Radiochemistry, PET Imaging, and the Internet of Chemical Things

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ABSTRACT: The Internet of Chemical Things (IoCT), a growing network of computers, mobile devices, online resources, software suites, laboratory equipment, synthesis apparatus, analytical devices, and a host of other machines, all interconnected to users, manufacturers, and others through the infrastructure of the Internet, is changing how we do chemistry. While in its infancy across many chemistry laboratories and departments, it became apparent when considering our own work synthesizing radiopharmaceuticals for positron emission tomography (PET) that a more mature incarnation of the IoCT already exists. How does the IoCT impact our lives today, and what does it hold for the smart (radio)chemical laboratories of the future?

The lives of chemists have immeasurably benefited from the development of the Internet. Some of these impacts are obvious because of their magnitude and far reaching effects. Consider, for example, how chemists now search for information. Oftentimes open source encyclopedias (e.g., Wikipedia) have become the go to place for general chemical information, while searching the literature or accessing physicochemical properties for compounds is usually accomplished using large online databases such as SciFinder and PubMed, or ChemSpider and PubChem, respectively.1 Electronic laboratory notebooks (ELN) coupled with structure drawing software suites (e.g., ChemBioDraw) and citation managers (e.g., EndNote, Papers) are further obvious examples,2 especially newer versions that enable electronic archiving and integration into laboratory inventory management and institutional procurement systems, and/or databases such as SciFinder. The way that chemists communicate, both with students and with peers, has also changed considerably in the digital age. Online courses, accessible by students all over the world, have been introduced,3 while virtual conferences4 and online forums (e.g., Facebook, Twitter, LinkedIn, ResearchGate, Reddit, MedChemNet, and countless others),5 coupled with electronic journals (many of which are open access or offer open access options), present new paradigms in how data and ideas are discussed and disseminated.6 Building on this electronic infrastructure, secondary platforms such as Bioz are being developed to provide chemists with real time insights and recommendations for products, reagents, equipment, and assays by using computers to mine the millions of articles available on, for example, PubMed.7 In the earlier days of the Internet, chemists accessed many of these resources (or at least earlier versions of them) using computers, either at home or in the laboratory. Further change has accompanied the smartphone revolution, however, such that many software packages, journals, and online resources now offer stripped down versions that are compatible with smartphones, tablet computers, and even smartwatches.8

What is perhaps less obvious is how the worldwide web, cloud computing, machine-to-machine communication (M2M), and an ever expanding network of connected machines impact chemists in the day-to-day laboratory setting. We were therefore particularly intrigued by a number of recent reports introducing machine-assisted organic synthesis,9,10 computer-assisted synthetic planning,11 automated small molecule synthesis,12 and on-demand continuous flow synthesis of pharmaceuticals,13 as well as a report from Ley and colleagues recognizing that such networked processes start to represent an Internet of Chemical Things (IoCT).14 The latter idea is an offshoot of the Internet of Things (IoT), a concept introduced by Ashton in 1999 describing the interconnectedness of machines through the architecture of the Internet.15 The concept is impressive in its magnitude, and its realization continues to gather momentum,16 with a staggering 24 billion things expected to be connected to the Internet by 2020.17

While the use of such systems is still in infancy across many chemistry laboratories and departments, when considering our own work synthesizing radiopharmaceutical drugs for positron emission tomography (PET), a form of functional molecular imaging, it became apparent that a more mature incarnation of the IoCT in many ways already exists. In this context, robust data generation, capture, and storage capabilities are an essential feature of reliable and automated PET drug manufacture according to current Good Manufacturing Practice (cGMP) in the modern radiochemistry laboratory. Herein we offer commentary on the current state of the art and possible future directions of the IoCT, using radiochemistry and PET imaging as a demonstrative example but recognizing that these directions of the IoCT, using radiochemistry and PET imaging as a demonstrative example but recognizing that these
changes are happening throughout chemistry, medicine, and the greater scientific community at an accelerating pace. For example, as PET radiopharmaceuticals move into clinical use, an equivalent Internet of Medical Things (IoMT) is similarly revolutionizing molecular imaging and the field of diagnostic radiology, and has been reviewed elsewhere.18

