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REGULATORY

NEWSLETTER N.28
October - December 2019

CROMSOURCE is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialised in clinical development and staffing solutions.

SUMMARY

MEDICINAL PRODUCTS/DRUGS

Europe

News from the European Commission

Guidelines in Good Clinical Practice for Advanced Therapy Medicinal Products

The European Commission adopted Guidelines on Good Clinical Practice (GCP) specific for Advanced Therapy Medicinal Products (ATMPs) in October 2019. These guidelines are to be read in conjunction with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines on good clinical practice (ICH GCP E6 Revision 2), which are also applicable to ATMPs. The guideline also complies with the requirements in EU Clinical Trials Regulation No. 536/2014.

Clinical Trials Application Form (Annex 1) Revised by EC

The European Commission made a revision to Clinical Trials Application form (CTA form) (Annex1), submitted for initial submission of clinical trials with medicinal products to national competent authorities (NCAs) and some Ethics Committees in the European Union. New version is dated 22 November 2019. Updates are made to the footnotes section of CTA form. The changes do not have an impact on the clinical trial application form in xml format, since footnotes are not included in it.

Recruitment and Informed Consent Procedure Template

In November 2019, a draft version of Recruitment and Informed consent procedure template Recruitment and Informed consent procedure template has been developed and endorsed by the EU Clinical Trials Expert Group to comply with European Union Clinical Trials Regulation No. 536/2014 (EU CTR). This template has been issued for describing recruitment arrangements and/or informed consent procedure. In case the template is not used for the purposes mentioned above, all the relevant information included in template should be included in the protocol as a minimum. The Expert Group underlines that "this template is also relevant under Directive 2001/20/EC and may be used in advance of the Regulation applying".

Clinical Trials Regulation Q&A

The European Commission has released an updated draft Questions and Answers (Q&A) document to provide further clarification on the implementation of the EU Clinical Trials Regulation No. 536/2014.

News from the European Medicines Agency (EMA)

The source of each news item below is the EMA website: https://www.ema.europa.eu/

European Union Clinical Trial Regulation-EMA Management Board Update

In October 2019, the EMA's Management Board met and discussed ongoing development of the EU clinical trial portal and database, now known as the Clinical Trials Information System (CTIS). The CTIS was originally to be ready for audit in July 2017, then June 2019. The December meeting of EMA's Management Board states that the audit of the system should commence by end of December 2020.

Summary of General Informed Consent Information for Paediatric Clinical Trials in Europe Updated by Enpr-EMA.

The European Network of Paediatric Research at the EMA (Enpr-EMA) has published updated Informed Consent for Paediatric Clinical Trials in Europe (23 October 2019). The document presents a legal age of consent to be signed by subjects, mandatory or suggested age of ranges defined for assent, number of required signatures under consent form, language requirements and links with access to source of these data for European countries.

Guideline on Clinical Investigation of Medicinal Products for the Treatment of Gout

The guideline presents general guidance on the development of medicinal products for the treatment of gout, including urate-lowering therapy (ULT) and anti-inflammatory treatment options. This guideline was adapted by EMA's Committee for Medicinal Products for Human Use (CHMP) on 14 November 2019 and will come into effect on **01 June 2020**.

Guideline on Good Pharmacovigilance Practices (GVP)-Product-or Population-Specific Considerations III: Pregnant and Breastfeeding women

This guideline was published for consultation by the European Medicinal Agency (EMA) on 11 December 2019. The consultation end date is **28 February 2020**. Comments should be submitted to: gvp@ema.europa.eu.

This Product-and Population-Specific Considerations Chapter P.III of the Good Pharmacovigilance Practices aims to provide guidance to marketing authorisation applicants/holders, competent authorities of Member States and the EMA for facilitating appropriate pharmacovigilance for medicinal products that may be used in pregnant or breastfeeding women.

News from Individual Countries

The United Kingdom

Interactive Costing Tool

The National Institute of Health Research (NIHR) giving support for the National Health Service (NHS) in England informed that interactive Costing Tool (iCT) will be the only system available for industry costing submissions for new commercial contract studies from April 2020. This will replace the current Excel Industry Costing Template. It is intended that Life science organisations and Contract Research Organisations (CROs) choosing to conduct clinical research in NHS in England will experience quicker and easier multi-site study set-up. In the new process "a national coordinator will be assigned to each commercial contract study to negotiate the resource and procedure allocation required to deliver the study in the NHS. Once the company has accepted the allocation it will be 'validated' and issued to all participating NHS sites for local costing."

