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French Jardé’s law and European regulation on drug trials: Harmonization and implementation of new rules

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Summary  Jardé’s law, concerning research studies in humans, was enacted in March 2012 but did not come into force until November 2016. This delay is largely explained by the adoption of a European regulation on clinical trials on medicinal products that will probably not be applicable until October 2018. In addition to covering the respective areas of the French and European legislation, the round table provided an opportunity to discuss the principal measures that will apply to future research, particularly those concerning the operational procedures of the ethics committees and the national committee for research in humans, as well as measures relating to the management of serious adverse effects, more specifically in phase I studies in subjects not presenting with any disorder. This round table also enabled the formulation of recommendations to better anticipate the practical difficulties that the regulatory changes might engender.

Finally, we highlight the numerous challenges in terms of training that these important regulatory changes impose and the absolute necessity to best adapt the restrictions to those that are planned in numerous other European countries so that France remains competitive in terms of clinical research and so that French patients may continue to benefit rapidly from the most innovative treatments.

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Abbreviations

- APP: assessment of professional practices
- ANSM: French National Agency for Medicines and Health Products Safety
- ARS: French Regional Health Agency
- CCTIRS: French Advisory Committee on Data Processing in Health Research
- CEREEs: French Expert Committee on Research, Studies and Assessments in Health
- CNCR: French National Research Coordinating Committee
- CNIL: French Data Protection Authority
- CRO: clinical research organisation
- DGS: French General Directorate for Health
- DRCI: Directorate of Clinical Research and Innovation
- EC: ethics committee
- EMA: European Medicines Agency
- FCRIN: French Clinical Research Infrastructure Network
- IRB: institutional review board
- MA: marketing authorisation
- MA: marketing authorisation

Introduction

Jardé’s law, whose scope specifically includes non-interventional research in humans, occupies a special position in the history of the regulation of French clinical research. In fact, although it was enacted on 5 March 2012, its application remained in suspense for over 4 years [1,2]. In addition to the changes anticipated by the various persons involved in conducting clinical research, the implementation of Jardé’s law was delayed on account of the adoption of the European regulation on clinical trials on medicinal products [3]. This regulation, adopted by the European Parliament and the European Council on 16 April 2014, but which will not come into force before 2018, replaces directive 2001/20/EC and will apply as it stands, without being transposed into French law [4]. Because of this change in Community legal rules and the existence of discrepancies between the French legislation and the European legislation, at least with regard to their scope, it was necessary to pass legislation again to adjust the French regulatory framework [5].

Besides these legal adjustments, the current problem remains that of the implementation of a law whose scope differs from what it was initially, while new interlocutors will be appointed and while it remains necessary to implement new procedures and new tools to facilitate the authorisation process. In accordance with the spirit of the Giens workshops, we shall propose recommendations to facilitate the implementation and application of this new regulatory legislation, with the objective of improving the efficiency of the authorisation process while preserving the safety of those participating in this research.

Jardé’s law and the European regulation on clinical trials on medicinal products

The long journey of a law finally adopted

European directive 2001/20/EC imposed new legislation in France by replacing Huriet-Sérusclat’s law which, up until then, governed clinical research activities [4,6]. In this new legislation, implemented in August 2006, a new category of interventional research appeared whose primary objective was to define a specific regulatory framework facilitating the implementation of low-intervention projects [7,8]. In contrast, this new category could not apply to research on medicinal products, as the directive did not make provisions for this possibility. As the purpose of this specific regulatory framework was not always fully understood by those involved in conducting clinical research, the initial commendable objective was never achieved [9–11]. Alongside this, numerous questions remained concerning the subject of so-called “non-interventional” research studies, particularly those requiring the follow-up of patients and those whose methods of notification, particularly to the French
Data Protection Authority (CNIL), facilitated neither their implementation nor their visibility.

