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The unprecedented Paxlovid journey from milligrams to millions of patient doses during the Covid-19 pandemic

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The SARS-CoV-2 infection triggered a global pandemic in 2020, and the identification of safe and effective oral antiviral treatments was critical in the fight against COVID-19. Here, we describe our adaptive approach to developing the antiviral nirmatrelvir/ ritonavir (Paxlovid) to treat COVID-19.

The spread of SARS-CoV-2 infection led to a global pandemic, resulting in >770 million cases and 7.1 million deaths to date[1]. Fast-paced vaccine development led to the successful launches of the Covid-19 vaccines reducing the impact of the pandemic. Antiviral treatments have played a key role in improving outcomes in individuals at high risk of severe COVID-19. Medicinal chemistry approaches used for discovery of the oral antiviral, nirmatrelvir[2], including artificial intelligence (AI) and structure-based drug design[3,4], were critical to development of Paxlovid™ (Pfizer Inc, New York, NY). An earlier effort in response to the 2002 SARS outbreak led to the identification of Lufotrelvir (prodrug of the active component PF-00835231) as a potent inhibitor of recombinant SARS-CoV-1 main protease (M^{pro}), which provided promising starting point for the discovery of Nirmatrelvir, a SARS-CoV-2 M^{pro} inhibitor with enhanced bioavailability suitable for oral delivery[2]. Nirmatrelvir is a peptide-based covalent-reversible inhibitor[5,6]. When co-administered with ritonavir, it is an oral antiviral COVID-19 treatment, Paxlovid[7]. In the EPIC-HR phase 2/3 pivotal clinical trial (NCT04960202), Paxlovid reduced hospitalization or death by 89% and 88% among unvaccinated nonhospitalized individuals at high risk of progression to severe COVID-19 when treated within 3 and 5 days of symptom onset, respectively[8]. Based on a review of medical records of 44,551 nonhospitalized ≥50-years-old individuals with COVID-19 in the United States during the Omicron wave, Paxlovid treatment reduced the risk of hospitalization or death by 44% compared with those not receiving treatment[9].

While the discovery and rapid clinical progression of nirmatrelvir were previously published[2,10,11], the unprecedented speed of Paxlovid's development has not been reported in detail[3]. Transition from the first lab-scale synthesis of nirmatrelvir to production of hundreds of millions of Paxlovid doses was achieved in 18 months, roughly 8-fold faster than a typical development timeline for a new medicine. This development paradigm was considered lightspeed and was achieved by balancing well-designed and efficient onsite laboratory work, rapid supply chain construction, supplier collaboration, and the use of state-of-the-art computational predictive technology during pandemic lockdown periods. This timeline is provided in Fig. 1. Use of established and optimized predictive tools for unit operations and in-silico assessment of bioperformance (drug performance in vivo) enabled risk-based decision-making to progress rapidly from laboratory to commercial-scale manufacture. The coupling of computational and targeted experimental approaches allowed medicine delivery to millions of patients at an unprecedented pace (to the best of our knowledge), while ensuring the highest quality, thus leading to Paxlovid being granted emergency use authorization (EUA). This paper provides an overview of behind-the-scenes examples of science, technology, and engineering enabling rapid development of a new chemical entity into a new medicine, presented as several development challenges.

Challenges

Challenge 1: ensuring adequate drug supply to enable rapid first-in-human study and seamless transition to phase 2/3. Nirmatrelvir became a lead candidate following preclinical demonstration of potent antiviral activity, clean toxicity profile, and acceptable oral bioavailability. Uncertainties associated with its oral absorption presented challenges to developing strategies to enable evaluation of a wide dose range required to establish safety and pharmacokinetics in phase 1 (NCT04756531). To address these, in silico modeling and profiling results obtained with only hundreds of milligrams of compound enabled us to confidently choose crystalline nirmatrelvir for first-in-human (FIH) study. During the design phase, the goal was maximizing nirmatrelvir concentrations to increase confidence in clinical efficacy and preventing resistance. Accordingly, pharmacokinetic profiles and safety of nirmatrelvir alone and in combination with the pharmacokinetic enhancer (ritonavir) were assessed in phase 1. Ultimately the selected phase 2/3 dose ((NCT04960202) included ritonavir to allow adequate free exposure of nirmatrelvir to achieve clinical antiviral effect and prevent resistance. The latter became increasingly important as SARS-CoV-2 variants emerged.

