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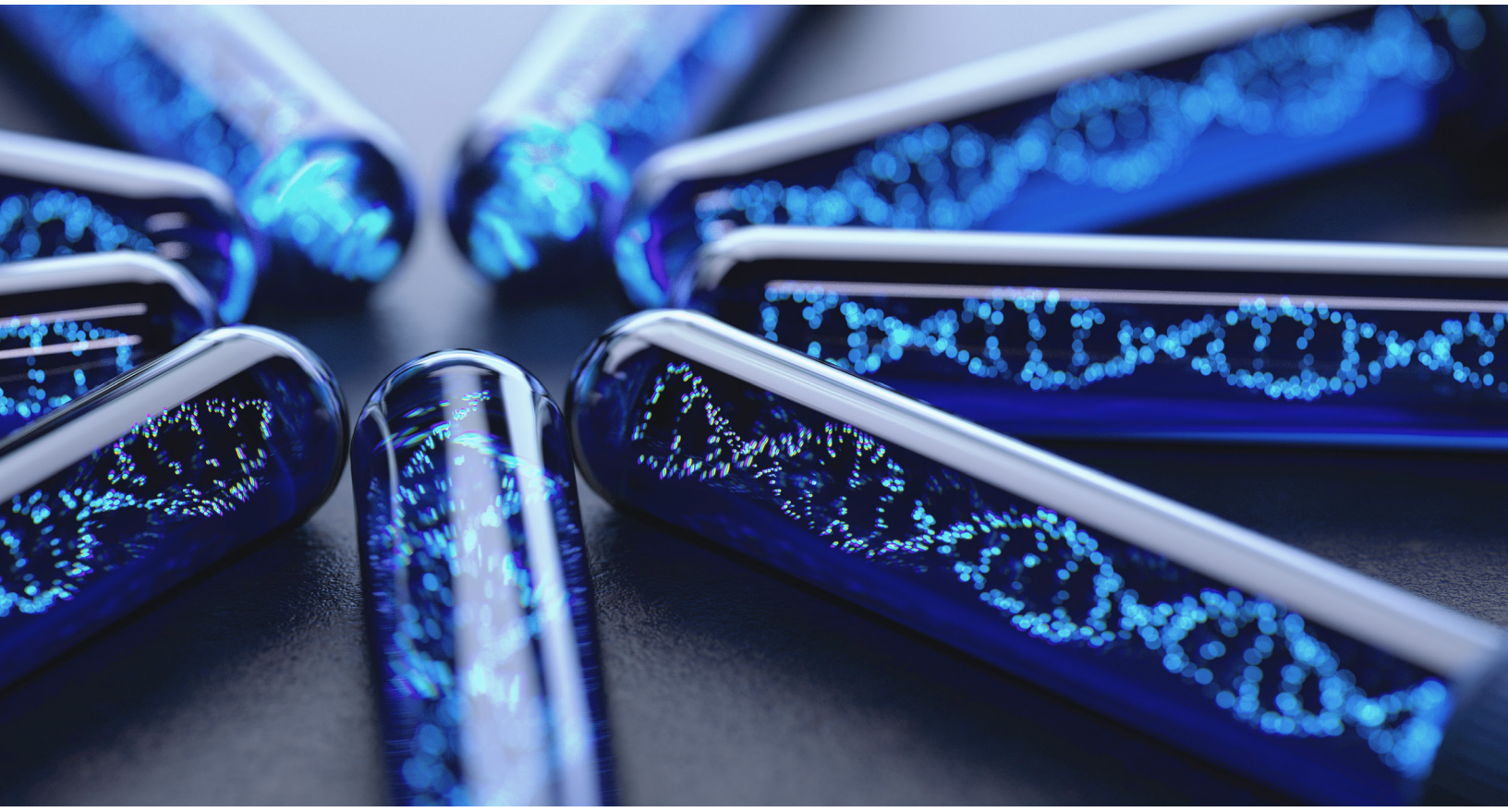
Pharma's digital Rx: Quantum computing in drug research and development

Quantum computing's ability to simulate larger, more complex molecules could be game changing. Pharmaceutical companies should reflect on their strategic stance to this promising new technology now.

by Matthias Evers, Anna Heid, and Ivan Ostojic



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The development of molecular formulations that become drugs to treat or cure diseases is at the heart of the pharmaceutical industry. Development is so fundamental that pharma spends a full 15 percent of its sales on R&D—a huge sum that accounts for more than 20 percent of total R&D spending across all industries in the global economy. This investment goes hand in hand with innovation: constantly seeking to improve the R&D process, pharma companies have for decades been early adopters of computational chemistry's digital tools, such as molecular dynamics (MD) simulations and density functional theory (DFT). More recently, pharma R&D has taken advantage of artificial intelligence (AI). The next digital frontier is quantum computing (QC).