In 2009, the objective of a new draft law, prepared by the Member of Parliament, Olivier Jardé, was to make the different categories of research clearer, to facilitate the implementation of low-intervention, and thus low-risk, research studies (article L1121-1, point 2) and to include non-interventional research within the area of application of the law (article L1121, point 3) [1,2]. Jardé’s law also provided that for all research studies “involving humans”, data protection should be assessed by the ethics committee (EC), this task having previously been fulfilled by the French Advisory Committee on Data Processing in Health Research (CCTIRS) prior to their submission to the CNIL. Moreover, the law provided for the implementation of a national committee for research in humans responsible for the coordination, harmonisation and assessment of EC procedures.

Several points in this legislation having been the subject of lengthy discussions between Members of Parliament and Senators, it was not until March 2012 that the so-called Jardé’s law was finally enacted [1]. At the same time, another workshop, aimed at revising European directive 2001/20/EC, was formed. Because of the delay in some European countries transposing the directive into their national law and the lack of harmonisation and of will to improve Europe’s competitiveness in terms of research on medicinal products, revision of the directive finally resulted in the drafting of a European regulation concerning clinical trials on medicinal products [3]. This legislation, adopted on 16 April 2014, was then imposed on all European countries and, in France, particularly on account of a difference in scope, justified the postponement of the publication of the implementing decree for Jardé’s law as well as a partial rewording of this legislative text.

The necessary redrafting of Jardé’s law

In order to avoid, among other things, the numerous toings and froings between the two parliamentary chambers, the order route was chosen and the amendments made to Jardé’s law were finally approved on 16 June 2016 [5]. In this context, the French legislator has elected to implement two complementary regulatory frameworks, more specifically, that stemming from the application of the European regulation for research studies on medicinal products and that from the amended Jardé’s law for other types of research. To this end, Jardé’s law, as adopted in 2012, has only been subject to the revisions required to render the regulatory framework that it creates compatible with the new European legislation.

In practice, this new regulation categorises different types of research in humans based on the estimated risk according to 3 levels: interventional research studies that include an intervention on the person not justified by his/her routine treatment (type 1); interventional research studies that include only minimal risks and constraints (type 2), the list of which will be stipulated by decree by the Minister for Health following advice from the Director-General of the French national Agency for Medicines and Health Products Safety (ANSM); non-interventional research studies (type 3) in which all the procedures are practised and the products used routinely, without any supplementary or non-routine diagnostic, treatment or surveillance procedure. In addition, the law provides that these research studies should be subject to an opinion from the EC, including research studies previously labelled as “non-interventional” (Fig. 1).

It should be pointed out here that, in January 2016, the Parliament adopted a law, the so-called Touraine’s law, modernising the healthcare system, which includes some provisions relating to research, particularly to its financing (single contract) and, above all, to the revision of the law concerning data protection [12]. These new provisions were incorporated into Jardé’s law in the order of June 2016 [2]. The essential point is that the CNIL has endorsed the distinction of Jardé law between research studies “in humans”, which will all be assessed by an EC, and research studies based on data, which will continue to be assessed by the French Expert Committee on Research, Studies and Assessments in Health (CEREEs), formerly the French Advisory Committee on Data Processing in Health Research (CCTIRS) (Fig. 2). However, a provision that could pose a problem in the future, the CEREEs clerical office will be the submission gateway for type 3 non-health-product-related research studies, which will then forward them to the ECs without examining them.

The other major change is the centralised management of the submissions with random selection of the EC responsible for examining the project. In order to harmonise the working practices of the ECs, a national committee for research in humans will be instituted. Among the other significant measures, highlights include the clarification of the provisions relating to biological sample collections, the possibility, subject to a favourable opinion from the EC, of conducting genetic analyses without specific consent, particularly in the context of research studies where the subjects are deceased, or to conduct certain research studies on individuals with no health insurance. Regarding this last provision, it should be noted, however, that, as the European regulation did not provide for it, it cannot be applied to interventional research studies on medicinal products, which reduces its scope considerably but undoubtedly contributes to maintaining a high level of protection of subjects.

