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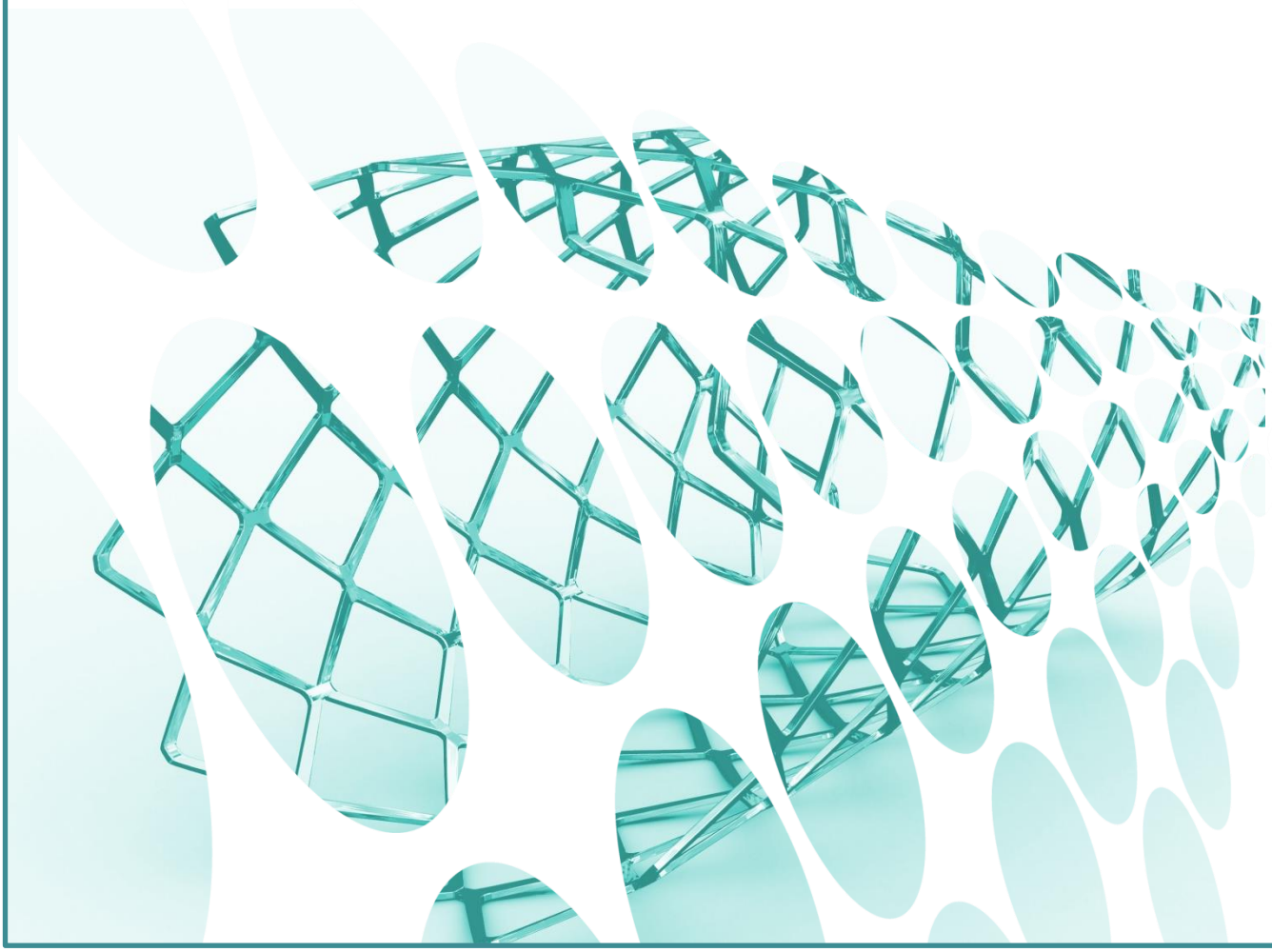
White Paper