To enable rapid FIH study progression, minor discovery synthesis process modifications were made to ensure multikilogram nirmatrelvir quantities were available to support early drug product development, regulatory requirements, and clinical studies. Because of the program's lightspeed development[3], the nirmatrelvir commercial synthesis (described in Challenge 2) was developed concurrently, and included crystallization process optimization to ensure material properties suitable for drug product were consistently obtained.

To support FIH study objectives (assess safety/tolerability and pharmacokinetics)[6], suspension and tablet formulations were developed to provide flexibility for dose escalation and rapid transition to phase 2/3 studies. With limited drug substance quantities available to support early-stage development, predictive experimental and computational tools were leveraged to execute drug product stability, bioperformance, and manufacturability risk assessments. Early in development, parallel accelerated

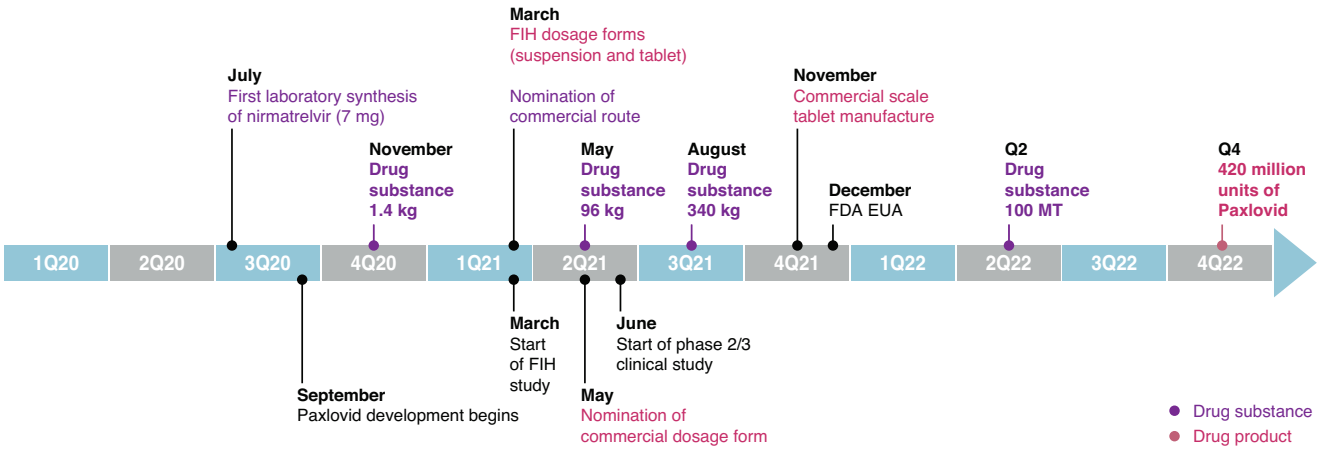

Fig. 1 | Development timeline of Paxlovid. EUA emergency use authorization, FDA US Food and Drug Administration, FIH first in human, MT metric tons.

chemical and physical stability evaluations of multiple test formulations were performed as a formulation screening tool. Preliminary pharmacokinetic models were developed using preclinical data and in vitro characterizations of drug substances and drug product dosage forms to provide initial bioperformance risk assessments. Drug product manufacturability was evaluated by assessing key drug substance and formulation properties by a series of material-sparing characterization techniques, and assessments were compared with an extensive internal database.