PET imaging works by injecting a patient with a radiopharmaceutical (a biologically active molecule tagged with a PET radionuclide) and subsequently detecting the coincident emission of the pair of $\gamma$ rays which result from annihilation of the positron emitted by the radiopharmaceutical.19 This allows calculation of the location of the annihilation event and, by inference, the location of the radiolabeled molecule in the body at the moment of decay. Commonly employed radionuclides include $^{11}$C and $^{18}$F, and the development of methods to incorporate such radionuclides into diverse bioactive molecules has become a dynamic and expanding research area in its own right.20 For example, in recent years there have been many exciting developments in late-stage fluorination using fluorine-$^{18}$, and new applications of $[^{11}\text{C}]\text{CO}_2$ fixation chemistry for carbon-11 labeling.24,25 The half-life of $^{18}$F is 110 min, while that of $^{11}$C is 20 min, meaning that both radionuclides need to be prepared on demand, usually with a cyclotron, and used within minutes ($^{11}$C) to a few hours ($^{18}$F). However, daily PET radiopharmaceutical synthesis and delivery for human studies presents unique challenges—a need for speed (using short-lived radionuclides, a total preparation time of 1–2 h), radiation safety (multi-Curie amounts of nuclides), pharmaceutical-quality procedures (FDA regulated), reliability (patient care), and economy (cost-containment for health care)—which we feel are being best met through the application of automation and the development of the IoCT. Fortunately, the use of computers to control cyclotrons, as well as computer-controlled robotics and remote systems for conducting radiochemical syntheses and purifications, has been an integral part of PET radiochemistry for more than three decades.26

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Through the years, the use of PET imaging (and the requisite methods for PET radiopharmaceutical preparation) has changed, driven in part by the approval of $[^{18}\text{F}]\text{fluorodeoxyglucose}$ ($[^{18}\text{F}]\text{FDG}$) by the US Food and Drug Administration (FDA) in the 1990s.27 Reflecting this, the early homemade remote synthesis systems of the 1980s (Figure 1A) were gradually replaced in the 1990s–2000s by more sophisticated fully automated radiochemistry synthesis modules and microfluidic systems from commercial vendors (Figure 1B) to facilitate compliance with FDA regulations.28,29 When considering the interconnection and networking of machines, such synthesis platforms can be considered early microcosmic versions of the IoCT. They are complete synthesis systems that contain modules for receiving radioactivity from the cyclotron, a synthesis component (usually a reaction vessel and heater), a vacuum pump for evaporating solvents, an integrated semi-preparative HPLC purification system, and a reformulation module for reconstituting radiopharmaceutical doses into a saline solution suitable for intravenous injection. All of the systems are interconnected, housed in a lead-lined fume hood (hot-cell), and managed by a computer from outside of the hot-cell. Computer programs control the entire synthesis, including setting parameters (e.g., reaction temperatures, HPLC flow rates), activating a series of valves which control gas flow, application of vacuum to the reaction vessel, addition of reagents, catalysts, and solvents, transfer of the reaction mixture to the purification system, and delivery of the final radiopharmaceutical into a sterile vial. Such systems allow the synthesis module to be set up by the radiochemist before radioactivity is delivered; the hot-cell can then be sealed and the radioactive isotope delivered from the cyclotron. From this point, the computer controls all steps in the synthesis of the radiopharmaceutical. Throughout the entire process, the computer logs data from numerous components and detectors (e.g., radioactivity values from detectors throughout the system, temperature and pressure measurements, UV and radioactivity detector values from the HPLC unit). The resulting data are then incorporated into the master batch record (MBR) associated with the synthesis, along with cyclotron performance and QC data, so that they are available for review and/or troubleshooting at a later date. As modules became more advanced, self-tests have been incorporated, such that the control computer can alert the operator if any system parameters are outside of defined ranges. The synthesis module and data recording system is, therefore, a miniaturized IoCT, defined by Ley as “the interconnection and networking of chemical machines, computing devices and all chemical services delivered through the infrastructure of the Internet”.14 The sensors within the module are constantly relaying actionable information to a responsive computer through a network, allowing the operator to synthesize, purify, and deliver a dose of a radiopharmaceutical with minimal direct input after delivery of radioactivity. In most cases during this period, separate computers controlled the cyclotron and synthesis module. However, there are examples, usually involving simpler chemistry such as the synthesis of $[^{15}\text{N}]\text{ammonia}$, where both the cyclotron and synthesis module are connected to a single computer that controls both components.30

