Regulatory Toxicology and Pharmacology 73 (2015) 361–366

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Impact analysis of ICH S9 on non-clinical development of anticancer drugs

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ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form
24 July 2015
Accepted 26 July 2015
Available online 30 July 2015

Keywords:
Oncology
Cancer
Drug development
International Conference for Harmonisation
ICH S9
Centralised procedure
EMA
3Rs
Animal welfare

ABSTRACT

Cancer presents a major healthcare challenge worldwide, with several millions new cases a year, and represents a therapeutic area with a high need for new drugs. To respond to this, the parties of the International Conference for Harmonization agreed in 2007 to develop a guideline on nonclinical requirements for oncology therapeutics' development (ICH S9), which came into effect in early 2010. This guideline includes recommendations to facilitate and accelerate the development and marketing of cancer therapeutic agents for serious and life threatening malignancies and aims to address this need through a refinement and a reduction in the use of experimental animals, following the 3Rs principles. To assess the impact of ICH S9 on drug development and reduction of animal use, we performed an analysis of Marketing Authorization Applications at the European Medicines Agency relevant to the period in which the development of the guideline was approaching the final steps and its early implementation period. From the analysis performed, a consistent trend towards a decrease in the average number of non-clinical studies performed (−40.7%) and number of animals used per development program (−58.1%) for new chemical entities has been detected, highlighting increasing compliance by companies to the recommendations of ICH S9.

1. Introduction

Cancer presents a major health care challenge worldwide, with several million new cases a year. It represents around a quarter of all deaths, and has a tremendous human cost in every country (WHO Global status report, 2010).

For the above-mentioned reasons a high need for new therapeutic options is present in this therapeutic field. To respond to this global need and to speed up access to new medicines, the parties of the International Conference for Harmonisation (ICH) agreed in 2007 (International Conference for Harmonisation, 10 May 2007) to begin a harmonization process of non-clinical requirements for oncology therapeutics' development. The final outcome of this process was the coming into effect in early 2010 in all ICH regions of the S9 Guideline (ICH Topic S9, 2008). This guideline includes recommendations to facilitate and accelerate the development and marketing of cancer therapeutic agents for the treatment of primary cancers – more specifically serious and life threatening malignancies - in order to address the state of disharmony present in guidance and practices at international level. This guideline also aims to address the above mentioned disharmony through a refinement and a reduction in the use of experimental animals in an area of extensive drug research and development, following the 3Rs principle (Russell and Burch, 1959). This takes into account that in the development of anticancer drugs, clinical studies often involve cancer patients whose condition is progressive and fatal. In addition, the dose levels in these clinical studies often are close to or at the adverse effect dose levels.

A fundamental point during the development of the ICH S9 guidance related to the definition of the scope of this guidance – i.e. what is considered to be a *"serious and life threatening malignancy"* – and exclusion criteria for its applicability. It was agreed that this guidance would describe the minimal considerations for initial clinical trials in patients with advanced cancer and whose disease is refractory or resistant to available therapy, or where current therapy is not considered to be providing benefit.

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http://dx.doi.org/10.1016/j.yrtph.2015.07.022
0273-2300/

In order to assess the impact of ICH S9 on medicinal product development, an analysis has been performed on data extracted from drug developers' submissions for Marketing Authorization Application (MAA) at the European Medicines Agency (EMA). By analyzing this material we have tried to define to what extent guideline ICH S9 has led to a paradigm shift in regards to the quantity of non-clinical data considered adequate to support the development and marketing of anticancer medicinal products. The data we analyze cover the period in which the development of the guideline was approaching the final steps - i.e. Step 4 (scientific consensus, reached in end 2009) and Step 5 (regional implementation) - of the ICH process up to end of 2013. In the context of this analysis we also try to quantify the impact of this guideline on animal welfare, in terms of 3Rs compliance.

2. Methods

The data used for the analysis of trends of non-clinical studies performed to support initial MAAs for new anticancer pharmaceuticals was extracted from the EMA records for MAA submissions, which are provided by companies in Electronic Common Technical Document (eCTD) format since 2008. For every initial MAA submission for anticancer pharmaceuticals resulting in a positive opinion from EMA for the period 2008–2013, eCTD Modules 2 and 4 (The Common Technical Document) were reviewed in order to identify the type of studies performed and the number of animals used in these studies. For products for which an electronic submission could not be retrieved, manual search for information was performed within the CTD. For the preliminary analysis on the quantity of medicinal products approved in the EU overall and for cancer treatment we considered all new Marketing Authorisations granted by the EMA between 2008 and 2013 (excluding Advance Therapy Medicinal Products and vaccines). Pharmaceuticals intended for cancer indications falling outside the scope of ICH S9 are excluded, as also applicable for medicinal products being developed for prevention, treatment of symptoms or side effects of chemotherapeutics.

