

Regulatory Affairs Professionals In Early Clinical Trials

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Abstract

This paper suggests new strategies in the duties of Regulatory Affairs Professionals (RAPs) inside current trends of research and development of new drugs, that is distinguished by many innovative targets and drugs candidates, overlaps basic research and optimization stages with early clinical trials, alliances between universities and private sector with pharmaceutical industries and revolutionary guidelines from regulatory agencies. From the analysis of bibliographic review is identified gaps where Regulatory Affairs Professionals could contribute to improve data to making decision, quality of submission and possibilities of clinical trials success.

Keywords: Regulatory Affairs professionals (RAP); Early clinical trials; Good review practices;

Introduction

The linear model for the development of new medicines is a paradigm almost totally discarded; modifying to an interactive process with overlapping stages and clinical trials before conventional preclinical GLP phase [1-5]. Early clinical trials with microdosis, human research with more than one candidate and concepts of Minimal Anticipated Biological Effect Level as criteria for dose selection have as background, data from basic research, optimization phase, preclinical in vitro studies and limited in vivo studies are some characteristic that distinguish this new context [6, 7].

For this paper was revised all regulatory guidelines on investigational new drugs published from 2003, publications and books on new process for R&D particularly optimization phase and early clinical trials, papers and blogs on regulatory affairs professionals and some papers and news on failed clinical trials.

Changing in research and development process for new drugs and regulatory environment

Innovative targets and drug candidates discover and partially characterize in scientific institutions belonging to governmental and private organizations not directly linked to the pharmaceutical industry is arising as a new source of marketed drugs. As consequence of these new sources have been appeared tendencies of alliances between universities, academies and polytechnic institutes with the pharmaceutical industry that

have generated a new dynamic relationship in the research and development of new medicines outside the industry [8, 9]. Another novelty to facilitate the management of new targets and candidates is the preparation of portfolios as a way to funding access [10-13]. Portfolios are dossiers that contain all basic research, development of drug candidates at laboratory scale, basic pharmacodynamic, pharmacokinetic and safety evaluation, that is presented to access to funding. After evaluation for Group of Expert, considering previously established parameters as probabilities of medical success, novelty, regulatory opportunities, market possibilities, feasibility, between other criteria, the winning portfolios will be part of Project Management System.

The Project Portfolio Management System is an activity inside the industry that is a dynamic decision process to manage multiple projects [13-15]. This management program systematically revise all research and development during R&D process to make "go no-go" decision as soon as possible early stage. The National Regulatory Authorities (NRA) within this environment have been introducing new regulations with specific requirements in the development of trials, others that allow the performance of clinical trials at earlier stages with requirements apparently limited in different clinical scenarios and more than one product under investigation [5-7 & 16-20].

Another aspect added to regulatory context is the improvement of the internal evaluation processes inside Regulatory Agencies, with the introduction of the Good Practices of Review (GRevP) from the World Health Organization (WHO) [21]. The objective of GRevP is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the contents and management of reviews. The Food and Drug Administration (FDA) has also established the procedures of Good Review Practices and considerations about the content of the submission [22, 23]. The pharmaceutical associations have developed the Submission Good Practices and Good Registration Management (GRM) and an extensive process to promote its implementation [21, 24 & 25].

Good Review Practices occurs in two stages, validation and scientific review. The validation stage occurs first, with the aim of ensuring completeness of the application in order to facilitate the subsequent scientific review [21, 22]. Validation involves an

examination of the application to ensure that it is well organized and that all the required forms and relevant documents have been submitted. The identification of missing information in the application prior to scientific review enables the National Regulatory Authority (NRA) to avoid spending time and review resources on an application that does not allow critical analysis, signal identification or regulatory decision-making.

Scientific review core competency starts with reviewers scientifically trained. Reviewers should have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy and/or quality in order to achieve a good understanding of the issues likely to be associated with the product under review [21, 22]. NRA could invite external experts for the scientific assessment as part of critical thinking. Invitation should include experts from academic institutions, industry associations, patient organizations and medical and scientific organizations with expertise that may be useful to the review.

All these Good Review Practices, as a whole, point to the need for greater integration between the scientific working groups of the research-development project and the RAP. One regulatory submission is not a compilation of reports, it is a mirror of all process and its appropriate building must be corresponding to an appropriated and integrated project.