The next seismic shift for the PET community came in the late 2000s, when the requirement to prepare PET radiopharmaceuticals for clinical use in accordance with cGMP became a mandate. In the United States, the cGMP regulations for PET drugs are described in 21CFR212 and enforced by the FDA.31 This new regulatory environment and the growth in PET imaging utilization have catalyzed a number of changes in the PET community. The IoCT has become an integral part in many of these changes and facilitated compliance with cGMP regulations. Manufacturing of PET drugs (or any pharmaceutical) according to cGMP is intended to ensure proper design, monitoring, and control of manufacturing processes, facilities, and personnel. To comply with cGMP regulations requires extensive documentation (with appropriate access controls, audit trails, and checks) that includes records of components used, production reports (e.g., from cyclotron and synthesis modules), analytical data (e.g., HPLC traces), QC test results, and documentation of release for use by a qualified person. Manual composition of all of these individual components into master batch records can be quite time-consuming, especially for commercial nuclear pharmacies running multiple national and/or international manufacturing sites. To address this time-consuming process a number of PET sites have adopted a Laboratory Information Management System (LIMS) to simplify the process.32 First and foremost, LIMS are connected
through the IoCT to synthesis and QC components (Figure 2), allowing them to automatically manage supply inventory and component lot numbers, simplify document management (standard operating procedures (SOPs) can be uploaded to LIMS by the quality assurance (QA) unit so that the latest version is always available to chemists working in the laboratory), collect raw production data (e.g., cyclotron and synthesis module production reports, balance and dose calibrator readouts) and analytical data (e.g., HPLC, TLC, and/or GC traces, bacterial endotoxin test (BET) results, multichannel analyzer (MCA) values), and enable user input of offline analytical results (e.g., postrelease sterility testing outcomes). As they capture all of this information directly through the Internet, and automatically collate this information into a master batch record and/or product label, proponents of such systems suggest that errors resulting from manual transcription errors are reduced, if not eliminated entirely.

Second, the LIMS allows for collective analyses of the extensive data sets recorded from all syntheses, so that production teams can easily track synthesis parameters (e.g., reactions yields), and quality assurance operations can readily monitor trends in process deviations, out of specification (OOS), events or failed QC tests.

Electronic documentation generated by all of these systems is bringing the PET community more in line with the electronic documentation flow being adopted by the FDA. Regulatory documents, qualification batch records, labels, and package inserts are all prepared by computer, using word processing programs and/or online XML templates. The various components are compiled into compressed files and sent to

Figure 1. (A) Early robotic system for conducting radiochemical reactions. Reprinted with permission from ref 26. Copyright 1988 Elsevier. (B) Fully automated radiochemistry synthesis module and (C) modern cassette-based system. Courtesy of GE Healthcare.