When looking at the content of MAA submissions for anticancer medicinal products (i.e. number of studies performed and animals used per development program) some subsets of medicinal product where excluded such as biotechnology-derived products (given the major differences in non-clinical development for these and also in view of the overlap with other applicable guidelines, such as ICH S6) and MAA submissions for old molecules which were recently developed for a cancer indication that referred to published literature references or to old studies. Furthermore, development programs for medicinal products containing more than one active substance were also excluded to allow a meaningful comparison. When reviewing the content of the MAA submissions, the following subsets of *in vivo* studies were considered for analysis:

- Safety Pharmacology studies to investigate Cardiovascular, Respiratory or Central Nervous System function – e.g. as per ICH S7A and ICH S7B
- Definitive Repeated-dose Toxicity studies of one month duration or more (with minor adaptations needed for medicinal products intended to be administered with particular dosing schemes)
- Reproductive Toxicity studies (both dose-range finding and definitive studies)
- Genotoxicity studies
- Carcinogenicity studies (i.e. 2-year carcinogenicity studies or 6-months studies performed in transgenic animals)

3. Results

3.1. New medicines approved in the EU for oncology indications

The EMA issued positive opinions to MAAs for an overall of 165 new medicines between 2008 and 2013. Within these 23.6%, an overall number of 39 new medicines have been approved for the treatment of cancer in patient populations where ICH S9 would be considered applicable (Fig. 1). Of these, 29 were MAAs for new chemical entities, four were biotechnology-derived products, three were old chemical entities recently developed for a cancer indication, two were antibody drug-conjugates and one application contained a combination of two active substances.

3.2. Number of studies performed and animals used per drug development program

Following the exclusion and inclusion criteria as defined in Materials and Methods, the overall number of development programs considered for analysis consisted of 31 anticancer pharmaceuticals, of which 7 in 2008–09, 8 in 2010–11 and 16 in 2012–13. Data from study reports contained in eCTD submissions to EMA were extracted and analyzed for 31 development programs. The average number of studies performed per drug development program (both in total and for each of the various study subsets relevant for this analysis) and the corresponding number of animals used can be seen in Tables 1 and 2. Of note, these results are grouped in two-year intervals for a period which encompasses the moment (mid-2010) when the ICH S9 Guideline came into effect. The tables demonstrate a constant reduction in number of studies performed (−40.7%) and animal used (−58.1%) across the period considered. Graphical representation for the average number of studies performed and number of animals used per development program in total is shown in Fig. 2.

3.3. Analysis of number of studies performed and animals used by subtype of non-clinical study

Taking a look at the single subsets of Non-Clinical *in vivo* studies underlying the overall numbers shown above, different scenarios were observed. As shown in Fig. 3 for safety pharmacology studies, a clear trend for reduction in the number of studies can be seen (−52.2%) together with a corresponding decrease in animal use (−49.3%).

Looking at Repeated-Dose toxicity studies (RDT), no notable

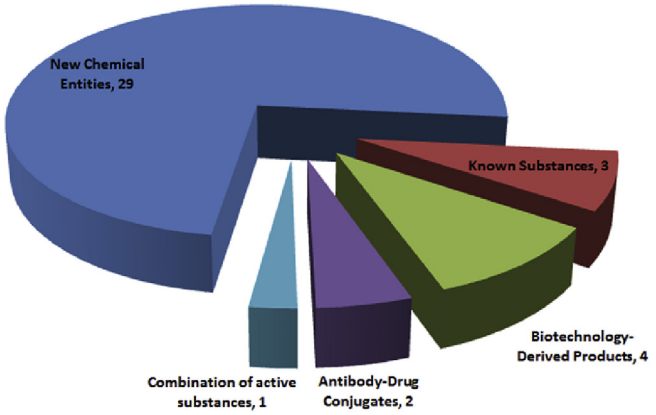

Fig. 1. New medicinal products approved for cancer treatment through EU centralised procedure (2008–2013).