Finland

New Administrative Regulation

The Finnish Medicines Agency, Fimea announced that the supervision of medical devices (MDs), operators in the sector and device trials will be transferred from Valvira to Fimea as of 1 January 2020. The new regulation requires applicants to submit all documents related to clinical trials electronically via CESP (Common European Submission Portal) or Fimea's Secure Mail Service.

There are minor changes concerning the submission dossier to be submitted to Fimea.
In addition the following have been made in the revised regulation:

- "The definition of an interventional clinical trial has been updated.
- The reporting of suspected unexpected serious adverse reactions occurring in Finland has been updated to be consistent with the current practice.
- Added the submission of trial results not only to Fimea, but also to the EU Register of Clinical Trials.
- The requirements pertaining to the labelling of investigational medicinal products have been clarified.
- The instructions concerning the reporting of vaccines and blood- and plasma-derived medicinal product batches used in clinical trials to Fimea have been clarified."

Italy

The National Contract Template

The National Coordination Centre of the Territorial Ethical Committees for clinical trials on medicinal products for human use and on medical devices established by AIFA, the Italian Medicines Agency published a national contract template to be negotiated with the sites involved in clinical trials with investigation medicinal products (IMPs) in compliance with the provisions of Article 2, Paragraph 6, Law no.3 /2018.

Use of the contract template is highly recommended for contract negotiation with Italian sites. It contains the minimum content and in case of specific study needs the template may be integrated. The current form of template must be kept to guarantee "the homogeneity of the administrative aspects, economic and insurance costs".

The national contract template became effective at the moment of its publication by Coordination Centre on 30 October 2019. The national contract template for clinical investigations with medical devices is still under discussion by Coordination Centre.

Lithuania

Changes of Submission to SMCA

The State Medicines Control Agency (SMCA), the Lithuanian Competent Authority states clinical trials application may be submitted electronically through the European Union portal the Common European Submission Platform (CESP). The submission concerns initial applications, substantial amendments, Development Safety Update Reports (DSURs), end of trial declaration and other documents related to clinical trials with medicinal products.

The Netherlands

New Subject Information Models

The Central Committee for Research Involving Human Subjects (CCMO) published three new models of Subject Information Sheets (SISs) including Consent Forms and one has been updated:

- Model discussion sheet for children up to 12 years old; (**new**)
- Model subject information for children aged 12 to 16 years; (**new**)
- Manual model test subject information for tests subject younger than 16 years (children); (**new**)
- Model subjects' information for subjects 16 years old and older (adults); (**updated**)

The CCMO strongly advises to use the templates. In addition, the CCMO published questions and answers about the data section of the updated model SIS for subjects aged 16 years old and older (adults).

North America

United States of America

News from FDA

Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry

What is the Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry? The September 2018 release replaces the 2010 draft guidance issued by the US Food and Drug Administration (FDA).

The FDA defines an adaptive design as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial." The FDA also explains how adaptive trial designs can allow a trial to adjust to information that was not available when the trial began.

The clinical trial landscape has changed since 2010 regards the FDA's stance on adaptive clinical trial design. The guidance provides examples for Biostatisticians to review where adaptive designs have been featured. Use cases include chronic heart failure, Ebola treatment, HPV vaccine, prostate cancer plus other successful cases of an adaptive design. This includes Bayesian adaptive designs and complex designs relying on computer simulations.

Canada

News from the Health Canada

New Clinical Trial Site Information Form

The Health Canada (HC), the Canadian Regulatory Agency informed about the new version of Clinical Trial Site Information Form (CTSIF) which must be provided to HC prior to commencement of the clinical trial. The revised version is mandatory from 2 January 2020. The old form will not be accepted after that date.

"The changes to the form are summarized as follows:

- Drug Product and Sponsor information sections removed, as they are already found with the Clinical Trial Application.
- Ability to use previous versions of a completed form to make revisions, along with the ability to identify exactly which sections of the form are revised.
- 'Submit' buttons on the form allow for direct electronic filing to Health Canada. An application control number is required prior to submitting a CTSI form, so that Health Canada can make the necessary link between the application and relevant CTSI form(s)."