Clinical Data for Medical Devices

Preparing for increased requirements in the EU

MEDICAL DEVICE



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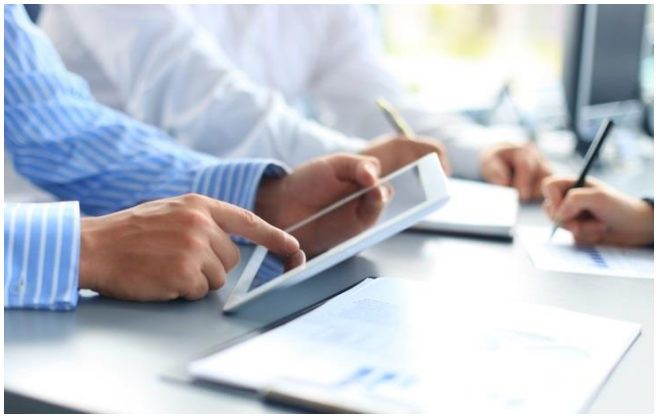
1. Regulation of medical devices in the EU: on the cusp of change

To market a medical device in the EU, a manufacturer must demonstrate that the device is safe, that it performs as intended, and that the risks associated with the use of the device are acceptable when weighed against the benefits to patients. Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device to verify its clinical safety and performance. It may be based on a literature review and/or clinical experience and/or clinical investigations. While some medical devices do require data generated from a clinical investigation, it is often possible, for low- to medium-risk devices (Class I, IIa, and IIb), to rely on a literature review and/or clinical experience to support the device's intended use.

The Medical Devices Directives (MDDs) form the foundation of Europe's regulatory framework for medical devices. The relevant EU legislation addressing the clinical evaluation of medical devices is the Medical Device Directive 93/42/EEC, as amended (March 2010) and the Active Implantable Medical Device Directive 90/385/EEC, as amended (March 2010). This legislation was transposed into national law in all concerned countries.

European regulation of medical devices is undergoing significant revision. On 26 September 2012, the European Commission published a proposal for regulation of medical devices[1] and a separate proposed regulation of IVD devices (which will not be discussed here). On 22 October 2013, the European Parliament voted to accept 347 amendments to the Commission's Medical Devices Regulation Proposal. The formal legislative vote was held on 2 April 2014, which resulted in the Parliament's adoption of the amended Proposal[2]. This action closed the first reading of the ordinary legislature procedure. On 5 November 2014, the Committee on the Environment, Public Health and Food Security of the European Parliament mandated the rapporteurs to enter into negotiations with the Council of the EU aiming to reach an agreement on these proposals.



A comprehensive discussion of the proposed changes to Medical Device Regulation can be found in the CROMSOURCE white paper "EU Recast of the Medical Device Directives: The Rocky Road to the new Medical Device Regulation".

This white paper focuses on the regulatory changes set to erode the traditional differences between medical device and pharmaceutical clinical studies. A significant aspect of The Medical Devices Regulation Proposal is that it represents a bid to raise the regulatory bar on clinical evidence requirements, exposed as inadequate by the scandal of defective breast implants produced by the French Poly Implant Prothèse (PIP). CROMSOURCE's companion white paper on "Clinical Evaluation

[1] http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

[2] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2013-428

Reports: Meeting the demands of a more stringent regulatory environment" discusses how increased demands placed on medical device notified body performance are leading to more rigorous inspections of manufacturers' clinical evaluation documentation ahead of the implementation of new regulations.

2. Traditional differences between medical device and drug clinical studies

The Good Clinical Practice (GCP) standard for medical device investigation is laid down in EN ISO 14155 (2010). European legislation also explicitly requires adherence to the Declaration of Helsinki, which defines the ethical principles to be respected when performing investigations on human subjects.

As a rule, all clinical investigations need to be approved by Ethics Committees and notified to the competent authorities of involved countries. Other regulatory institutions may need to be involved in the regulatory process depending on national law.

The essential documents for a medical device investigation are similar to the ones required for a pharmaceutical study. The term Clinical Investigation Plan is generally used to refer to the study protocol in the case of a clinical investigation of a medical device. There is a requirement to include a section on risk management in the Clinical Investigation Plan.