Figure 2. PET LIMS system working through the IoCT.
FDA using the Internet via their Electronic Submissions Gateway (ESG), an electronic system described as "an Agency-wide solution for accepting electronic regulatory submissions" that "enables the secure submission of regulatory information for review".33

One result of this changing regulatory environment is that the costs of synthesizing PET radiopharmaceuticals have increased considerably, an issue further exacerbated by declining reimbursement for healthcare. To cover these increasing costs, PET drug manufacturers strive to maximize uptime of their production facilities (including cyclotron, synthesis module, and quality control components), usually aiming for >99%. To accomplish this, PET radiochemistry laboratories are invested in improving reliability of production and reducing unscheduled downtime due to equipment failures. One approach aimed at improving reliability is the push to develop fully automated cassette-based synthesis systems for the daily routine production of radiopharmaceuticals (Figure 1C). Unlike the automated systems described above, these newer modules use cassettes that are preloaded with chemicals as well as synthesis and purification components. Cassettes are assembled under cGMP-compliant clean room conditions, sterilized with gamma-radiation, and vacuum-packed. The cassette is attached to the synthesis module by the radiochemist, and a barcode on the cassette is read, communicating to the module which synthesis program the module should run for the installed cassette. The use of sterile, disposable cassettes ensures easy handling and reliability, reducing errors associated with setup and operation of the earlier synthesis modules.

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A similar effort is underway to simplify and automate PET drug quality control testing. Quality control requirements are described in 21CFR212 and the US Pharmacopoeia, and involve analyzing doses to determine radiochemical and chemical purity (HPLC or TLC), residual solvent levels (GC), visual inspection, pH, osmolality, radionuclidic identity (half-life) and purity (multichannel analyzer), bacterial endotoxin levels, sterile filter integrity, and sterility. A batch must pass all of the QC tests before it is released to the imaging site for use in a clinical PET study. This battery of tests has historically required separate pieces of specialized analytical chemistry equipment, which are expensive to initially purchase as well as subsequently maintain, and which require trained personnel to operate. To simplify the process, there has been a move to develop miniaturized analytical systems that incorporate all of these tests into a single automated unit with the goal of simplifying, automating, and accelerating quality control analysis of PET radiopharmaceutical doses.35 Existing systems employ a central sample-handling module that uses robotic pipetting systems and is coupled with interchangeable and customizable modules for the QC tests outlined above. The systems have reduced laboratory footprints (and waste) compared to ten or more individual pieces of analytical equipment, require less sample than traditional QC testing, and thus are expected to be simpler to use and more economical to operate than traditional QC laboratory setups.

Maintaining >99% uptime is also not straightforward because of delays due to unplanned equipment downtime and associated maintenance. Cyclotrons themselves have complex components related to the ion source, high voltage RF system and magnet, diffusion pump and vacuum system, target filling systems, and numerous cooling systems (e.g., helium-, air-, and water-based). These components can have their own mechanical and/or electronic issues associated with everyday wear and tear, but many are often further exacerbated because of exposure to Curie levels of radioactivity on a daily basis. The synthesis modules also contain a range of moving parts (valves, pneumatic actuators, and magnetic stirrers) liable to wear and tear, and which are also exposed to the same high levels of radioactivity in addition to a range of solvents and (potentially) corrosive chemicals (e.g., acids and bases).

To maintain uptime and facility productivity, most cyclotrons and radiochemistry synthesis modules are under some form of manufacturer maintenance contracts. These contracts can be expensive, and as a result commercial vendors are frequently under pressure to improve service and maximize customer uptime. Large vendors have gravitated toward managing parts and service through electronic systems and databases, frequently keeping customers and service engineers updated (through the Internet and e-mail) about timing and progress of maintenance by connecting them with the global couriers responsible for shipping parts. All of these approaches have improved service and reduced downtime in the laboratory, but still remain reactive in their nature.