In a recent article, we analyzed the impact of QC on the chemical industry, which, similarly to pharma, relies on the development and manufacture of molecules, and concluded that it will be one of the first industries to benefit.[1] In this article, we explain the profound impact that QC could have on the pharma industry and present use cases for its application. We also provide a set of strategic questions to get clarity on the path forward for industry players.

Pharma's focus on molecular formations makes it well suited for QC

Identifying and developing small molecules and macromolecules that might help cure illnesses and diseases is the core activity of pharmaceutical companies. Given its focus on molecular formations, pharma as an industry is a natural candidate for quantum computing. The molecules (including those that might be used for drugs) are actually quantum systems; that is, systems that are based on quantum physics. QC is expected to be able to predict and simulate the structure, properties, and behavior (or reactivity) of these molecules more effectively than conventional computing can. Exact methods are computationally intractable for standard computers, and approximate methods are often not sufficiently accurate when interactions on the atomic level are critical, as is the case for many compounds. Theoretically, quantum computers have the capacity to efficiently simulate the complete problem, including interactions on the atomic level. As these quantum computers become more powerful, tremendous value will be at stake.

While the technology behind quantum computing is rather difficult to understand intuitively (see sidebar, "The basics of quantum computing"), its impact is much easier to grasp: it will handle certain kinds of computational tasks exponentially faster than today's conventional computers do. Thus, once fully developed, QC could add value across the entire drug value chain—from discovery through development to registration and postmarketing.

The basics of quantum computing

A conventional computer, built on transistor-based classical bits operated by voltages, can be in only one of two states: 0 or 1. A quantum computer, instead, uses systems based on quantum physics, such as superconducting loops or ions hovering in electromagnetic fields (ion traps), which are operated by microwave radiation or lasers, respectively. As a result of the laws of quantum mechanics, such systems can be held in a special physical state, called a quantum superposition, in which quantum bits (qubits) exist in a probabilistic combination of the two states—0 and 1—simultaneously.

The implications of these effects for QC are dramatic. Qubits can process far more information than conventional computers can. Qubits use the characteristics of quantum-mechanical systems to solve complex equations in a probabilistic manner, so a computation solved with a quantum algorithm enables sampling from the probabilistic distribution of being correct. The combination of greater speed with probabilistic solutions means that quantum computing fits well with a certain subset of computing needs and applications, such as optimization, the simulation of chemicals, and AI.

[1] For more, see Florian Budde and Daniel Volz, "The next big thing? Quantum computing's potential impact on chemicals," July 12, 2019, McKinsey.com.

QC's biggest impact on pharma will be in the discovery phases

While QC may benefit the entire pharma value chain—from research across production through commercial and medical—its primary value lies in R&D (Exhibit 1).