Regulatory requirements for clinical investigations of medical devices are different to pharmaceuticals and this has an impact on the design of their clinical investigations[3]. There is no legal requirement to demonstrate the efficacy of the device to obtain CE marking. The objective of the clinical investigation is to demonstrate the safety and performance (conformity with claims) of a medical device. In a pharmaceutical study the objective is to demonstrate the safety and efficacy of the medicinal product. One consequence is that case numbers in a medical device investigation are usually lower than in pharmaceutical studies. The stage of a clinical investigation which needs to be satisfactorily completed for CE marking may therefore be likened to Phase II in drug development, where evidence of clinical activity of a drug is sought, rather than Phase III. Since efficacy does not need to be demonstrated, randomised controlled trial designs for medical devices are rarely necessary and therefore proof of statistical significance may not be necessary. Interim analysis of study data may be feasible, provided it has been written into the investigation plan.

In comparative pharmaceutical studies the most robust comparator is a placebo control, which is often applied and generally required by authorities. In a medical device investigation, a placebo control is usually not feasible. This is particularly the case with implantable devices, where placebo control groups (involving sham surgery) are not possible. However, studies comparing a medical device with standard therapy are possible, although in some cases there may be no standard therapy available which is similar enough to warrant comparison, especially for novel devices. In addition the user (usually a healthcare professional) often cannot be blinded to the study intervention.

[3] http://www.hra.nhs.uk/documents/2013/09/approval-of-medical-devices-research-version-2-april-2008.pdf

A specific feature of medical device investigations is that product performance may be influenced by user. Furthermore, the use of a medical device may sometimes be associated with a learning curve for the user, where the outcomes improve with experience.

Another feature is that adverse events, in particular adverse device effects, may not only concern the investigation subjects but also third parties, such as users of the device. In contrast, adverse events in pharmaceutical studies are only monitored for the clinical study subjects.

Due to the wide range of types of device, testing methodologies vary widely. Some performance data might simply require user handling feedback; other data might be more analytical. Medical devices often create large amounts of data that are transmitted, processed and stored via specific software interfaces. For such data sets, specific monitoring rules have to be established focusing on supervising data processing rather than individual data points.

Moreover, medical devices are subject to frequent incremental innovation. Results from long-term clinical studies with predicate devices may no longer be relevant to improved products and medical procedures.

3. Proposal adopted by the European Parliament introduces new requirements

With EU action pending, the European Commission's proposal, including the proposed amendments from the European Parliament, outlines new clinical data requirements for the regulations for medical devices. Key initiatives in this area will be highlighted in this section.

The reach of the regulation is also being extended to manufacturers of products not hitherto considered to be medical devices. The Proposal states (Article 2, paragraph 1, point 1; amendments in bolded italics): "The implantable or other invasive products, ***as well as products using external physical agents,*** intended to be used for human beings, which are listed on a non-exhaustive basis in Annex XV, shall be considered medical devices ***for the purposes of this Regulation*** regardless of whether or not they are intended by the manufacturer to be used for a medical purpose". The following types of products are listed Annex XV: contact lenses; implants for modification or fixation of body parts; facial or other dermal or mucous membrane fillers; equipment for liposuction; invasive laser equipment intended to be used on the human body; intense pulsed light equipment.

New device definitions introduce the concept of clinical benefits

The amended Proposal introduces the concept of "clinical benefit" of medical devices. It will no longer be sufficient to demonstrate safety and claimed performance; medical devices will need to show actual clinical benefit for patients. Failure to do so using available clinical data may require a clinical investigation to be performed.

Location in the Commission's Proposal	Quotation (European Parliament's amendments in bolded italics)
Article 2: Definitions, paragraph 1	***(31a) 'performance' means any technical characteristics, any effects and any benefit of the device when used for the intended purpose and in accordance with the instructions of use*** ***(31b) 'benefit' means the positive health impact of a medical device based on clinical and non-clinical data*** (32) 'clinical evaluation' means the assessment and analysis of clinical data pertaining to a device in order to verify the safety**,** performance ***and clinical benefits*** of the device when used as intended by the manufacturer

Failure to prove equivalence may necessitate a clinical investigation

In Annex XIII "Clinical evaluation and post-market clinical follow-up" the Proposal states that existing clinical evidence with comparable devices can be used for the clinical evaluation, provided device equivalence can be demonstrated. This instruction is similar to the current medical device directive; however, the criteria will be stricter and it will be more difficult to convincingly prove equivalence. Without clinical evidence to demonstrate performance and safety, a clinical investigation will be needed.