MEDICAL DEVICES

EUROPE

News from the European Commission

Second Corrigendum for MDR

On 25 November 2019, the European Council issued a second corrigendum proposal to Medical Device Regulation 2017/ 745 (MDR), in which the most significant change was made to Article 120 (3). The proposal was voted by the European Parliament Committee on 3 December 2019. It was confirmed that manufacturers of Class I medical devices have now a further four-year transitional period, until 26 May 2024 to meet the requirements of the new Regulation. Paragraph 3 of the Article 120 has been modified in the draft document as follows:

"By way of derogation from Article 5 of this Regulation, a device which is a class I device pursuant to Directive 93/42/EEC, for which the declaration of conformity was drawn up prior to 26 May 2020 and for which the conformity assessment procedure pursuant to this Regulation requires the involvement of a notified body, or which has a certificate that was issued in accordance with Directive 90/385/EEC or Directive 93/42/EEC and that is valid by virtue of paragraph 2 of this Article, may be placed on the market or put into service until 26 May 2024, provided that from 26 May 2020 it continues …"

The proposed draft must be submitted by the European Council to the European Court of Justice, by no later than January 2020, for approval.

News from the European Medicines Agency (EMA)

The source of each news item below is the EMA website: https://www.ema.europa.eu/

Questions & Answers on Implementation of MDR and IVDR

The European Medicines Agency (EMA) published a Questions and Answers document. This document focus on questions and answers relating to the implementation and applicability of the requirements of Medical Device Regulation 2017/745 to medicinal products with an integral or co-packaged medical device.

Other initiatives

IMDRF Clinical Guidelines

The International Medical Device Regulators Forum (IMDRF) has released three final clinical guidelines to replace earlier guidelines by the Global Harmonization Task Force (GHTF). The guidelines cover clinical evaluations, clinical investigations and clinical evidence for medical devices. The guidelines refer to general principles and intended to provide guidance to manufacturers, regulators and other stakeholders when assessing clinical evidence provided by manufacturers. The guidelines do not apply to in vitro diagnostics medical devices.

News from Individual Countries

Switzerland

Revision of Requirements for Combination Products

The Swiss Agency for Therapeutic Products (Swissmedic) revised the requirements for integral and non-integral combination products (medicinal products with a medical device component) in Swissmedic Journal 06/2017. As of 26 May 2020, applications for the authorisation of integral combination products must demonstrate that it bears a CE certification mark, or if lacking certification must demonstrate that the medical device component satisfies the applicable basic safety and performance requirements of Annex I of the new Medical Device Regulation 2017/745.

The Netherlands

Changes in Submission Due to the MDR

The Central Committee for Research Involving Human Subjects (CCMO) has published information on how applicants should proceed with clinical investigations with medical devices.

The CCMO will be the national competent authority for clinical investigation (NCA). A separate notification to the Health and Youth Care Inspectorate (IGJ) will be no longer obligatory. There are minor changes in the submission dossier compared to the current situation. One of the new documents that needs to be submitted is the Clinical Evaluation Plan (CEP) in case of clinical investigation for conformity assessment (i.e. in the framework of product development and obtaining a CE-mark).

The National Office of the CCMO will be responsible for the validation of clinical investigations for conformity. It will be checked whether the clinical investigation falls within the scope of the MDR and whether the application dossier is complete. After a positive validation, the CCMO assigns the study to an accredited Medical Research Ethics Committee (MREC).

An accredited MREC will review the clinical investigation in accordance with specified legal frameworks.

Submissions for which no decision has been reached before 26 May 2020 will be reviewed subject to MDR Article 62 or Article 74.2.

Finland

Transfer a Supervision of Medical Devices to Fimea

The Finnish Medicines Agency, (Fimea) announced that the supervision of medical devices (MDs), operators in the sector and device trials will be transferred from Valvira to Fimea as of 1 January 2020.

North America

United States of America

News from FDA

FDA Outlines Plans for Medical Devices with Artificial Intelligence

The US Food and Drug Administration (FDA) has volunteered new plans for regulating medical devices based on artificial intelligence (AI) or machine learning algorithms.