Regulatory affairs professional inside this new environment

Miller and Cocchetto, described expectation and activities for Regulatory Affairs Professional (RAP) inside a pharmaceutical industry involved in R&D of new drugs [27],

They identify as minimal tasks that they classified as hardware:

- Knowledge and ability to interpret regulations
- Communication capacity to inform the research team of the content required for the application dossier for regulatory proceedings.
- Provide a table of contents for this dossier
- Inform the established times for regulatory procedures

They cataloged other task as software, less tangible but with a significant contribution and they are:

- Transmit the regulatory breath within the multidisciplinary team
- The ability to predict the updating movement and regulatory innovation
- Suggest taking advantage of the regulations governing accelerated approval of certain new drugs,
- Ability to serve as a productive, constructive and credible liaison between sponsor and regulators.
- Disseminating specific and pertinent information to development and drug approval

- Regulatory intelligence on any information on competitive products and their basis for approval

This innovative proposal was published in 1997 when the conception of RAPs was only as specialized secretaries. At that time, the regulatory requirements for clinical trials in the chemical-pharmaceutical and preclinical aspects were much more extensive, and generated entirely within the industry and could take development periods of 7 to 10 years [27].

The activities for the RAPs today are described with much more extension, but in essence these papers reflect the content previously described [28, 29]. Today there is a better understanding of the needs of these type of specialists in companies. Companies request specific skills for the RAPs and there are offers for training and certifications, with appropriate expectations for their job.

However, in the proposal of Miller and Cocchetto appear two approaches that are not in the most current criteria and aligned with our vision [27].

They are:

- Transmit the regulatory breath within the multidisciplinary team and
- “The RAP must have critical input to the project team to assure selection of robust endpoints that meet both scientific and regulatory needs. This may be accomplished by helping to build consensus among scientists, providing the scientists on the team with summaries of regulatory precedents” [27].

Current challenges for the RAPs and proposed duties in this new environment

What are current challenges that RAPs confront in the context of alliance universities-private center-pharmaceutical industry during R&D new drug process?

In the new millennium, there are suggestive changes in the beginning of clinical trials. Clinical studies with microdose and other exploratory studies propose new alternatives [30, 31]. The fundamental characteristic is that, the information required for the start clinical studies proceed from basic and optimization phase of R&D, prior to the Good Laboratory Practices Phase (traditional pharmacology, pharmacokinetic and toxicology studies) [7, 32-35]. The requirements for the request for regulatory clinical trial authorization apparently reduced, but they have been modified and made more precise with greater introduction of new technologies. In response to this new vision, Regulatory bodies have introduced more specific and defined requirements for risk management when using this investigational drug [33].

ICH Topic M3 (R2) regulation, Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, describes some possible scenarios for exploratory clinical studies [6]. In all them regulatory requirement specify, “In vitro target / receiver profiling should be conducted. Appropriate characterization of primary pharmacology (mode of action and / or effects) in a pharmacodynamically relevant model

should be available to support human dose selection”

For example, regulatory bodies consider as a risk factor, novelty and extent of the supposed mode of action, including the nature and intensity (extent, amplification, duration, reversibility) of the effect of the medicinal product on the specific target and non-targets and subsequent mechanisms, and could ask on the knowledge about this concern. For Regulatory Authority it is a risk factor [33]. Other example of this kind of information is the impact of polymorphisms on the pharmacological effects of the medicinal candidate³³. All these information have impact in design risk control inside clinical trial protocol.

Comparison between requirements from both regulations shown the level of details to give complete technical report [6, 33].

All these aspects represent a significant challenge for the RAPs. These data are the background for clinical trial protocol design and relevant regulatory decisions, and the RAP must organize clinical trial submission giving data from a context not habituate to regulatory practices. Researchers usually don't give methodological details, because they consider that their methods are well known and accepted, but for regulatory bodies these information have great relevance [36]. Sponsor could need respond about it, many years after completion of study. That situation could be a great problem that should affect regulatory acceptance.

Other example could be Good Laboratory Practices for “in vitro” studies, this guideline has specific requirements between them [37]:

- Data on validity of the qualification of the equipment, the solutions and reagents during research and the documented evidence about them.
- Documentation on characterization all the test substance used.
- Demonstrated training of personnel for conducting the experiments.
- Supplier's evaluation documented
- Collection and preservation of the original data, according specific requirements
- Ability to archive and retrieve data, documents and specimens

These and other specifications, although applied in Universities and Institutes, do not usually require the regulatory precision, documented and kept in archives for many years, as required in the regulatory context.

What could RAPs do?

He needs transmitting regulatory breath and interpretation of guidelines to researchers external to industrial pharmaceutical context. Only if they have understood regulatory background, they could cooperate. A RAP will need great communication skills and strong capacity of persuasion to achieve those scientific personalities, with more academic rank and on which RAPs do

not have any authority, want to accept these requirements, and that also the administrative ones, understand and accept the new expenses, time and necessity of additional spaces for storage for long periods.