Simultaneously, concerning the handling of data obtained from these research studies, the CNIL published a revision of reference document MR001 and reference document MR003, applicable to research studies requiring express consent or a lack of opposition from the subjects taking part, respectively [13,14]. These reference documents, which impose strict data handling conditions, make it possible, subject to agreeing to comply with them, to circumvent the application process for authorisation from the CNIL. To the extent that it will be the ECs that have to validate the compliance with these reference documents from now on, the deadlines may be shortened, thus facilitating the initiation of numerous research studies. In case of non-compliance with the reference document, examination by the CEREEs, then the CNIL, will become necessary (Fig. 2). However, it should be pointed out that, as the reference documents were published prior to adoption of the decree relating to Jardé’s law, they could, in fact, generate a certain amount of confusion because the different research categories are still
Figure 1. Development of the regulations and authorisation procedures in clinical research. The top part of the diagram shows the development of the regulatory frameworks following the implementation of the Jardé’s law, followed by the European regulation on trials on medicinal products. The bottom part, indicated by the different shades of grey, shows the specific reporting procedures for each regulatory framework. CCTIRS: French Advisory Committee on Data Processing in Health Research; CEREES: French Expert Committee on Research, Studies and assessments in Health; CNIL: French National Research Coordinating Committee; EC: Ethics committee.

Does the project fall under one of the regulatory framework?

No
- Project without a claim of furthering biological or medical knowledge
- Practical professional assessment without a research purpose
- Databases without direct identification

Yes

Secondary use of data
- Medico-administrative databases (SNIRAM...)
- Legally constituted registers (systematic, exhaustive collection of data obtained from care...)
- Other databases with direct identification or interfacing of existing databases

Direct access to the person (prospective studies...)
- Specific evaluation or impact on care "Protocol-based" approaches
- Type 1 and 2 including low-intervention cohorts
- Type 3 observational studies
- Type 3 qualitative studies with no impact

Validation / Requalification
- Biological sample collections, including those with a change of purpose
New regulations in clinical research

defined on the basis of the preceding regulatory legislation [13,14].

Implementation of the European regulation and the French pilot phase

The European regulation exclusively covers the field of research on medicinal products. The primary advantage is the centralised and single nature of the assessment, which enables the authorisation of a multi-national trial within a period of 60 to slight more than 100 days depending on whether queries have been issued or not. This single assessment must be coordinated by a Member State, the so-called rapporteur, responsible for validating the general, scientific and technical parts of the application dossier. As for the ethical component, this must be examined within each Member State participating in the trial [3]. Also, the European regulation provides for the possibility of specific methods for obtaining consent, including an initial global consent to the future reuse of research data. The proportionality of the provisions and the risks-based approach are also at the heart of the regulatory framework created by this regulation, which provides for a specific status for low-level interventional clinical trials on medicinal products subject to marketing authorisation (MA), either relating to the indications in that MA or off-label. Moreover, in this latter case, the decree provides for a complex system of health insurance coverage for treatments that are the subject of research studies being conducted for non-commercial purposes [2,3].

However, the implementation of the European regulation will not be effective until after a website becomes available that facilitates the submission process and, above all, until the proper operation of this website has been verified. While awaiting October 2018, the date currently assumed for the implementation of the regulation (Fig. 1), France has implemented a pilot phase with a view to preparing itself for these new constraints. Despite some difficulties, particularly for the ECs regarding the computerisation of application dossiers and access to the European Medicines Agency (EMA)’s secure messaging system, Eudralink, overall, the assessment appears positive. In fact, sponsors, the ANSM and ECs were able to carry out a collaborative work enabling specification of the structure of common application dossiers and timetables as well as a coordinated assessment of the requests for authorisation of a clinical trial. The computerisation of the ECs and the future impact of random selection for the allocation of application dossiers thus constitute major challenges for the implementation of the European regulation.

