manufacturing process, with critical path analysis, processes run in parallel, and independent critical milestones, triggering the next development step. Anything interfering with those critical milestones is undesirable and usually causes delay. In early drug development one cause of a potential delay is … new information. For example, data emerging from a preclinical or clinical study that must be digested before the objectives and design of an ongoing or the next study can be finalized and initiated.

New data requiring reassessment of the development plan are the reason we do studies: we learn about the product, and if needed we adjust and improve the plan with the ultimate goal of patient safety and the optimal package insert and label claims in mind. We run the risk, at any phase of development, that new data requiring us to pause, rethink, and reassess the clinical development plan effectively are an unwelcome distraction for those who consider drug development as a tick box exercise in the race through law- and guideline-imposed hurdles prior to marketing approval.

In a recent article, Richard Peck *et al*. made a strong case that promoting "truth-seeking" rather than "progression-seeking" behavior[6] would increase R&D success by learning more in early clinical development. Peck *et al.* cited the main obstacles in effective learning in early clinical development as behavioral, cultural, and organizational; they underscored that a progression-seeking drug development approach contributes to development success if pursued in tandem with adherence to quality criteria. Similar comments were made by European Medicines Agency (EMA)-related authors, referring to deficits in learning in early clinical development contributing to failing development strategies in Europe, along with underfunding, understaffing, and insufficient team experience.[7,8]

Professionals involved in industry-sponsored drug development are exposed to opposing forces, including the scientific need to learn and think, and the pressure to progress. Ironically, both forces are aimed at the same final development goal where science, business, and ethics come together: to develop a medically meaningful product available to patients as soon as possible. Where these forces mismatch, failure may loom.

The Temporary Specialist Scientific Committee (TSSC) reviewing the FAAH inhibitor case made various recommendations. In the absence of key details available on the case in the public domain, including compound information, some comments of the TSSC leave large question marks, and underscore the urgent need of full disclosure of all underlying data, as voiced earlier by Eddleston *et al.*[1] In particular, the TSSC report refers to cerebral damage, including gliosis and inflammatory cell infiltration in the hippocampus in mice

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and rats, and axonal dystrophy in the medulla oblongata in monkeys (p. 10), with the following notes:

- The damage in mice and rats is labeled as "fairly common in rodents in studies of this type" (p. 12).
- The report mentions the neurological damage in general as "initially non-alarming" (p. 12).
- The TSSC states "we do not observe any toxicity […] specifically targeting a given organ" (p. 9).

These statements are difficult to understand when read in isolation in the TSSC report, raising the question whether they will be supported by independent, experienced preclinical safety experts after their review of the full data package.

The protocol of the clinical study with the FAAH inhibitor is in the public domain, originally courtesy of Le Figaro.[9] Page 27 of the protocol declares: "Treatment with BIA 10–2474 produced no signs of toxicity in mice, rats, dogs and monkeys up the no observed adverse effect level (NOAEL) […]." At first glance, this statement may come across as reassuring; the experienced drug developer, however, concludes that this sentence is noninformative, and is simply a rewording of the definition of the NOAEL. The questions arise what this sentence was meant to say, and why it was not replaced by more detail during the various protocol review rounds. Of critical importance, the study protocol made no reference to cerebral damage and axonal dystrophy in the medulla oblongata observed in animals.

In the process flow of clinical drug development, two important documents come together as major pieces in the puzzle of the clinical trial application (CTA): these are the investigator's brochure (IB) and protocol. In the pressurized drug development setting described earlier in this Commentary, both documents are typically written in parallel, possibly by different teams. In order to ensure that both documents are mutually consistent, however, a reading, thinking, and consolidation pause is required, prior to CTA submission. In the FAAH inhibitor case, currently available, limited insight into the event raises a question of timely review of these documents, in particular a thorough review of the clinical study protocol with a timely available, close-to-final IB. It should be noted that a review of a protocol in the absence of such a near final or final IB can at best only look at the logistical aspects of a study.

Presumably at least partly driven by the FAAH inhibitor case, the EMA outlined proposed changes to current guidance on first-in-human clinical trials to further improve strategies to identify and mitigate risks to trial participants.[10] Proposed topics for change comprise good science and good operations: better translation of nonclinical data to the clinical plan, better use of escalation and stopping criteria, and better handling and communication of safety findings. Whether regulation thus updated will essentially reduce the risk of a repeat of the FAAH inhibitor event remains to be seen; if the issue was with the processing of information rather than the volume of information, updated regulation calling for more data will not help.

This Commentary calls for an open and frank scientific discussion of the FAAH inhibitor case, with full public access to the IB and underlying data as needed, and with insight into the flow of information from preclinical data to principal investigator. Thorough understanding of the event and thereby learning from it will contribute to safer and more effective clinical drug evaluation, and will help avoid the creation of off-target revised regulatory guidance.

In conclusion, three key principles in the design of the first clinical evaluation of an experimental product in humans are recommended:

- That there is a single **accountable person (AP)**. Designing a first-in-human study is truly a team effort in which members bring with them various expertise, experience, and backgrounds. However, it is vital that the AP is responsible for integrating all information and ensuring that all pieces fit into one completed puzzle. Key elements of the professional curriculum of this AP are translational medicine, clinical pharmacology, and "first-in-human" experience.
- The **AP signs the IB** in the "first-in-human" package, **and co-signs the protocol** of the clinical study, to ensure consistency between the preclinical dossier and the first evaluation in humans.
- **Good science is the driver** of the process. The process must be compatible with and adhere to applicable regulatory guidance, as it is the crystallization of the collective thinking on good practices in clinical drug development.

Conflict of Interest. The author is an employee of PRA Health Sciences. The author declares no conflicts of interest.

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