It should be noted that in 2011 the Institute of Medicine in the US called for a revamp of the 510(k) clearance process warning that "reliance on substantial equivalence cannot assure that devices reaching the market are safe and effective."

Location in the Commission's Proposal	Quotation
Annex XIII "Clinical evaluation and post-market clinical follow-up", Part A: Clinical Evaluation	(4) *Equivalence can only be demonstrated when the device that is subject to clinical evaluation and the device to which the existing clinical data relates have the same intended purpose and when the technical and biological characteristics of the devices and the medical procedures applied are similar to such an extent that there would be not a clinically significant difference in the safety and performance of the devices.*

The range of devices requiring clinical investigations will be extended

Under the amended Proposal, the range of high-risk devices that will require clinical evidence collected via a clinical investigation is being extended to include: Class IIb devices intended to administer and/or remove a medicinal product and devices manufactured utilising tissues or cells of human or animal origin, or their derivatives, which are non-viable or are rendered non-viable. These devices are listed in Article 43a(1) along with: implantable devices; devices incorporating a substance; and all other class III devices. Special notified

bodies will be involved in the conformity assessment procedures of these devices. The rule will not apply to devices intended for short term use (up to 30 days).

Location in the Commission's Proposal	Quotation (European Parliament's amendments in bolded italics)
Annex XIII "Clinical evaluation and post-market clinical follow-up", Part A: Clinical Evaluation	(5) In the case of devices falling within ***Article 43a(1)***, ***with the exception of those used for a short term,*** clinical investigations shall be performed unless it is duly justified to rely on existing clinical data alone. Demonstration of equivalence (…) shall generally not be considered as sufficient justification within the meaning of the first sentence of this paragraph.

Efficacy, not performance, will need to be verified in a clinical investigation

Chapter VI (which has been amended to Chapter V) and Annex XIV "Clinical Investigations" of the Proposal introduces the requirement for the demonstration of "efficacy" of the device in a clinical investigation.

It should be noted that objections have been raised to this requirement by Eucomed[4] on the basis that, unlike pharmaceuticals, the efficacy of devices often relies on the skills and experience of the healthcare professional, the quality of the hospital, and many other factors.

Location in the Commission's Proposal	Quotation (European Parliament's amendments in bolded italics)
Chapter VI (amended V) "Clinical evaluation and clinical investigations", Article 50: General requirements regarding clinical investigations, paragraph 1	[regarding purpose of clinical investigations] (b) to verify ***the clinical safety and efficacy of the device, including the intended benefits to the patient, when used for the intended purpose, in the target population and in accordance with the instructions of use***
Annex XIV "Clinical Investigations", Part I: General requirements, section 2: Methods	(2.1) Clinical investigations shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute ***the technical performance of the device, the clinical safety and efficacy of the device when used for the intended purpose in the target population and in accordance with the instructions of use, and*** the manufacturer's claims for the device as well as the safety, performance and benefit/risk related aspects referred to in Article 50(1); these investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions.

Aim is randomised controlled clinical trials with well-chosen controls

Early on in the Proposal, the requirement for clinical investigations to be appropriately targeted and controlled is stated. Annex XIV to the Proposal "Clinical Investigations" dictates the use of randomised controlled investigations and states that the use of any other design would need to be justified. The amendment specifically references the control therapy and the involvement of independent experts in relation to randomised controlled investigations.

[4] http://www.eucomed.org/key-themes/medical-devices-directives/devices-pharmaceuticals

As pointed out by Eucomed[5], it is not clear how randomised controlled designs will be implemented in cases where it would be hard randomise devices due to strong ethical and practical issues in the choice of the "comparator" (for example, it would be impossible to use a comparator for an implantable cardiac defibrillator). Furthermore, standards of care and therefore the control therapies differ depending on a specific country and healthcare expert.