Additionally, RAP could need asking to scientists including some suggestions during the design stage of the experiment, such as introduction of more doses, any reference substances required as part of the regulatory intelligence process, blinding samples, histological peer review, between other specifications that could seem irrelevant or disturbing to researchers, but critical for regulatory purposes. For studies with laboratory animals, Non-clinical Good Laboratory Practices and ARRIVE guidelines could help to review completeness of report [38, 39 & 40]. This is another relevant point. All information, including raw data, exhaustive description of methods and materials, humane final end point, between others are required in complete individual reports.

Therefore, it may be relevant considering the role of RAPs inside scientific team as functional member. For effective impact is necessary that RAPs develop the capacity to join to the working groups as an assimilated and accepted member, able transmitting regulatory thinking and to serve as a point of contact between all the basic research groups, facilitate, and ensure the free flow of sensible information between the different disciplines and working groups. The acceptance of this new duty of RAP could be part of the process alliance negotiation.

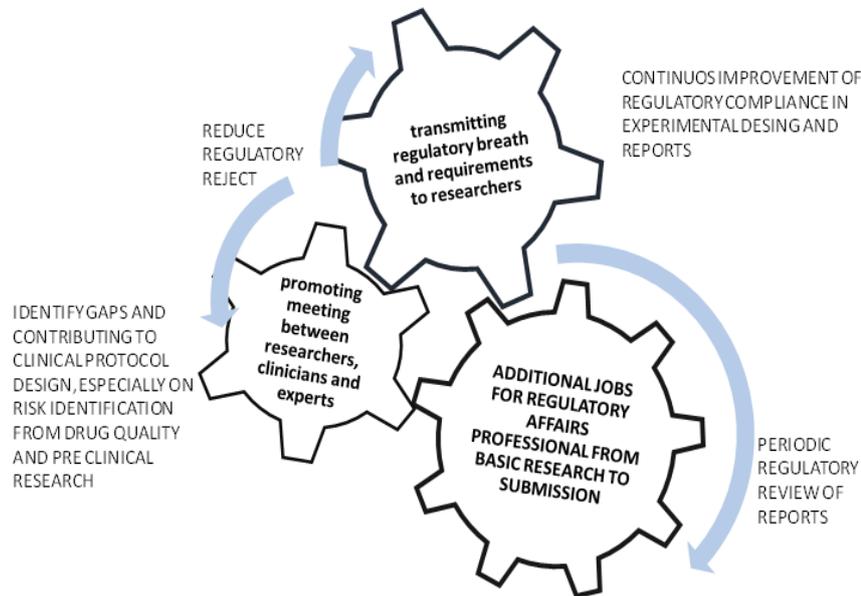
Other insight for RAPs is promoting meeting between researchers, clinicians and experts (including external experts) before and after design of clinical protocol. Risk concern must be taking in consideration inside protocol. Clinicians and researchers need mutual clarification and recognition of information that in clinical and research context could seem not connected. Pharmacodynamic or pharmacokinetic results irrelevant from statistical context could be biological impact that is more different for human beings and these possibilities need clarification in multidisciplinary group.

These meeting could help to identify scientific gaps inside overall dossier that it is impossible to detect by RAPs, because technical specialties are excessively specific. Regulatory Authority review will have expert specialized in concrete subjects that looking for total scientific coherence. Reduce time and increase success in regulatory interphase need considering this aspect. This internal regulatory comprehension has a great effect for the development research project and scientific quality of submission. At the level of detail that is performing on today, based on the mechanism of action of the substance and the management of specific targets, only researchers and experts in the field in a multidisciplinary team may be able to identify the lack of coherence or the absence of relevant data for the decision-making.

Therefore, bring the regulatory context closer to the researcher and frequent support of their regulatory understanding and assimilation in specific situations of their work, will be a great opportunity for companies. In turn, these interactions will

generate a positive feedback for the RAP that will allow to him be more efficient in the task of organizing the dossiers and more

effectively support the activity of the Sponsor during clinical trials and response to regulatory bodies and contributing to the Portfolio Management System



Conclusion

In conclusion suggestion of new duties of RAPs could be:

- Revisions of portfolio dossier of drug candidates before expert evaluation for a subvention, particularly, relevance, quality of data and reports and coherence of information.
- For winning portfolio, revision of raw data from target characterization and mechanism of action and all basic research performed, that could be require in the future, according regulatory characteristic of product and diseases to be treated.
- Promote regulatory understanding in researcher groups, particularly Guidance for Industry and Good Practices.
- Promote multidisciplinary meetings, especially before clinical protocol design and before send the submission to NRA.

If its recommendations are understood then, could be pertinent considering all these activities of RAPs during negotiations of alliances with universities and public and private sector.

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