In a new service paradigm, the IoTCT enables manufacturer and third party service centers to be constantly connected to systems that are installed at customer sites (Figure 3). For example, because cyclotrons are particularly sensitive to power fluctuations, they are often equipped with a third party voltage monitor, which transmits data about any fluctuations in incoming power quality to an off-site server via an ethernet (or modem) connection. The data is collected and analyzed, and instant notification of an event is sent to subscribers via text message or e-mail. This online monitoring provides a continuous monitoring solution that allows operators to address equipment issues arising in real time as opposed to uncovering problems randomly if/when they manifest later. The connectivity resulting from the IoTCT also enables equipment manufacturers to conduct remote service (rapid and remote monitoring, access and repair of products at customer sites) and, in the case of minor issues, frequently eliminate costs and uptime delays associated with deploying an engineer to service equipment on-site. This system also allows service engineers to run system diagnostics in advance of planned maintenance, so that they know which replacement parts to bring with them to the customer site. As the IoTCT matures, however, maintenance is becoming increasingly proactive, and, although this capability has not been entirely developed yet, we can envision a time in the near future when data sent by the customer’s system (in our case the cyclotron or synthesis module, but it could be any connected thing) will be monitored 24 h per day by computers at the remote monitoring center (RMC). The RMC will then provide engineers with advanced notice that system components are deteriorating and that maintenance will be required soon. Replacement parts can then be ordered and service scheduled in advance of a part failure,
enabling a prompt response from the service team to further minimize customer downtime.

Finally, following synthesis and quality control, the PET radiopharmaceutical is delivered to the clinical site for use in a PET imaging study. Just as the modern chemistry (and radiochemistry) laboratory is being changed by the IoCT, a related Internet of Medical Things (IoMT) is impacting healthcare, including diagnostic radiology (Figure 4). A detailed discussion of how networked devices are impacting health systems and the practice of medicine is outside of the scope of this article, but has been commented upon previously. Briefly, however, telemedicine was introduced in the late 1980s as a broad concept covering the use of telecommunications and computers to provide clinical healthcare to patients at remote locations for whom visits to large hospitals in metropolitan areas were impractical. Nowadays telemedicine, connected to IoMT devices, allows healthcare professionals to interact with patients remotely while they are at their home to obtain basic information (e.g., weight and height, diet and exercise, amount and quality of sleep). If further testing is required (e.g., blood pressure readings, neuropsychometric testing), this can also frequently occur in the patient’s place of residence if they are provided with a dedicated medical device and/or tablet computer for use while at home.

Concurrent with the integration of telecommunications and computers into telemedicine, similar advances have occurred in radiology. With the introduction of sophisticated imaging modalities such as nuclear medicine techniques (e.g., PET imaging), computed tomography (CT), and magnetic resonance imaging (MRI), images on traditional radiological films (e.g., X-rays) have been replaced by digital images on computer screens. Powerful networked computer systems (e.g., Picture Archiving and Communication Systems, PACS) that facilitate image acquisition, image storage, and data management are commonplace. These systems include a transmission network that uses the Internet to move images (locally within an institution, or off-site) and image viewing systems that allow radiologists and nuclear medicine physicians to retrieve images for clinical management, research, and teaching purposes.

When a patient comes to the hospital for a PET scan, they receive an intravenous injection of the radiopharmaceutical under authorization of a nuclear pharmacist and/or nuclear medicine physician. The dose is injected either manually via a syringe or, increasingly commonly, through an automated PET drug infusion system designed to minimize radiation exposure to hospital workers who would otherwise have to handle numerous radioactive syringes on a daily basis. These infusion systems can be connected to the radiology PACS system, and detailed infusion records, which include radiopharmaceutical dose delivered to the patient and estimated absorbed radiation...
dose by organ, are automatically transferred to PACS. Following injection, the patient is placed in the scanner and the PET scan is acquired using the scanner control computer. Just as the systems in the radiochemistry laboratory are all connected to the Internet, so too are the clinical systems, and analogous infrastructure for remote monitoring, service, and maintenance is concomitantly being developed for the PET scanner and PACS systems. Following the scan, imaging data is then transferred to PACS, from which it can be accessed at a later date for analysis and interpretation using either a PACS viewing station (equipped with a dedicated PET module) or, increasingly, apps on mobile devices such as tablet computers or smartphones.