On 2 April 2019, the FDA published a discussion paper, "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) – Discussion Paper and Request for Feedback" that outlines the FDA's foundation for a possible approach to premarket review for AI software modifications. Under the proposed framework, AI/ML-based SaMD would require a premarket submission when a software change or modification "significantly affects device performance or safety and effectiveness; the modification is to the device's intended use; or the modification introduces a major change to the SaMD algorithm.

FDA has defined artificial intelligence as: "A device or a product that can imitate intelligent behavior or mimics human learning and reasoning. Artificial Intelligence includes machine learning, neural networks, and natural language processing. Some terms used to describe artificial intelligence include: computer-aided detection/diagnosis, statistical learning, deep learning, or smart algorithms."

2018 was a defining year for medical devices that utilize artificial intelligent algorithms. Even though medical devices have been using 'software algorithms' to help assist clinicians, 2018 saw the first FDA approved medical device that uses artificial intelligence and doesn't require a clinician to interpret the input.

What does the rest of the world think about health and AI? The EU is also introducing new regulations that will apply as of 26 May 2020, regulations that contain additional provisions that specifically address software medical devices. Of particular relevance, software with a medical purpose of "prediction and prognosis" will fall within the scope of the Regulations.

This means that AI software that currently is excluded from being regulated as software medical devices under the existing regulatory regime, because they do not provide a treatment recommendation, but only a prediction of risk to or predisposition of a disease, may in the future be reclassified as medical devices.

Canada

News from the Health Canada

Canada Releases Final Guidance on Software as a Medical Device

As of January 2020, Health Canada has finalized guidance on software as a medical device (SaMD) that clarifies how it fits into the agency's regulatory framework and how device makers can comply.

Health Canada Creates New Medical Devices Directorate for 2020

Health Canada has announced at the end of 4Q 2019, the creation of a new Medical Devices Directorate to better respond to the challenges and opportunities related to the growing medical device industry. Similar to the US FDA's push for a lifecycle approach to regulating devices, the new Canadian devices directorate will take a lifecycle approach by bringing together post-market functions now led by the Marketed Health Products Directorate and the pre-market functions of the Therapeutic Products Directorate.

OTHER "HOT" TOPICS IN EUROPE

MDR-latest status

Major Concerns Remain With MDR, Industry Group and Experts Warn

As the 26 May 2020 date of application for the Medical Devices Regulation 2017/745 (MDR) approaches, there are lingering concerns about notified body (NB) capacity, a lack of guidance and the two-year Eudamed delay.

Earlier this week, industry group MedTech Europe outlined some of the challenges in a "call to action," while also explaining the risk of device shortages. Currently, 55 NBs are legally allowed, until 26 May, to renew or extend the validity of device certificates issued under the former device directives, but their capacity to do so "is extremely limited, putting at risk the continued availability of existing devices."

And with only nine NBs designated under MDR, future challenges await.

Considering economic aspects and request from competent authorities the European Commissioner for Health Stella Kyriakides, on behalf of the Directorate-General for Health and Food Safety (DG SANTE) announced that the European Commission is going to put the Eudamed Actors module live on the date of MDR application 26 May 2020 and actor registration will be on a voluntary basis for manufacturers.

Medical Device Coordination Group (MDCG) Offers New Guidance:

- Multilingual Legend for the Summary list of harmonised standards
- Guidance on Unique device identifiers (UDIs)
- Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR
- Guidance on Cybersecurity

Other MDCG endorsed guidance:

- https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en

Eudamed Nomenclature

European Commission last week released new documents on the Eudamed nomenclature's basic principles and the structure of the Italian "Classificazione Nazionale Dispositivi medici" (CND), which was selected last March as the basis for the future European Medical Device Nomenclature. The commission said it is also currently collaborating with the World Health Organization (WHO) on a future international medical device nomenclature. Last February, WHO discussed some of the progress on the international nomenclature.

Medical Devices: Latest Notified Body Designations

The European Commission (EC) has announced Netherlands-based DARE!! Services B.V. and BSI Group The Netherlands B.V. designated under MDR.