Location in the Commission's Proposal	Quotation (European Parliament's amendments in bolded italics)
Article 2: Definitions, paragraph 1	(33) ***Clinical investigations for medical devices, where made compulsory in accordance with this Regulation, shall include clinical investigations in the appropriate target population and well-controlled investigations.***
Annex XIV "Clinical Investigations", Part II: Documentation regarding the application for clinical investigation	(1.11) Summary of the clinical investigation plan (objective(s) of the clinical investigation, number and gender of subjects, criteria for subject selection, subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation). ***As randomised controlled investigations usually generate a higher level of evidence for clinical efficacy and safety, the use of any other design or study has to be justified. Also the choice of the control intervention shall be justified. Both justifications shall be provided by independent experts with the necessary qualifications and expertise.***

4. Conclusion

The amended Medical Devices Regulation Proposal aims to ensure more solid clinical data to support medical device CE marking applications. Clinical evaluation requirements will be more stringent, and there will be a requirement to demonstrate clinical benefits of the device and provide a rigorous proof of equivalence if the evaluation is based on comparable devices.

In a move that is likely to have the greatest impact on manufacturers of medical devices, the amended Proposal has introduced a requirement for efficacy into the European medical device regulatory system, which, since its inception, has been based upon essential requirements for safety and performance. Demonstration of efficacy is best achieved with a randomised controlled investigation. Although a randomised controlled study design may not be feasible or ethical with some implantable devices, such a study design provides clear potential advantages. Large, multi-centre randomised controlled clinical trials allow reliable general conclusions to be drawn from results while enabling the detection of small, clinically significant effects that smaller trials might miss. This evidence is currently lacking for most medical devices.

The proposal, as amended, would result in an increased need for randomised controlled clinical studies to gain and maintain CE approval for high-risk devices, a classification which

[5] http://www.emedical ucomed.org/key-themes/medical-devices-directives/devices-pharmaceuticals

has been extended and now includes some class IIb devices. In addition, the requirement for demonstrating clinical benefit will bring more randomised study designs regardless the classification. For lower risk devices, clinical investigations would have to be performed to achieve CE approval, if relying on existing clinical data could not be justified. Also, independent experts would be needed to provide justification for the choice of the control intervention or to justify clinical study design for studies other than randomised, controlled investigations.

A Progress Report[6] prepared by the Italian Presidency of the Council of the EU and published on 25 November 2014 stated that the discussion of the Working Party on Pharmaceuticals and Medical Devices is moving in the direction of further aligning the provisions on ethical and methodological principles to those for clinical trials of medicinal product. As the regulatory stakes are being raised for clinical investigations of medical devices manufactures will need to acknowledge that quality standards will need to be increased in order to approach those expected for clinical trials of pharmaceutical products.

5. Why use a CRO?

The process of receiving approval for new medical devices (in particular high risk devices) will become more onerous. Manufacturers of medical devices should begin implementing the necessary systems for compliance as soon as possible to ensure full compliance when the regulations come into force. Resources need to be committed by manufacturers to clinical evaluation of devices including high quality clinical investigations and steps taken to secure input from individuals with good understanding of the regulatory requirements as well as individuals qualified in GCP procedures.

Many medical device manufacturers, especially those of medical devices in lower risk classes have neither sufficient resources nor expertise to perform high quality clinical investigations in-house. Also, the new legislation will require a wider range of products to be classified as medical devices and regulated as such; therefore, companies who did not deal in devices previously may find that they will do so under the new laws. All these companies, as well as some established large medical device companies with overstretched resources may need to consider outsourcing clinical investigations.