Recommendations

The following recommendations have been formulated in order to best facilitate the transition and limit any potential difficulties:

- implement a single examination procedure by the ECs for application dossiers falling under Jardé’s law and under the European regulation, with alignment of the deadlines with those of the European regulation;
- update reference documents MR001 and MR003 so that the definitions therein correspond with the new regulatory frameworks;
- specify the respective roles of the future CEREES and of the ECs in terms of gateways and develop a simple algorithm for selecting projects (Fig. 2);
- simplify the means of making available medicinal products with MA and their social security financing arrangements in the context of research studies for non-commercial purposes by means of a coordinated and efficient procedure for management of the applications by the French National Authority for Health and the health insurance system.

Which changes affect the role and operation of the ECs?

Random selection and extended responsibilities

The major change in the new regulation relating to the ECs concerns their random selection for the allocation of the research projects to be examined. This random selection should lead to an equitable distribution of the projects for each EC, while only taking their availability into account. This measure, applicable as of the publication of the decree, will be organised by the clerical office of the national committee for research in humans. The operational implementation of this structure, which will have to manage the random selection and centralise the applications (estimated at more than 3500 per year across the country on the basis of the activities of the ECs and the CCTIRS over the last few years), is a major issue. In addition to the provision of a computer system dedicated to the submission of the projects, by 31 December 2017 [2] at the latest, the communication between the structure and the ECs will also have to be clarified.

In particular, it will be necessary to define the respective roles of this clerical office and those of CEREES, so that the activities of these two structures are not redundant or do not cause additional delays. The problem of deadlines may also arise from the coexistence of two application processes, one for research studies falling within the regulatory framework of Jardé’s law and one for research studies coming under the European regulation on clinical trials on medicinal products, with this second application process and its pilot phase (currently being implemented) being particularly efficient in terms of deadlines. In fact, there is no reason why a project assessed under Jardé’s law could not enjoy the same deadlines. Thus, an increasing number of projects will soon have to be processed by the ECs, given the expansion of their area of activity to non-interventional research studies in humans. In this context, the implementation of a ”simplified examination” procedure within the ECs, by holding select committee, including virtual, meetings as suggested by the decree, is, without doubt, a solution enabling the activity of the ECs during plenary meetings to centre around discussions relating to interventionnal studies with or without medicinal products [2]. A simplified examination like this has been implemented by the US ethics committees.
(institutional review boards or IRBs) since 1998 [15] and in Europe by the Vienna ethics committee [16] without this causing any specific problems.

The national committee for research in humans

The decree specifies the business and operating procedures of the national committee responsible for the coordination, harmonisation and assessment of the working practices of the ECs. While the composition of the committee may be subject to controversy with regard to a possible lack of representation of EC members, the issue is, above all, the ability of this committee and its clerical office to actually harmonise the working practices of all French ECs. In particular, this includes providing a single application dossier template that can be submitted everywhere according to the same procedures. Harmonisation of the procedures for issuing opinions concerning the initial submission or subsequent amendments should also be considered, so that the randomness of the allocation of a project to an EC is not synonymous with randomness in the decision. The roles of the committee and its clerical office with regard to training matters are discussed in a separate section.

Recommendations

The recommendations proposed by the round table concern both points to be considered as soon as possible (the first three, in particular) and others that can be implemented further down the line:

- while awaiting application of the European regulation, immediate opening of the pilot phase to all ECs;
- one-time training in the receivability of application dossiers, associated with a precise timetable;
- creation, as soon as possible, of a national website dedicated to the submission of application dossiers to the ECs;
- computerisation of the ECs and complete digitisation of the exchange of application dossiers;
- definition of the executive role of the clerical office of the national committee (practical organisation of the random selection and appeals procedures, training activities, 6-month assessment and adjustment, if necessary);
- compilation of common procedures relating to the working practices of the ECs (qualification of the investigators, classification and management of the amendments, appeals procedures in case of an unfavourable opinion, including for the amendments);
- training or even “certification” of members of the ECs.

New definitions and new reporting procedures for serious adverse effects

Definition of serious adverse effects and new events

The death of a healthy volunteer, which occurred in Rennes during a phase I clinical trial in January 2016, lead the Ministry of Health, then the ANSM, to publish circulars detailing new methods for reporting serious adverse effects and events [17,18]. These circulars, which transcended a simple reminder about good practices, indicated, in particular, that any hospitalisation or death of a healthy volunteer should be described as a new fact, be subject to an immediate notification to the competent authorities and to the EC and, above all, result in an immediate suspension of the trial until an absence of risk to healthy volunteers has been demonstrated [17,18].