At the juxtaposition of radiology, telemedicine, and the IoMT lies teleradiology. In the 1950s and 1960s, teleradiology focused upon using early televisions to allow radiologists to look at medical images from other locations such as the emergency room but, in the 1970s and 1980s, became more computer-based. However, early adoption was slow due to the high costs of computers and Internet access, as well as early Internet connections becoming overwhelmed when moving the large amounts of data associated with radiology images. In recent years, with the combination of advances in computer hardware and ready availability of low-cost high-speed Internet connections heralding the advent of the IoMT, FDA-approved teleradiology platforms have become both functional and affordable. These systems allow images to be acquired at either the main hospital or an off-site location (e.g., outpatient clinic, other hospital, specialized imaging center) and then forwarded via the Internet to a radiologist for interpretation, and are transforming the practice of radiology in the age of the IoT. As we look to the future, we expect radiology and medical imaging to be integral to the continued development of the IoT. With storage requirements for U.S. medical imaging data alone expected to exceed 1 exabyte (1,000,000 terabytes) in 2016, the field is at the forefront of the big data revolution. To effectively store, manage, share,

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secure, and efficiently utilize and/or mine this amount of data is going to require health systems make large and sustained investment in maintaining (and consistently improving) IT infrastructure a high priority in the coming years.

Herein we have demonstrated how the IoT is changing the way operations are conducted in both (radio)chemistry laboratories and a healthcare setting, presenting numerous examples of positive impacts in both disciplines. It would be remiss of us however to not also include a word of caution concerning security issues in this new interconnected world. Two notable security concerns stem from ransomware and cyberattacks, and governments are still wrestling with how to combat such cybercrimes. First, 2016 has seen several healthcare systems around the world targeted by ransomware attacks, where hackers have held files and internal networks for ransom, demanding payment before returning access. These incidents serve to highlight the need for hospitals and healthcare systems to implement increased security measures to prevent unauthorized access to these networks. Second, as more devices are connected to the IoMT and the IoCT, they become vulnerable to cyberattacks and pose safety risks to operators or, in the case of the IoMT, patients. PET centers use devices, including cyclotrons and PET-CT scanners, capable of delivering high amounts of radiation. Without adequate protections, PET radiochemists risk being exposed (accidentally or, possibly, deliberately) to high levels of radiation if the cyclotron is turned on without their knowledge through a compromised network. Patients and medical staff face similar risks if, for example, they are unaware that the PET drug infusion system has been started, or the CT portion of the PET-CT scanner turned on. Such concerns have already begun to attract attention from safety regulators, such as the FDA, who recently published an advisory to continue the use of a network-connected infusion pump because the device could be accessed remotely by unauthorized users, posing a dire risk to patients. Beyond the physical risks posed by the digital hijacking of these devices, healthcare systems have a legal duty to ensure that the confidentiality and integrity of patient records are maintained. As more patient information is collected, transmitted, and stored online, such systems must be secured to ensure that the data is not vulnerable to unauthorized access. The scientific and healthcare communities, as well as countless other disciplines such as manufacturing, energy, transport, architecture and construction, urban planning of smart cities, and military and space exploration, are all embracing the change and possibilities brought by the IoT, and the almost immeasurable value offered to society justifies its development. While the security issues are potentially large, they are not insurmountable if the IoT is developed in a responsible manner with careful attention to cybersecurity aimed at protecting individual privacy and sensitive information (e.g., intellectual property, classified documents) in addition to preventing unauthorized access to networked devices.