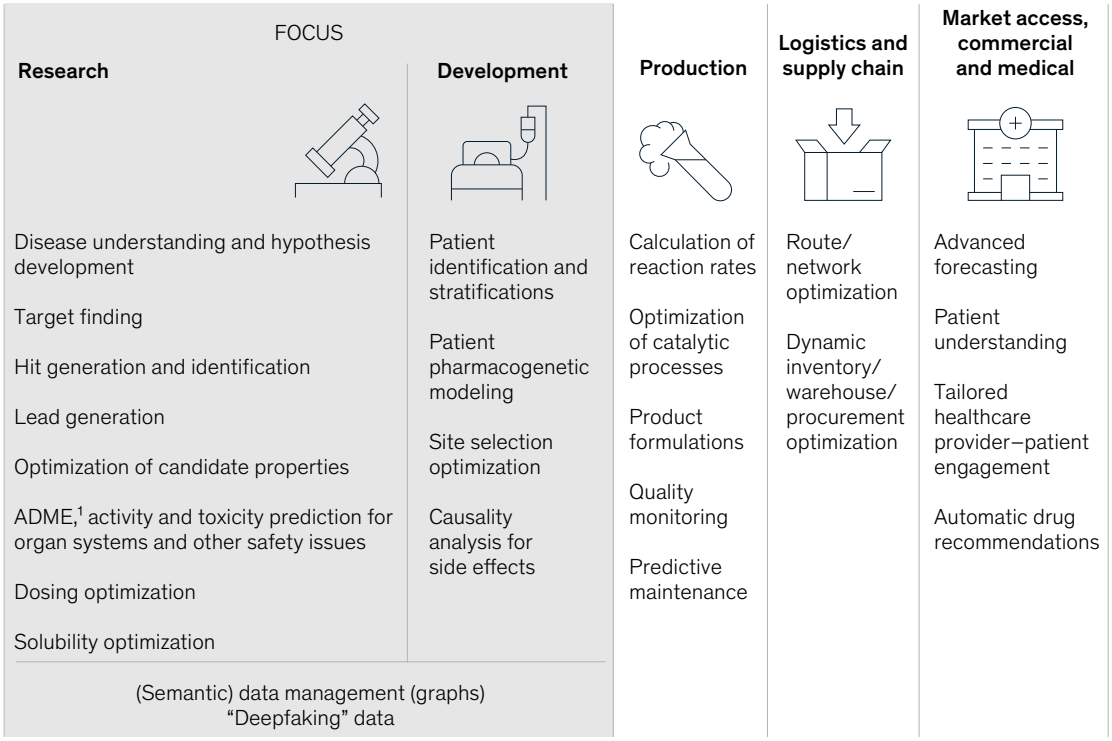
Currently, pharma players process molecules with non-QC tools, such as MD and DFT, in a methodology called computer-assisted drug discovery (CADD). But the classical computers they rely on are sorely limited, and basic calculations predicting the behavior of medium-size drug molecules could take a lifetime to compute accurately. CADD on quantum computers could increase the scope of biological mechanisms amenable to CADD, shorten screening time, and reduce the number of times an empirically based development cycle must be run by eliminating some of the research-related "dead ends," which add significant time and cost to the discovery phase. Exhibit 2 shows where QC-enhanced CADD would improve the development cycle.

QC could make current CADD tools more effective by helping to predict molecular properties with high accuracy. That can affect the development process in several ways, such as modeling how proteins fold and how drug candidates interact with biologically relevant proteins. Here, QC may allow researchers to screen computational libraries against multiple possible structures of the target in parallel. Current approaches usually restrict the structural flexibility of the target molecule due to a lack of computational power and a limited amount of time. These restrictions may reduce the chances of identifying the best drug candidates.

Exhibit 1

Quantum computing's primary value for pharma lies in R&D.