Key Brexit updates

Extension of the Period under 'Article 50'

On 29 October 2019, the European Council agreed to a further extension of the date for the UK's withdrawal from the EU. The extension will last as long as necessary and, in any event, no longer than 31 January 2020. On 21 October 2019 "the Council of the European Union approved the draft Council Decision on the conclusion of the Withdrawal Agreement and forwarded it to the European Parliament in order to obtain its consent. The Union and the United Kingdom have not yet completed the internal procedures necessary for the ratification of the Withdrawal Agreement." The Withdrawal Agreement Bill is currently discussed by the British Parliament. The EMA updated the Questions and Answers related to Brexit says:

"If a withdrawal agreement is endorsed and enters into force, there will be a transition period during which EU law will continue to apply in the UK. This means that access to medicines will not be affected."

For more information, see also:

- European Council decision taken in agreement with the United Kingdom, extending the period under Article 50(3) TEU (28/10/2019)
- European Commission: Brexit preparedness activities
- https://www.ema.europa.eu/en/about-us/uks-withdrawal-eu/brexit-related-guidance-companies

OTHER "HOT" TOPICS FROM UNITED STATES

Is it Possible that FDA's Reforms Need Reforming? Report Looks Back on Four Decades

A new report appearing in JAMA on 14 January 2020 outlines why the reforms at the US Food and Drug Administration (FDA) over the past four decades may need further changes.

The most significant of those changes, according to the authors, include FDA's commitment to review applications for new drugs and biologics in less time; the creation of expedited review programs at FDA, including priority review, fast track, breakthrough therapy designations and accelerated approval; and new incentives for bringing products to market and conducting paediatric studies. Overall, the authors found that the use of FDA's expedited programs has increased over the last three decades, from half (48%) of drugs approved from 1986-1996 qualifying using one or more expedited programs to two-thirds (64%) of drugs approved from 2008-2018 using such programs. The authors chart the increase in the use of these programs and designations and note that "the legally mandated requirement that efficacy claims be supported by 'adequate and well-controlled' trials has become more flexible and controversial."

The number and characteristics of pivotal studies used to support the approval of new drugs has also changed dramatically over time. "The proportion of new approvals supported by at least two pivotal trials decreased from 80.6% in 1995-1997 to 52.8% in 2015-2017, based on 124 and 106 approvals, respectively," the authors write, though they note that the number of patients studied in aggregate did not change significantly between the two periods.

But the authors found that amid reforms aimed at accelerating the development and review of new medicines, the time necessary to take a drug from clinical testing to FDA approval remained relatively flat over the decades, increasing slightly from 7.8 years from 1986-1996 to 9.1 years from 2008-2017.

They offer some explanation for why development times have held steady overall: "The resistance of total development times to efforts to shorten them could be the result of more submissions of applications for rare disease drugs, which can sometimes pose trial recruitment challenges; a shifting emphasis to more challenging therapeutic categories, such as central nervous system disorder treatments; longer time horizons needed to establish efficacy when early intervention is important (e.g., cancer); or other factors."

Notably, one category of products has bucked that trend. Citing previous research, the authors point out that the development time for breakthrough-designated drugs is much shorter than others, at just under five years for those approved through 2016.

Some of the differences in development times for breakthrough drugs stem from the fact that FDA has approved those products based on fewer and earlier stage studies.

"One study found that 52% (16/31) of all breakthrough designated drugs approved between 2013 and 2016 were approved on the basis of Phase I or Phase II trials, 45% (14/31) on the basis of a single trial, and 42% (13/31) without using either an active or a placebo control," the authors write, noting that the findings were more pronounced for oncology drugs.

Similarly, the proportion of orphan drugs approved has increased from 18% of approvals from 1984-1995 to 41% from 2008-2018. In 2018, four-fifths (81%) of newly approved drugs qualified for one or more expedited program and more than half (58%) received orphan designation.

The report also notes that advances in understanding the genetic underpinnings of many diseases will increasingly make it possible to divide common diseases such as lung cancer into smaller, genetically defined subtypes.

"Despite the political popularity and perceived success of many of the programs implemented since the 1980s, the facilitated review processes they made possible appear to have led to both the benefits of earlier access, as well as the potential disadvantages of rapid approval of treatments with clinical outcomes that are not adequately characterized," the authors write.

About CROMSOURCE

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

CROMSOURCE was founded in 1997. Its successful growth over the last 20 years has been built on stability, integrity, and high levels of customer satisfaction, all of which contribute to a high rate of repeat business. We have grown steadily, but responsibly, to become an organisation of over 550 organised and well-trained experts.