CONCLUSIONS AND FUTURE OUTLOOK

The impact of the IoT on science and medicine is transforming healthcare. Ready access to inexpensive computers, high speed Internet connections, and sophisticated software systems are leading to vast interconnected networks of computers, databases, communication interfaces, scientific instruments, and medical equipment that can be plugged into as needed by scientists, physicians, medical professionals, administrators, service engineers, and patients alike. The incorporation of the IoT in the PET environment has largely been driven by the need to minimize radiation exposure and reduce costs, while concomitantly meeting increasing regulatory demands. While the driving forces for other chemists may differ, similar benefits, including streamlining of processes, observation of new trends through big data analysis, and more efficient use of resources, will no doubt encourage more laboratories to embrace the IoCT.

Theoretically, the future is now; the architecture of the Internet already supports such connectivity, and the instruments used in radiochemistry and PET imaging are already equipped with many of the features required for such automated communication to occur. In practice, however, challenges must still be overcome before such systems are a reality.

These large networks of machines have already had enormous impact on radiochemistry and PET imaging, transforming day-to-day operations such as ordering, servicing, and data collection. However, we believe that PET facilities heavily integrated into IoCT technologies have yet to fully realize all of the opportunities that this technology presents. As the IoCT concept evolves, we can envision a system where these machines are granted autonomy to communicate among themselves and make decisions on their own. By way of example, when a patient is scheduled for a given PET scan, this information could be passed from healthcare systems connected into the IoMT to PET center systems on the IoCT. The PET systems could then communicate with each other through the IoCT infrastructure to check inventory, order any supplies that are needed, check system suitability of cyclotron, synthesis module, and QC equipment (scheduling maintenance as needed), and finally schedule radiochemists to prepare the PET radiopharmaceutical. Extending the concept further, radiochemists could set the synthesis up the day before, and then the whole process, including cyclotron production of radionuclides, synthesis of the radiopharmaceutical, and quality control, could be run through the night, either automatically or through remote control, such that doses are ready to send to the imaging center when chemists arrive in the laboratory the next morning. Notifications of the completion of each stage could also be sent to the production chemists, keeping them updated on progress, as well as warning them about any problems that may require them to get on-site earlier to address. Extensive data from these processes, too burdensome to be manually collected and analyzed, could also be recorded, tracked, and trended through the IoCT, potentially enabling the machines to improve manufacturing processes in ways we cannot currently imagine. Small, automated and miniaturized QC systems might be fully integrated into the synthesis systems, allowing automated quality control as well as real-time data analysis and product release by quality control personnel located anywhere with an Internet connection.

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ments used in radiochemistry and PET imaging are already equipped with many of the features required for such automated communication to occur. In practice, however, challenges must still be overcome before such systems are a reality. The biggest obstacle to a full deployment of an integrated IoCT and IoMT in the PET community remains the time sensitivity of PET radiopharmaceutical production. Anyone working with systems that rely on the IoT will be at the vulnerability of routine IT problems such as computer failures, software bugs, hardware and software obsolescence, etc. However, when performing dose-on-demand manufacture of short-lived radiopharmaceuticals, such problems are exacerbated because the radiopharmaceutical will decay to unusable levels in the time it can take to fix a routine computer problem. Beyond the IT infrastructure, do mission critical instruments and computers can be duplicated so that backups are available, but it is impractical and unaffordable for many sites to back up large and expensive pieces of equipment such as cyclotrons. Therefore, it is critical that manufacturers demonstrate long-term reliability of such components if PET centers are going to trust the multimillion dollar business of PET radiopharmaceutical manufacture in its entirety to the IoCT.

In closing, it is ultimately our hope and expectation that the development of these smart, IoCT-integrated radiochemistry laboratories is poised to make the process of PET drug manufacturing more streamlined, reliable, and economical. This in turn will relieve PET radiochemists from straightforward repetitive tasks (e.g., scheduling, inventory management, data collection, and documentation) so that they have more time to devote to their research endeavors developing the radiopharmaceuticals and/or imaging technologies that will be a critical part of healthcare in the smart cities and interconnected world of the future.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this work from the U.S. DOE (DE-SC0012484) is gratefully acknowledged.

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