Quantum computing (QC) use cases along pharma value chain

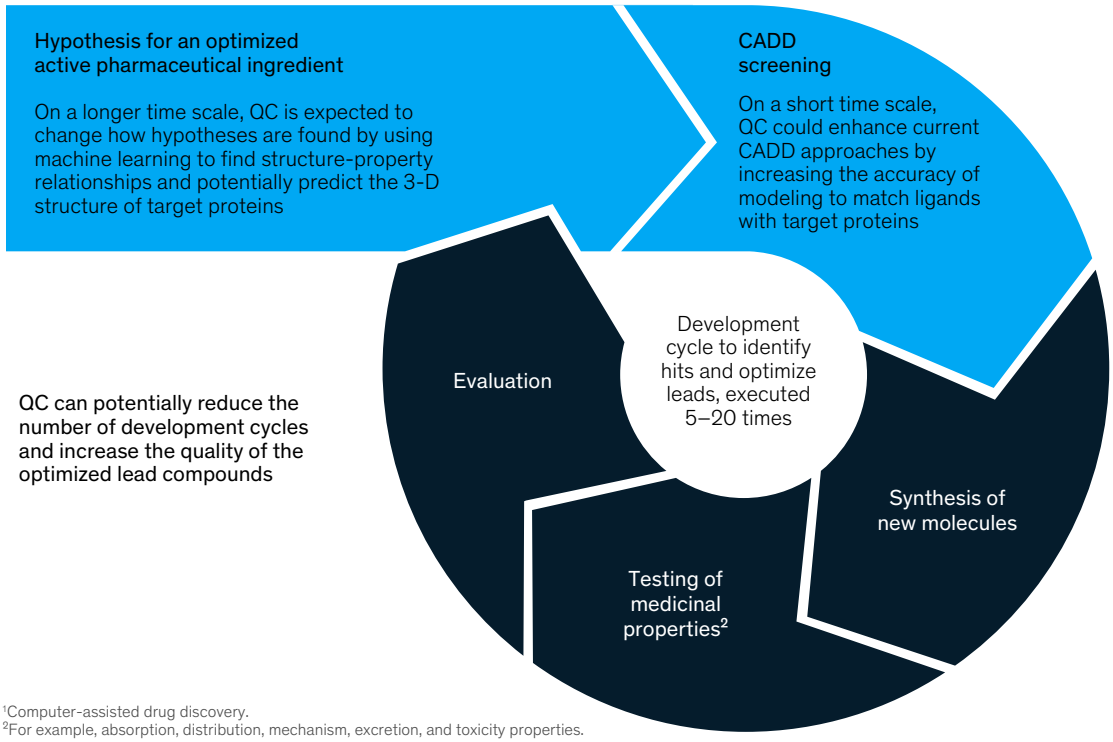


[1]Absorption, distribution, metabolism, and excretion.

Exhibit 2

Leveraging quantum computing in CADD and hypothesis development could significantly improve the early steps in drug discovery.

Effects of quantum computing (QC) on CADD[1]



[1]Computer-assisted drug discovery.
[2]For example, absorption, distribution, mechanism, excretion, and toxicity properties.

In the longer term, QC may improve generation and validation of hypotheses by using machine-learning (ML) algorithms to uncover new structure-property relationships. Once it has reached sufficient maturity, QC technology may be able to create new types of drug-candidate libraries that are no longer restricted to small molecules but also include peptides and antibodies. It could also enable a more automated approach to drug discovery, in which a large structural library of biologically relevant targets is automatically screened against drug-like molecules via high-throughput approaches.

One could even envision QC triggering a paradigm shift in pharmaceutical R&D, moving beyond today's digitally enabled R&D toward simulation-based or in silico drug discoveries—a trend that has been seen in other industries as well.

The following QC use cases apply to different aspects of drug discovery and will emerge at different points over an extended timeline. All of them, however, may enable more accurate and efficient development of targeted compounds.

Target identification and validation

During target identification, QC can be leveraged to reliably predict the 3-D structures of proteins. Obtaining high-quality structural data is a lengthy process often leading to low-quality results. Despite

all efforts, researchers have yet to crystallize many biologically important proteins—be it due to their size, solubility (for example, membrane proteins), or inability to express and purify in sufficient amount. Pharma companies sometimes develop drugs without even knowing the structure of a protein—accepting the risk of a trial-and-error approach in subsequent steps of drug development—because the business case for a given drug is potentially so strong.

AlphaFold, developed by Google's DeepMind, was a breakthrough in AI-driven protein folding but has not resolved all of the challenges of classical computing-based simulation, including, for example, formation of protein complexes, protein-protein interactions, and protein-ligand interactions. It's the interactions that are most difficult to classically solve and, thus, may benefit from QC, which allows for the explicit treatment of electrons. Additionally, QC may allow for strong computational efficiencies here given that Google's AI model—which is trained on around 170,000 different structures of protein data—requires more than 120 high-end computers for several weeks.

Hit generation and validation

QC's ability to parallel process complex phenomena would be particularly valuable during hit generation and validation. With existing computers, pharma companies can only use CADD on small to medium-size drug candidates and largely in a sequential manner. Computing power is the bottleneck. With powerful enough QC, pharma companies would be able to expand all use cases to selected biologics as well, for instance, semi-synthesized biologics or fusion proteins, and perform in silico search and validation experiments in a more high-throughput fashion. This use case would go beyond the identification of the protein and eventually encompass almost the entire known biological world. With a robust enough hit-generation and validation approach, this step would already deliver potential lead molecules that are much easier and quicker to optimize.

Lead optimization

During lead optimization, which is a top-three parameter to improve R&D productivity,[2] QC may allow for enhanced absorption, distribution, metabolism, and excretion (ADME); more accurate activity and toxicity predictions for organ systems; dose and solubility optimization; and other safety issues.

