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Challenge and Opportunity in Crisis
- Quality and Sustainability

March 25, 2020

危机中的挑战和机遇
- 关于质量与可持续性发展的思考

2020 年 3 月 22 日

Coronavirus Disease 2019 (COVID-19) has spread to the whole world. World Health Organization (WHO) on March 11, 2020 characterized COVID-19 as a pandemic. Each affected country has started containment and control procedures. However, coronavirus is still spreading, till March 21, already reached 185 countries, with 267 thousand confirmed cases, and 11.2 thousand died from COVID-19[(1)], which further increased to 196 countries, with 375.5 thousand confirmed cases, and 16.4 thousand died from COVID-19 as of March 24, 2020[(1)]. In the crisis, the governments, healthcare organizations, private sectors and people have all come together with tremendous efforts to contain the virus, to save life, and to bring back the economy for people's livelihood. In the meanwhile, many aspects of life have been sacrificed, including the most stringent requirements on effectiveness and safety of healthcare products in US. The US FDA has since loosened requirements in dealing with shortage on diagnostic tests, personal protective equipment (PPE), and treatment. The US FDA initiated the Emergency Use Authorization (EUA) process in February to allow faster distribution of COVID-19 diagnostic tests under EUA. On March 16, 2020, the FDA further issued a policy, "Policy for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency""[(2-4)] to accelerate the availability of COVID-19 diagnostic tests in the US, by allowing clinical laboratories and commercial manufacturers to distribute the tests prior to EUA or without EUA approval. The FDA sent letter to US Healthcare providers with strategies on conserving surgical mask and gown, and allowed the use of industrial N95 in protection

against SARS-CoV-2[5-6]. The FDA also permitted compassion use through expanded access of Chloroquine and remdesivir for treatment of COVID-19[7-8].
新型冠状病毒病(COVID-19)肆虐全球。世界卫生组织(World Health Organization, WHO)于 2020 年 3 月 11 日将之定性为全球大流行(pandemic)，各国采取相应防控和应对措施。但新冠病毒仍在进一步扩散，时至 3 月 21 日，已在 185 个国家流行，26.7 万确证病例，死亡病例已达 1.12 万[1]。在危机中，各国政府、医疗机构、私企和民众，摆上国力、财力、人力、物力，为控制病毒流行、抢救维护生命、维持民众生计而与看不见的共同敌人争战。与此同时，其他各个方面都在做出牺牲，包括美国医疗诊断行业最严格的有效性和安全性标准。美国食品药物监督局(FDA)已经放松规定以解决诊断试剂、防护用品、治疗药物等各环节的紧缺。FDA 在 2 月已经启用紧急使用授权(Emergency Use Authorization, EUA)通道加速新冠病毒(SARS-CoV-2)检测产品在美国上市，并于 3 月 16 日进一步允许临床试验室和试剂生产厂家在申请 EUA 之前或没有 EUA 的情况下，提供测试试剂及测试服务[2-4]。FDA 在 3 月 11 日向全美医疗机构发出节约外科用口罩和防护服的公开信，并放宽外科口罩等防护用品的适用范围[5-6]。FDA 在 3 月 19 日启用氯喹(Chloroquine)和瑞德西韦(remdesivir)慈恩疗法(compassionate use, expanded access)[7-8]。

In the crisis, the IVD industry also faces challenges and opportunities. Due to less stringent regulatory requirements from the US and other countries, IVD manufacturers have a chance to move their COVID-19 diagnostic tests to the market much faster. However, while racing with time, it is imperative for IVD manufacturers to consider how to speed up the development and manufacture of the tests to make them available earlier, at the same time preserving the quality, safety and effectiveness of the tests.
在危机中，体外诊断试剂行业同样面临挑战和机遇。因为美国 FDA 和其他国家地区的医疗监管部门为解决试剂紧缺的现状而放松规定，体外诊断试剂企业有机会更快更早地把新冠病毒诊断试剂推向市场。然而在与时间赛跑的同时，怎样快速研发生产新冠病毒诊断试剂并将产品送抵用户，同时保证诊断试剂产品的质量、有效性和安全性，是体外诊断试剂生产企业需要认真思考和应对的问题。

Product quality is the assurance for users and patients, the prerequisite for market penetration, and the most important factor for sustainable growth of a company. Quality Management System (QMS) is a systemic management approach involving many departments and functions in an organization and spanning the product realization process from product design and development, manufacture to servicing through documentation and record keeping to assure that product quality is maintained. ISO 13485:2016[9] certification or passing (Medical Device Single Audit Program, MDSAP)[10] audit is an indication of QMS establishment, while consistent and effective implementation is critical in ensuring product quality.