A well established full service CRO, **CROMSOURCE** is unique in offering an end-to-end guarantee covering trial timelines, enrolment and contract price. This guarantees our clients that their trials are delivered on time and within the contract price with no CRO-initiated change orders. **CROMSOURCE** operates through offices across all regions of Europe and North America and delivers a comprehensive breadth of services.

CROMSOURCE supports the full spectrum of clinical development via our Pharmaceutical, Medical Device and Staffing Solutions divisions. We seamlessly move biopharmaceutical products from first-into-human conducted in our exceptional early phase unit, through all subsequent phases of pre and post-approval research internationally. We also support medical device projects through regulatory planning and execution, to pilot and pivotal clinical investigations in Europe and North America.

Global Reach

CROMSOURCE, with world headquarters in Verona, Italy, is a leading CRO in Europe and the US with a solid infrastructure and operational subsidiaries in Belgium, France, Germany, Poland, Russia, Spain, Switzerland, the UK, the Netherlands, and the US.

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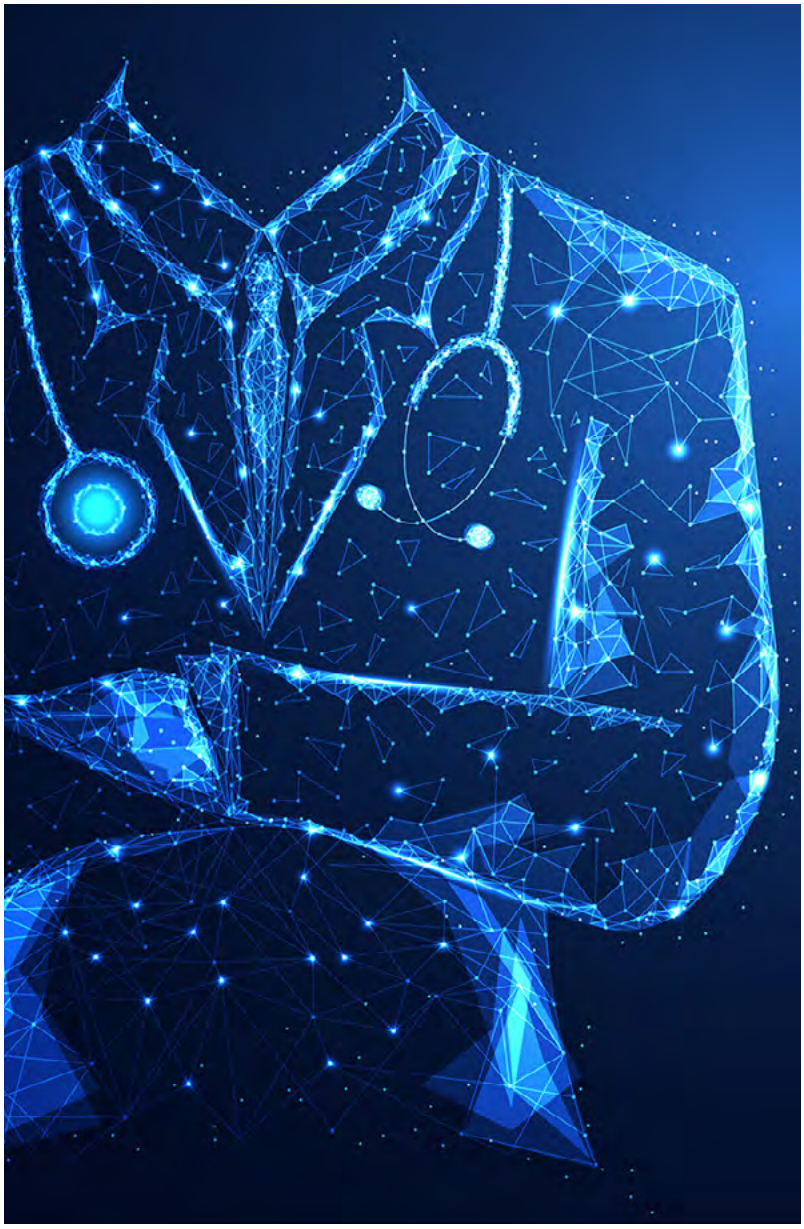

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CROMSOURCE Quality

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