Data linkage and generation

The metalevel of R&D very much consists of linking appropriate data together—for instance, creating sensible connections between data points through effective (semantic) management. The more complex the biological information that can be processed, the more extensive the graphs that inform the drug discovery research process become. There is currently research on "topological data analysis" under way that aims to identify "holes" and "connections" across large data sets.[3] This may at some point enable R&D specialists to identify concrete cases and "industry verticals" where such algorithms are applicable, for example, in identifying connections across brain cells in response to a drug.

Moreover, QC could be used to "deepfake" missing data points throughout the research process, that is, generate a type of fake data by using ML algorithms. This could be particularly useful wherever there is a scarcity of data, such as in rare diseases, that can then be mitigated through artificial data sets. QC will set a new bar here regarding speed in training ML models, amount of initial data needed, and level of accuracy.

Clinical trials

Clinical trials could be optimized through patient identification and stratification and population pharmacogenetic modeling.[4] In trial planning and execution, QC could optimize the selection of the trial sites. QC could also augment causality analyses for side effects to improve active safety surveillance.

[2] Steven M. Paul et al., "How to improve R&D productivity: The pharmaceutical industry's grand challenge," *Nature Reviews Drug Discovery*, March 2010, Volume 9, pp. 203–214, nature.com.
[3] Silvano Garnerone, Seth Lloyd, and Paolo Zanardi, "Quantum algorithms for topological and geometric analysis of data," *Nature Communications*, January 2016, Volume 7, Article 10138, nature.com.
[4] Paul et al., 2010.

Beyond research and development

While the potential value of QC in pharma R&D is immense, it will also likely play a role further down the value chain. In the production of active ingredients, QC may aid in the calculation of reaction rates, optimize catalytic processes, and, ultimately, create significant efficiencies in the development of new product formulations. In the business-related value pools, QC in pharma could include the optimization of logistics (for instance, the optimization of on-site flows of materials, heat, and waste in production facilities) and improvements in the supply chain. Finally, toward market access and commercial, QC may even enable automatic drug recommendations.

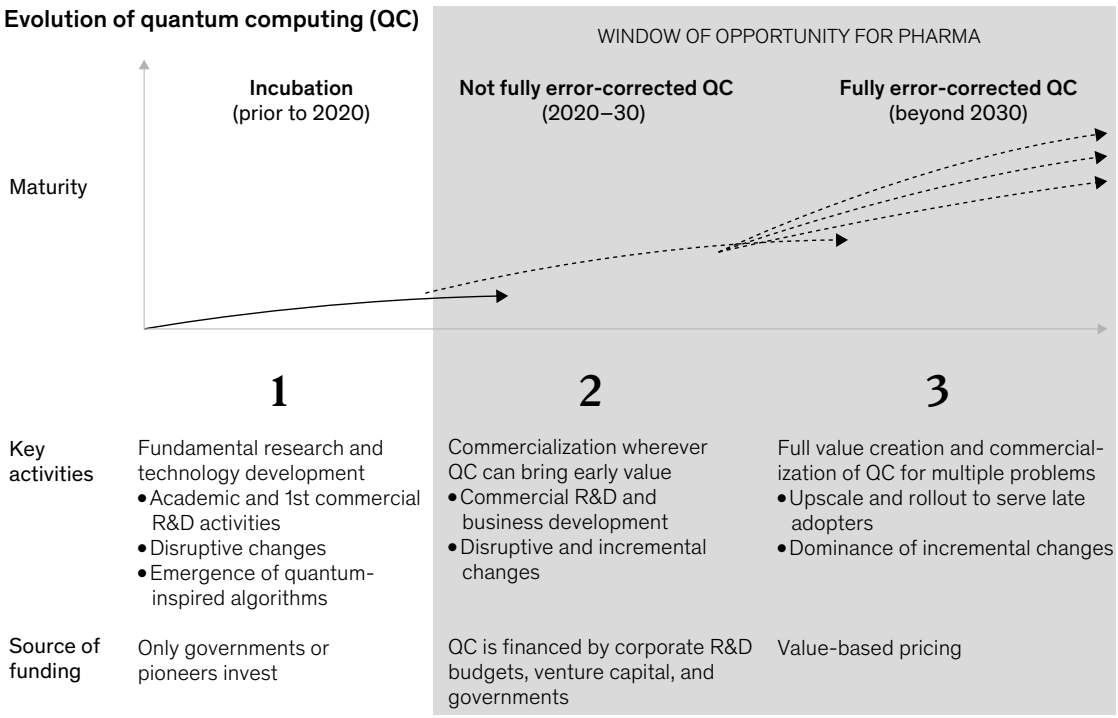
Rollout of QC in pharma R&D will occur over two clear time horizons, characterized by a gradual tech transition