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产品质量保证是用户和患者权益的保障，是企业立足市场的根本和长期可持续发展的基本条件。质量管理体系(Quality Management System, QMS)以保证产品质量为中心、以文档记录为基础、涉及公司各部门各环节、从产品设计生产安装到售后服务针对质量保证进行系统性的管理。获得 ISO 13485:2016[9]质量审核认证或者通过医疗器械单一审核程序(Medical Device Single Audit Program, MDSAP)[10]质量审核是检验医疗器械和体外诊断试剂生产企业质量管理体系(Quality Management System, QMS)建立及运作的基本标准，同时有效地执行仍是保证产品质量的关键。

1. Establishment of QMS 质量管理体系的建立：
   - Standard: ISO 13485:2016 and / or US FDA 21 CFR Part 820 Quality System Regulation (QSR). The change of laws and regulations from relevant countries, for example, EU in vitro diagnostic device regulation (IVDR), China National Medical Products Administration (NMPA) regulations, should be continuously followed up on and integrated into the existing QMS.
     标准：ISO 13485:2016 和/或美国 FDA 21 CFR Part 820 质量系统法规(Title 21 Part 820 Quality System Regulation)[11]。积极追踪相关国家和地区针对体外诊断试剂监管的法律法规，比如欧盟体外诊断医疗器械法规(EU IVDR)[12]、中国国家药品监督管理局(National Medical Products Administration, NMPA)法规[13]等，整合入或更新调整企业内部质量规程。

     EU will conclude the transition period and start to enforce IVDR starting May 26, 2020. IVD manufacturers should consider to prepare from now on for the full implementation of QMS that fulfills IVDR requirements.
     欧盟将于 2022 年 5 月 26 日结束过渡期政策并全面执行体外诊断医疗器械法规(IVDR)。体外诊断试剂生产企业需未雨绸缪，积极做好准备。

     QSR in the US stays similar though small modification and changes of requirements are regularly updated by the US FDA. The US FDA has a world-wide reputation on the strictness in enforcing the requirements on medical devices especially the QMS implementation. The IVD manufacturers who would like to distribute the IVD products in the US market should start to consider to update existing QMS to be compliant to requirements in QSR and other relevant 21 CFR part 800's, and implement in daily operation, to prepare for premarket notification (510(k)) and premarket approval (PMA) of their products with FDA, and distribute the IVD products in the US.
     美国 FDA QSR 政策基本未变。因其严格执行声名远扬，有计划进入美国市场的企业需要严格执行此标准，为产品在美国上市前 FDA 审核批准和在美国顺利上市做好准备。

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- Establishment of QMS: 4-level documentation system, including level 1 Quality Manual, Policies, Regulations, level 2 Quality System Procedures, level 3 Work instructions, quality record forms, specification, and level 4 quality records.
  质量体系的建立：建立 4 级文档系统[9]，包括一级质量手册，二级程序文件、标准作业程序，三级操作规程、质量记录表格、质量标准等，四级质量记录