Because a circular is not legally binding and these new definitions were also inconsistent with the European legal framework [3], it was necessary to proceed with an amendment of the legislation currently in force. The order of June 2016 and the decree relating to Jardé’s law also clarify several issues for us [2,5]. In this context, the definition of serious adverse effects remains unchanged. However, the adverse effect may be described as being unexpected if “its nature, its severity, its frequency or also its outcome are not compatible with the reference information available” [2]. Besides these definitions, which remain the same, the principal change concerns the definition of a new fact, which corresponds to “any new data that could lead to a reassessment of the risk—benefit ratio of the research or of the investigational medicinal product, to changes in the use of that product, in the conduct of the research or in the documents relating to the research or to suspending, interrupting or modifying the research protocol or similar research studies” [2]. Only unexpected serious adverse effects that caused death or were life-threatening should be reported immediately to the ANSM, other unexpected serious adverse effects should be reported within 15 days. In addition to the changes to deadlines and to definitions appearing to be in disagreement with the European legislation, their application may prove problematic in the context of first administration trials conducted in healthy volunteers.

The specific case of phase I studies in “healthy volunteers”

For trials based on the first administration or use of a healthcare product in “individuals not presenting any disorder” (and no longer healthy volunteers), any serious undesirable effect, such as defined previously, is described as a new fact [2]. In the decree, the definition has in fact expanded to the extent that it is no longer just death or hospitalisation that are described as new facts. In this context, the sponsor shall be obliged to report these new facts immediately to the ANSM, the ECs and to the French regional Health Agency (ARS). The sponsor shall also be obliged to suspend the administration or use of the product in individuals participating in the research while awaiting the adoption of definitive measures [2]. In addition to taking appropriate urgent safety measures, the sponsor shall immediately inform the competent authorities and the EC about the suspension of the treatments. Thus, the both tragic and exceptional accident that occurred in Rennes has contributed to the profound modification of the procedures for reporting serious adverse effects in studies concerning the first administration or first use of a healthcare product. However, it should be pointed out that these new definitions and
reporting procedures only apply to individuals not presenting with any disorder and not to all of the subjects who could be subject to a first administration of first use of a healthcare product. Thus, the regulation, in its current form, makes a special case of first-administration studies in individuals not presenting with any disorder and does not, however, clearly stipulate the procedures for restarting studies. All of these changes, if they remain applicable only to France and its territories, could lead to a decrease or even disappearance of first-administration studies in healthy subjects in France, as has already been observed over these last few months [19].

Recommendations

In the context of these regulatory changes, several points merit clarification:
- harmonisation of the definitions of serious adverse effects and of new facts as well as the reporting procedures between the French regulation and the European regulation, especially for first-administration studies;
- exact definition of the procedures for restarting studies in the case of suspension (respective roles of the sponsor and of the competent authorities, deadlines, procedures for obtaining consent).

Numerous training challenges

In order to accompany and facilitate the implementation of the numerous and profound modifications inscribed in Jardé’s law and in the European regulation, a special place should be given to training. This recommendation is based on the observation, reported by several round table participants, that communication and training efforts were further up the agenda during the implementation of Huriet’s law than during that of the law of 2004 and that this has probably contributed to a somewhat more chaotic start and to some persistent misunderstandings, for example, concerning research studies aimed at assessing routine treatments. The aim here is to both define the populations that will require to be trained and to specify the procedures underlying this future training. In addition, it is necessary to determine the various training institutions that should eventually become involved.