The development of quantum computers began nearly four decades ago, but it is the gains in QC technology realized over the past few years that paved the way for practical applications in pharma. We see the key, value-adding QC activities in pharma unfolding over two distinct eras as the technology further matures (Exhibit 3):

— *From 2020–30: Not fully error-corrected QC.* Early commercial activities related to quantum

Exhibit 3

Value creation through quantum computing in the pharmaceuticals industry is expected to start by 2030.



computing are already under way as we leave the first horizon—which focused on quantum-inspired algorithms over the past 40 years—and enter the horizon of not fully error-corrected QC. Often referred to as "noisy intermediate-scale quantum" (NISQ), this phase describes the not-error-corrected characteristics of near-term devices that are based on an initially considerable number of quantum bits (qubits) to solve problems classic computers can't solve yet and do not provide fault tolerance. The timeline for the development and implementation of QC technology, and its adoption across companies, is very much under debate. NISQ, as a class of probabilistic computers that still (mostly) produce error-prone results, may potentially provide a near-term solution for a limited set of use cases. Companies eyeing QC's potential should take this uncertainty into consideration.

— *Beyond 2030: Fully error-corrected QC.* Beyond 2030, fully error-corrected QC is expected, in which full value through QC will be captured. In this horizon, QC gets implemented at scale, and later adopters also implement the technology. In other words, chemicals players may start creating value with QC by the mid-2020s[5]; pharma companies are expected to move more solidly into the space shortly thereafter. Compared with the chemical industry, pharma researchers primarily target more complex and larger molecular systems, which can't be replicated with either high-performance computers or today's limited quantum computers.

Exactly when a particular company begins to capture QC's benefits will depend on its tech starting point (that is, its current level of R&D digitization) and its business focus: the number of small active pharmaceutical ingredients (APIs) in its portfolio. Pharma companies that have a strong footprint in CADD and focus their R&D on smaller molecules will be among the first to take advantage of emergent QC. Exhibit 4 maps key CADD methods along the drug-discovery continuum and offers an indication of the applicability of QC. It's expected that QC will be mostly applicable in the discovery phase of hit generation, hit-to-lead, and also in lead optimization.

In the next five to ten years, we expect that the first QC tools pharma players deploy will rely on hybrid methodologies that use classical algorithms alongside QC subroutines when they can create additional value. The prominent examples are the imaginary time evolution (an algorithm to find the ground-state and excited-state energy of many-particle systems) and the variational quantum eigen-solver, or VQE (an algorithm to calculate the binding affinity between an API and a target receptor). The value that algorithms such as VQE will add depends on the size of the quantum hardware. Describing small-molecule drugs generally requires less-mature quantum computers, while biologicals will be tackled only as QC matures.

Taking steps now can position pharma players for QC success later

The pharma sector is well positioned to take full advantage of this opportunity. Its tech-ready culture already embraces a wide array of digital tools: CADD, AI, ML, and non-QC DFT- and MD-simulation tools already play a big role in the sector's R&D. On top of this, pharma players are already working with quantum-chemical simulations, so the barrier to entry is quite low. Scientists will not have to change the way they develop drugs in any fundamental way—they will just be working with more capable tools.

That said, companies will make their own decisions regarding whether and how to move toward a QC-enabled business. Some pharma players may take a pass on deploying QC, others may wait and observe, while still others are going "all in," ginning up early in-house development. Most pharma players, however, will likely undertake joint-development strategies with upstream players. No matter what, answering some key strategic questions will help companies make more informed decisions on their stance for QC.

[5] "The next big thing," July 2019.

Exhibit 4

Quantum computing is expected to be mostly applicable for hit generation and hit-to-lead, and for further lead optimization.