2. Implementation of QMS 质量管理体系的执行：
   - Paradigm shift: The establishment of QMS will need efforts and investment from the organization, but it is essential. Product quality assurance is the prerequisite to have the product stay the market and to achieve sustainability for the organization. Executive Team should establish the quality policy, and root the importance of quality deep into the corporate culture, to have quality been realized in each step from product development, manufacture to servicing.
     典范转移：质量管理体系的建立和执行会在一定程度上增加企业的工作量和资金等各项投入，但不可或缺。产品质量保证是企业立足市场的根本和长期可持续发展的基本条件。企业最高管理层应该制定相应质量方针和政策，并培育**以质量为重心的企业文化**，使质量观念深入产品设计、生产、服务的每一个环节。
   - Quality Department should directly report to the executive management member, independent of other departments or functions including marketing, R&D, manufacture, purchasing, sales and customer service, etc.
     质量部门直接向企业最高领导汇报，独立于其他职能部门包括市场、研发、生产、采购、销售、售后服务等。
   - The executive management member or team should be actively involved in the monitoring and reporting. 企业最高领导参与质量管理体系执行的内部监测和定期汇报。
   - All relevant departments should participate in the establishment and implementation of the QMS, consistently execute the procedures as defined in the QMS, produce and keep the quality record. 各相关部门参与质量管理体系的建立和改进，并坚定不移的按体系界定的程序执行，建立并保持各项质量记录。
   - Evaluate and assess the weak links in the QMS implementation, such as risk analysis, risk management, corrective action and preventive action (CAPA), complaint handling, medical device reporting (MDR), Design Control procedure and documentation, design history file (DHF)[14], etc, and strive to strengthen each.

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分析评价企业质量管理体系执行的薄弱环节，比如风险分析和管理(risk analysis, risk management)、矫正及预防措施(corrective action and preventive action, CAPA)、客户投诉处理(complaint handling)、医疗器械报告(medical device reporting, MDR)、设计控制程序和文档(Design Control procedure and documentation)、设计历史文档 (design history file, DHF)[14]等，并努力加强执行力度。

3. Monitor of QMS Implementation 质量管理体系执行的监督：Three types of Quality Audits are effective in monitoring the status and assessing the effectiveness of the QMS implementation 三类质量审核(Quality Audit)[15]有效地检查监督质量管理体系的执行状况。
   - First-Party Audit (Internal Audit): The audit that is executed inside an organization across department or function can detect potential or actual problems fast. This is a highly rewarding approach with relatively small investment.
     内部质量审核：按计划实施的企业内部跨部门跨职能的质量审核；及早发现并解决潜在或已出现的问题，这是减少投入，提高效能，同时保证企业产品质量的方式。
   - Second Party Audit: These include the customer's audit on the organization, or supplier audit by the organization. Supplier audit is very important to be sure the raw materials or services provided by the supplier are meeting the predetermined quality specifications, to ensure the product quality in the organization.
     第二方质量审核：包括顾客对企业的质量审核和企业对供应商的质量审核(Supplier Audit)。企业对供应商的质量审核，以保证原材料和服务满足预定质量标准，来确保企业自身产品质量。
   - Third-Party Audit 第三方质量审核：
     - International Certification 国际认证：ISO 13485:2016 Quality Audit and Certification, Medical Device Single Audit Program (MDSAP) Quality Audit
       ISO 13485:2016 质量审核认证、医疗器械单一审核程序(MDSAP)质量审核
     - Inspection by regulatory agencies 各国监管部门质量检查：such as FDA inspection, and inspections by China National Medical Products Administration (NMPA)
       比如 FDA 检查(inspection)、中国国家药品监督管理局飞行检查等
     - Quality Audit by Audit Organization: Inviting audit organization or consultant as auditor to audit the QMS or a specific department or function brings in impartial and objective assessment, which gives the organization opportunity to find problems in time and correct.

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专家顾问质量审核：邀请专家顾问针对企业质量管理体系或特别部门、职能进行质量审核。专家顾问给予企业的中立、公正的评判，让企业及时发现并纠正问题，进一步有效执行和改进质量管理体系。

4. Implementation of QMS in crisis 危机时期的质量管理体系执行：
   - Regulatory agencies' shifted focus: In crisis, the regulatory agencies are focused on accelerating the availability of what is in need, and in the meantime may temporarily alter or lessen certain requirements. At this special time, effective implementation of QMS inside the manufacturer's organization becomes even more important.
     监管部门重心转移：满足市场紧急需求成为危机时期的工作重心，政府部门对相关产品质量的要求和监管在一定程度上有所放松。这时，**企业内部的质量管理体系的有效得力执行更显得至关重要**。
   - Effective implementation inside the organization: The manufacturer should continue to implement and execute the procedures as defined in the procedures. If modification is needed to adapt to the need in the crisis, the organization should consider to pursue thorough risk analysis focusing on quality related risks, have and execute a remediation plan to properly manage risks. For example, the manufacture can enhance the post-market surveillance efforts, collect and analyze data from the field, report to regulatory agencies (such as medical device report, MDR, to the FDA) of the adverse effect or product malfunction, to ensure product quality. In the meantime, the organization should continue to implement the normal procedures on other non-crisis related products and make sure they are produced and served with claimed quality.
     企业内部有力执行：在产品研发和生产过程中继续有力执行质量管理体系规定。如因危机时期的特殊要求需要调整相关程序或操作规程等，竭力做好以质量受损为主的风险分析并制定相关措施以控制风险，比如增强售后市场监督、及时收集并分析临床数据、向监管部门汇报等以保证产品质量。继续有力执行质量管理体系以保证与危机不相关的其他产品的质量。