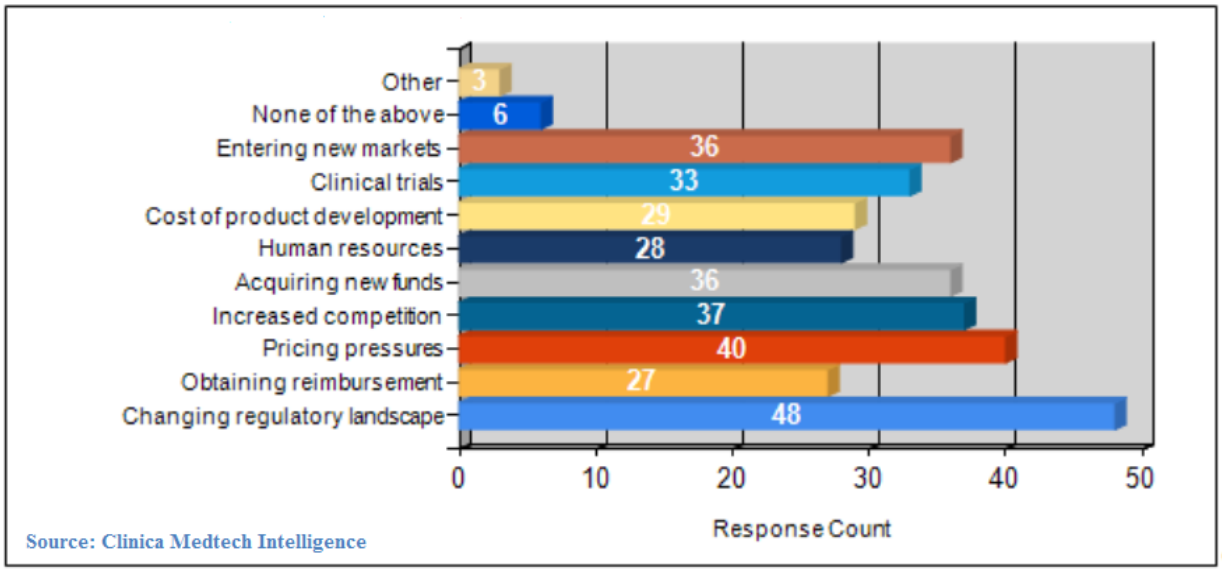
In February 2015 Clinica Medtech Intelligence published findings[7] from its survey of the medtech industry's outlook for the year 2015. A total of 105 individuals took part in this global survey. The survey found that many medtech (medical device and diagnostics) companies are looking to expand their operations, within what they believe to be an improving financing climate. However, the respondents expressed a number of concerns for their business, top of which was the changing regulatory landscape (in the EU, as well as in

[6] http://register.consilium.europa.eu/doc/srv?l=EN&f=ST%2015881%202014%20INIT

[7] http://www.clinica.co.uk/business/SURVEY-2015-looks-rosy-for-money-flow-but-regulations-a-global-worry-356681

the emerging markets). More than half (53%) of the respondents believe regulations will become more stringent compared with 2014.

Medtech companies' key concerns for business in 2015



By outsourcing clinical investigations to a full-service CRO device manufacturers can access external regulatory, clinical, and statistical expertise and realize significant efficiency gains, saving time and money. Potential benefits include avoiding the need to hire additional in-house staff or purchase expensive data management software.

6. How CROMSOURCE can assist

CROMSOURCE will ensure that the clinical investigation will be performed to the most recent regulatory requirements, and that the client is made aware of important areas undergoing regulatory changes. Full service outsourcing services we offer encompass the entire trial process but some device companies may only require specialised services such as regulatory consulting, clinical monitoring or data management support.

A critical first step is the preparation of a Clinical Evaluation Report to determine if a clinical investigation will be required. If a clinical investigation is deemed to be necessary, we can prepare or assist in the preparation of the necessary documentation, including the Investigator's Brochure and the Clinical Investigation Plan.

With randomised controlled investigations, establishing statistical significance will be necessary. CROMSOURCE is experienced in pharmaceutical clinical trials of pharmaceuticals and can provide comprehensive statistical analysis, an advantage that some specialised medical device CROs may not be able to match.

We can help design a clinical investigation to meet individual product needs and identify the best data measurements to support product claims. We can assist with protocol

design, study management, data management, clinical trial monitoring, biostatistical analysis, and final report preparation.

7. About the Author

Beata Wilkinson, Head of Regulatory Services Unit, CROMSOURCE

After gaining her PhD in biomedical science from the University of Glasgow (UK), Beata was a university lecturer before moving to consulting and medical writing. She is a biomedical business intelligence specialist and has worked with leading pharmaceutical and medical device companies. Beata researched and wrote over 50 off-the-shelf biomedical technology and market reports for sale by global publishers of healthcare business information, including Informa plc. Prior to joining CROMSOURCE, Beata was at the Clinical & Regulatory Affairs Department at ConvaTec where her responsibilities included preparation of the company's clinical evaluation reports.

8. About CROMSOURCE

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

Operating through offices across all regions of Europe and North America CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first in human conducted in our exceptional early phase unit, through all subsequent phases of pre- and post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions Team ensures that high quality professionals are available to support your work whenever you need more resources.

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