Target identification and validation

Quantum computing applicability (not exhaustive) — High · Medium · Low · None

Computer-aided drug discovery approach	**Identify/validate druggable targets**	**Predict protein structure**	**Identify binding site**
Omics	Supervised machine learning Unsupervised machine learning for genetic effects on diseases		
Reverse protein blocking	Template structures (PDB[1] or PSILO[2]) Grid-based pocket probes Surface-mapping methods		
De novo modeling/ protein folding		Classical molecular dynamics Monte Carlo AI-based methods[3]	
Comparative modeling		Classic homology modeling Genetic algorithms Supervised machine learning for model optimization	
Binding energy calculations		Absolute binding calculations Thermodynamic integration Free-energy perturbations	Grid-based pocket probes Surface-mapping methods
Conformational analysis			
Reaction path simulation/kinetic predictions			
QSAR[4]			
Molecular docking			
Automated retrosynthesis			

[1]Protein Data Bank. [2]Example for a protein structure database system. [3]For example, AlphaFold. [4]Quantitative structure-activity relationship.
Source: Expert interviews; McKinsey analysis

Exhibit 4 (continued)

Quantum computing is expected to be mostly applicable for hit generation and hit-to-lead, and for further lead optimization.

Hit generation and hit-to-lead

Quantum computing applicability (not exhaustive) — High · Medium · Low · None

Computer-aided drug discovery approach	**Conduct virtual screening/ docking**	**Identify leads**	**Develop synthetic route**
Omics			
Reverse protein blocking			
De novo modeling/ protein folding			
Comparative modeling		Grid-based pocket probes Surface alignment	
Binding energy calculations	Classical molecular dynamics Quantum-inspired statistical mechanics QM/MM[1] approach (eg, pKA)[2]	Classical molecular dynamics Absolute binding calculations Thermodynamic integration Free-energy perturbations QM/MM approach (eg, pKA) Fragmentation approaches[3]	
Conformational analysis		Classical molecular dynamics QM/MM approaches (eg, pKA) Fragmentation approaches[3]	
Reaction path simulation/kinetic predictions		Fragmentation approaches[3]	Quantum mechanic calculation
QSAR[4]	Supervised and unsupervised machine learning	Supervised machine learning to derive empirical evidence Fragmentation approaches[3]	
Molecular docking		Fragmentation approaches[3]	
Automated retrosynthesis		Unsupervised machine learning	Supervised machine learning

[1]Quantum mechanics/molecular mechanics. [2]Measure for physiochemical property. [3]For example, density matrix embedding theory (DMET) and dynamical mean field theory (DMFT). [4]Quantitative structure-activity relationship.
Source: Expert interviews; McKinsey analysis

Exhibit 4 (continued)

Quantum computing is expected to be mostly applicable for hit generation and hit-to-lead, and for further lead optimization.

Lead optimization

Quantum computing applicability (not exhaustive) — High · Medium · Low · None

Computer-aided drug discovery approach	**Optimize ADME(T)**	**Optimize drug activity**
Omics		
Reverse protein blocking		
De novo modeling/ protein folding		
Comparative modeling	Supervised machine learning for solubility, property improvement, toxicology	
Binding energy calculations	Simulation methods	Synthetic biology approaches Absolute binding calculations Thermodynamic integration Free-energy perturbations
Conformational analysis		
Reaction path simulation/kinetic predictions		
QSAR	Quantum-inspired ADME[1] Descriptor calculation Supervised machine learning for solubility, property improvement, toxicology	
Molecular docking		Classical molecular dynamics QM/MM[2] approaches
Automated retrosynthesis		Supervised machine learning

[1]Absorption, distribution, metabolism, and excretion. [2]Quantum mechanics/molecular mechanics.
Source: Expert interviews; McKinsey analysis

Assess the opportunity

Pharmaceutical companies should assess QC *now* and potentially lay the groundwork to reap the benefits of the technology later. QC may give many of them a huge opportunity, yet each pharma player needs to figure out how much exposure it has and the size of its QC opportunity in the context of its current pace of development. Thus, pharma players should consider three key strategic questions to determine their optimal QC strategy (Exhibit 5):

— Will QC demonstrate promise to disrupt my area of play and reorganize the competitive landscape?

— Have I identified opportunities in my value chain where QC's potential may translate into value and in which time horizon?

— Can I dedicate resources to investigate QC opportunities, and can I scale up capabilities?