5. QMS Implementation post crisis 危机结束后的质量管理体系执行：
   - Internal assessment and adjustment: The organization should pursue systemic analysis on and assess the quality of all the products manufactured and distributed during the crisis, add risk analysis as needed. If any product was impact by the crisis and had quality impact, the organization should consider to re-strategize, remedy the existing problems, and apply the organization's highest standard on the product quality to all relevant steps to improve quality of the impacted products.

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企业内部评估和调整：对危机时期所生产、销售的产品做系统分析评估，按需加入风险分析，对质量受到影响的产品，调整策略，重新启用企业最高标准改进各程序执行并提高产品质量。

- Follow up on regulatory requirements from various countries and update the QMS.
  追踪各国各地区针对体外诊断试剂监管的法律法规，更新企业内部操作规程。
- In normal time, continue to have a focused effort on assuring quality, and continuously improve.
  在和平时期，把质量继续做为企业工作重心，不仅坚定不移的执行下去，而且继续投入以持续改善。

A crisis comes and goes, but the society will move forward and the manufacturers will continue to produce and provide products and services. Quality is still the most important factor for any manufacturer to be relevant in the market and grow sustainably, which asks for each manufacturer to be firm on implementing a QMS that is to requirements, and continuously improve the process to ensure product quality.
危机会成为过去，社会将继续前进，企业会继续提供产品，然而产品质量保证仍然是医护和患者权益的基本保障，是企业生存和长期发展的基本条件，这需要企业坚定持续有效地执行质量管理体系界定的程序。

Reference 参考信息：

1. WHO on COVID-19 as pandemic WHO 定性新冠病毒疾病(COVID-19)为全球大流行：https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. FDA announcement of the policy on COVID-19 diagnostic tests FDA 新冠病毒诊断试剂指导文件发布说明：https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-diagnostic-tests-coronavirus-disease-2019-during-public-health-emergency
3. FDA policy on COVID-19 diagnostic tests FDA 新冠病毒诊断试剂指导文件：https://www.fda.gov/media/135659/download
4. FDA policy on COVID-19 diagnostic tests FAQs FDA 新冠病毒诊断试剂指导文件常见问题解答：https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2
5. FDA letters on surgical mask and gown conservation strategies FDA 节约使用外科用口罩和防护服的公开信：https://www.fda.gov/medical-devices/letters-health-care-providers/surgical-mask-and-gown-conservation-strategies-letter-healthcare-providers

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6. FDA FAQs on shortages surgical masks and gowns FDA 外科用口罩和防护服短缺常见问题解答：https://www.fda.gov/medical-devices/personal-protective-equipment-infection-control/faqs-shortages-surgical-masks-and-gowns
7. Coronavirus Task Force, White House Press Conference, March 19, 2020 美国白宫新冠病毒特别工作组 3 月 19 日新闻发布会
8. FDA Expanded Access https://www.fda.gov/news-events/public-health-focus/expanded-access
9. ISO 13485:2016: https://www.iso.org/standard/59752.html
10. FDA on MDSAP FDA 官网医疗器械单一审核程序(MDSAP): https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap
11. FDA 21 CFR Part 820 Quality System Regulation (QSR) FDA 质量管理体系法规: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820
12. EU IVDR 欧盟体外诊断医疗器械法规: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN
13. China NMPA regulations on medical devices 中国国家药品监督管理局(NMPA)法规：http://www.nmpa.gov.cn/WS04/CL2178/
14. FDA Inspection Observations FDA 检查发现: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations
15. The ASQ Auditing Handbook, 4th Edition ASQ 质量审核手册，第 4 版, J.P. Russell

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