Involvement of a broad body of people

It is necessary to quickly anticipate the training of people who will be at the heart of the management of future clinical research projects. In particular, this includes all persons who will be involved in the authorisation process (members or personnel of the ANSM, the ECs, of CEREES, of the national committee for research in humans, etc.). It will also be necessary to train the personnel of the sponsors of clinical research, both academic or industrial, with a more specific problem concerning the investigator “sponsor” in certain non-interventional research studies, or those of the heads of departments of general medicine of the Faculties of Medicine who will have to implement practical solutions in the context of the submission of numerous theses by their students. Another very broad population requiring training is that of the investigators and personnel exercising the various professions associated with clinical investigations, such as the clinical research associates and technicians, the clinical trial nurses, the data managers, the biostatisticians, the pharmacists or the various technical personnel. All individuals working at contract research organisations (CROs) should also be included here. The challenges of implementing training for a large number of people are, of course, not the same when it comes to continuing education for professionals who are already in post or when it comes to initial training in clinical research for students who will carry out these activities in a few years’ time.

The necessity to develop suitable tools

The initial training could easily be adapted to the existing graduate training programmes (DIU-FARC, DIU-FIEC, other degrees or masters specialising in clinical research). Conversely, the problem of educating future doctors remains, to the extent that their training essentially is based on the grading examination at the end of year 6 and is founded on a degree programme where learning about the context and the responsibilities associated with clinical research activities does not figure strongly. A consultation with the Assembly of Deans of Faculty of Medicine may prove necessary in order to plan more robust training for future investigators.

Regarding continuing education, the problem is much more complex and arises immediately. How to correctly and quickly train hundreds, if not thousands, of professionals? In this context, the implementation of innovative teaching methods in the form of distance teaching using short and specific modules (modules by type of responsibility: EC member, sponsor, CRO, investigator; subject-based modules: regulatory filing, management of adverse effects, research sites, management of medicinal products, etc.) is probably one solution. In addition, it may also be appropriate to use the experience of personnel involved in clinical research, some of whom could be trained as a priority to become future trainers, as has been proposed by the French Clinical Research Infrastructure Network (FCRIN) infrastructure in collaboration with the Paris Diderot University. The implementation of this type of solutions will thus make it possible to facilitate the training of the largest number. Finally, there is the question of the involvement of the various current or future training institutions, particularly the position of the DGS (French General Directorate for Health) and of the national committee for research in humans and its clerical office, which, one would hope, would become a leading executive body in this context. Similarly, the Directorate of Clinical Research and Innovation (DRCis), the French National Research Coordinating Committee (CNCR), the ANSM and the industrial sponsors could play a decisive role.

Recommendations

The recommendations issued by the participants of the round table aim, in particular, to specify the priorities in terms of training, the supporting information as well as the responsibilities of the various training institutions or partners:
• prioritise training activities of all members of the ECs and of the national committee before that of other personnel involved; the opening of discussions concerning graduate training courses, including for future doctors;
• offer tools such as an explanatory and reading guide for the new regulatory procedures (DGS/national committee partnership) from which one could homogeneously construct distance training modules according to type of responsibilities or activities;
• involve the partner institutions of clinical research (DGS, DRCI, CNCR, ANSM, national committee, pharmaceutical companies, etc.) for the provision of content or the implementation of a specific subject matter.

Conclusion
The publication of the implementing decree for Jardé’s law and the harmonisation of the different regulatory elements with regard to the restrictions of the European regulation on studies on medicinal products is the prelude to substantial changes to clinical research both in terms of authorisation procedures and in terms of numerous other practical aspects associated with conducting research, aspects that will be specified by numerous decrees to be issued subsequent to the implementing decree. This development affects numerous participants from both academia as well as the healthcare products industry who fervently wish that clinical research in our country retains its dynamism and its attractiveness while ensuring the best possible protection for individuals agreeing to participate in it. In the environment created by the new regulatory legislation, it will, no doubt, be necessary to consider a regular assessment, every 3 to 6 months for the next 2 years, of the new procedures for managing projects, in order to refine the processes implemented, if necessary. The harmonisation of practices nationally as well as at European level must not create obstacles but, instead, generate opportunities for French clinical research to be able to retain its reactivity to the benefit of innovation and new treatments that could be offered to patients.

Disclosure of interest
The authors declare that they have no competing interest.

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