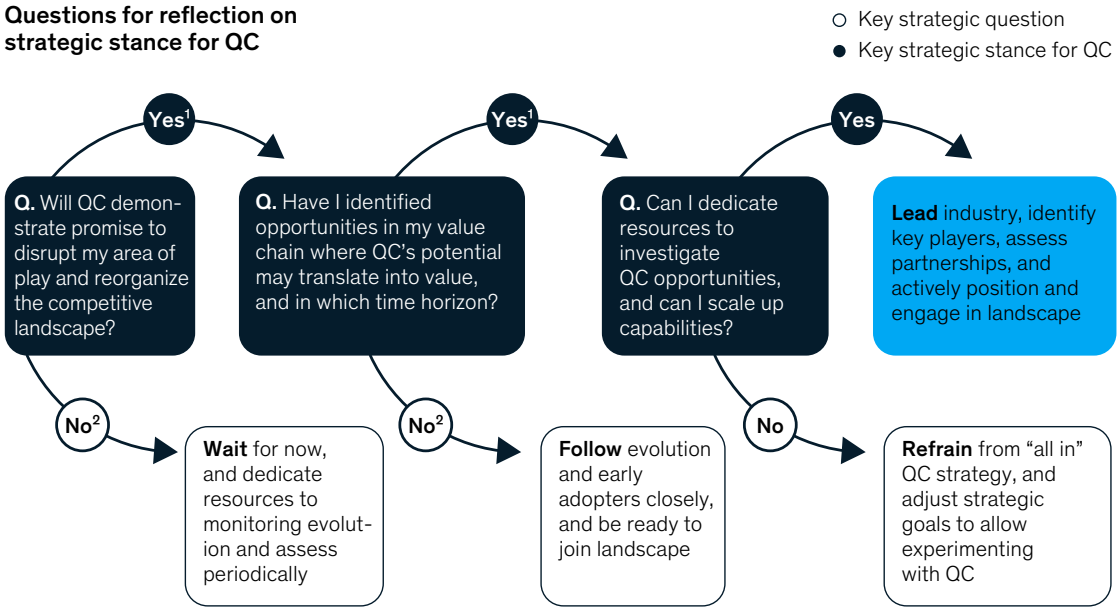
Subject to the above answers, moving early can help secure valuable intellectual property for the algorithms that drive QC and can also address a key issue: pharma won't be the first industry sector to benefit from QC, so late-moving players could face a lack of suitable talent.

Establish partnerships

Some pharmaceutical players have already realized the need to join forces on the topic of QC and have started to collaborate and/or form partnerships. For example, QuPharm formed in late 2019 by major pharmaceutical players to pool ideas and expertise around QC use cases. QuPharm also collaborates with the Quantum Economic Development Consortium (QED-C), which was created in 2018 by the US government as part of the National Quantum Initiative Act and aims to enable commercial QC use-case efforts. Additionally, the Pistoia Alliance is a life sciences membership organization, which was organized to facilitate precompetitive collaboration and foster R&D innovation.

Exhibit 5

Pharma players have three key questions to answer when considering a quantum computing strategy.



[1]Yes, or less than 10 years.
[2]No, or more than 10 years.
Source: Expert interviews; McKinsey analysis

Partnering with pure quantum players taps into their existing expertise to test early use cases and facilitate development. At the moment, there are more than 100 QC-focused companies—both start-ups and established firms—around the world, focusing on software, hardware, or enabling services. Approximately 25 companies are targeting applications in the pharma industry. Less than 15 focus on algorithms or solutions for pharma players, and very few are focusing exclusively on the needs of pharma players.

Develop capabilities

Digital talent gaps are already a reality, and QC may only exacerbate them. Unlike other important digital tools, such as AI, quantum computing depends on niche know-how. Pharma companies already struggle to attract people with capabilities in the less specialized digital technologies, and hiring quantum-computing experts may prove to be even more of a challenge.

Ensure organizational collaboration

A pharma company's "way of working" will also be central to its success in QC. The traditional walls that separate the work of the organization's various functions and units—for example, research, tech, business—will have to fall away. Cross-functional collaboration in both spirit and action will characterize the pharma companies that are able to take full advantage of QC.

Quantum computing could be the key to exponentially more efficient discovery of pharmaceutical cures and therapeutics as well as to hundreds of billions of dollars in value for the pharma industry. Experts predict, for example, that today's $200 billion market for protein-based drugs could grow by 50 to 100 percent in the medium term if better tools to develop them became available.[6] Given QC's vast potential, we expect global pharma spending on QC in R&D to be in the billions by 2030. Pharma companies would be well advised to assess the QC opportunity for themselves and begin laying the groundwork in securing their place in this new competitive and technological landscape.

[6] See Anna Heid and Ivan Ostovic, "Recalculating the future of drug development with quantum computing," October 23, 2020, McKinsey.com.

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