Concurrent with the FIH study and using preliminary clinical data, population pharmacokinetic model construction expedited dose selection and informed phase 2/3 study designs. To help finalize dose selection for these trials, a relative bioavailability (rBA) study was conducted to bridge suspension bioperformance to a prototype tablet formulation at the end of the FIH study. Using rBA results and the population pharmacokinetic model, a twice-daily nirmatrelvir/ritonavir dose regimen (300 mg/100 mg) was selected for phase 2/3 study[8].

Challenge 2: supply continuity of clinical and commercial drug substance. Through infrastructure established within the lightspeed paradigm, a fit-for-purpose synthetic route enabled from medicinal chemists' synthesis experience allowed for early development and clinical continuity. In parallel, early engagement to identify a commercial synthesis protocol supported a rapid nirmatrelvir scale-up. The fit-for-purpose route was completed on a timeline that did not allow exploration of all possible routes. Some key issues that needed overcoming included improving synthetic convergency by avoiding use of protecting groups (potentially extensive procedures to add and remove chemical structures to temporarily mask the reactivity of parts of the molecule), identifying solid intermediates that would not pose undue burdens to handling and isolation, computer-modeling of mixing effects to support rapid and seamless transfer to large-scale manufacturing, and identifying reagents and solvents available in appropriate quantities. An added challenge was the effort expended within the Chemical Research & Development group on development and manufacture of several small molecule components of the mRNA lipid nanoparticle program. Accordingly, other programs were paused to allow requisite focus on both COVID-19 programs.

Nirmatrelvir (1 in Fig. 2) is a polypeptide lending itself to modular disconnection. Key to success of the lightspeed development was having these building blocks from existing commercial sources (2), previous development candidates (3), or from published literature (4)[12,13]. Even with this head start, sourcing the necessary >100 metric ton (MT) quantities required robust chemistry development and used reagents and solvents more readily available at scale. These requirements were also important for synthetic steps required to convert the building blocks to nirmatrelvir (Fig. 2), which were designed to avoid use of reagents, such as Burgess reagent in Step 4 dehydration, 4-dimethylaminopyridine (DMAP) in Step 2 amidation, and cyclopentyl methyl ether and 2-methyltetrahydrofuran. Shown in Fig. 2 is a more convergent synthesis, use of well-behaved solid intermediates, and, in the case of intermediate 7, a telescoped process (a method that combines two or more reactions into a single isolation) for Steps 3 and 4 with isolation of the penultimate intermediate 8, the methyl tert-butyl ether (MTBE) solvate of nirmatrelvir (1). Selected solvents and reagents needed to be sustainable and available in volumes required for clinical and commercial supply needs. An initial version of this route used the lithium salt of intermediate 5 and alternate reagents for Step 2 amidation, including the use of DMAP. To achieve enhanced process intensification (see Challenge 4), the route was updated to include sodium salt (5) and amidation conditions shown in Fig. 2.

Predictive science tools were applied throughout development of drug substance synthesis; the following examples are representative of those used. First, some early batches of Step 1, a 2-phase liquid−liquid system, suffered incomplete reaction conversions in certain reactor configurations. Computational fluid dynamic modeling explained these failures allowing for equipment and stir rate selection that rapidly resolved the issue across a range of reactor configurations, manufacturing sites, and batch scales. Second, the Step 5 crystallization process was optimized by statistical modeling to achieve parametric control of particle size distribution appropriate for drug product quality without the need of milling. The drug substance particle size target was consistently met with over 2000 consecutive batches at a variety of scales and equipment configurations across multiple global manufacturing plants. Finally, crystal structure prediction tools were applied to the nirmatrelvir drug substance to de-risk crystalline polymorph selection, allowing for enhanced understanding and confidence in selecting the thermodynamically most stable polymorph for development and commercialization.

The drug substance manufacture scale from first nirmatrelvir synthesis in July 2020 to EUA in December 2021 is shown in Fig. 1. The accelerated timeline and parallel execution of multiple activities account for the remarkable scale increase from first laboratory synthesis (7 mg) to EUA and global supply manufacture (~100,000 kg), an increase of >10 billion-fold.

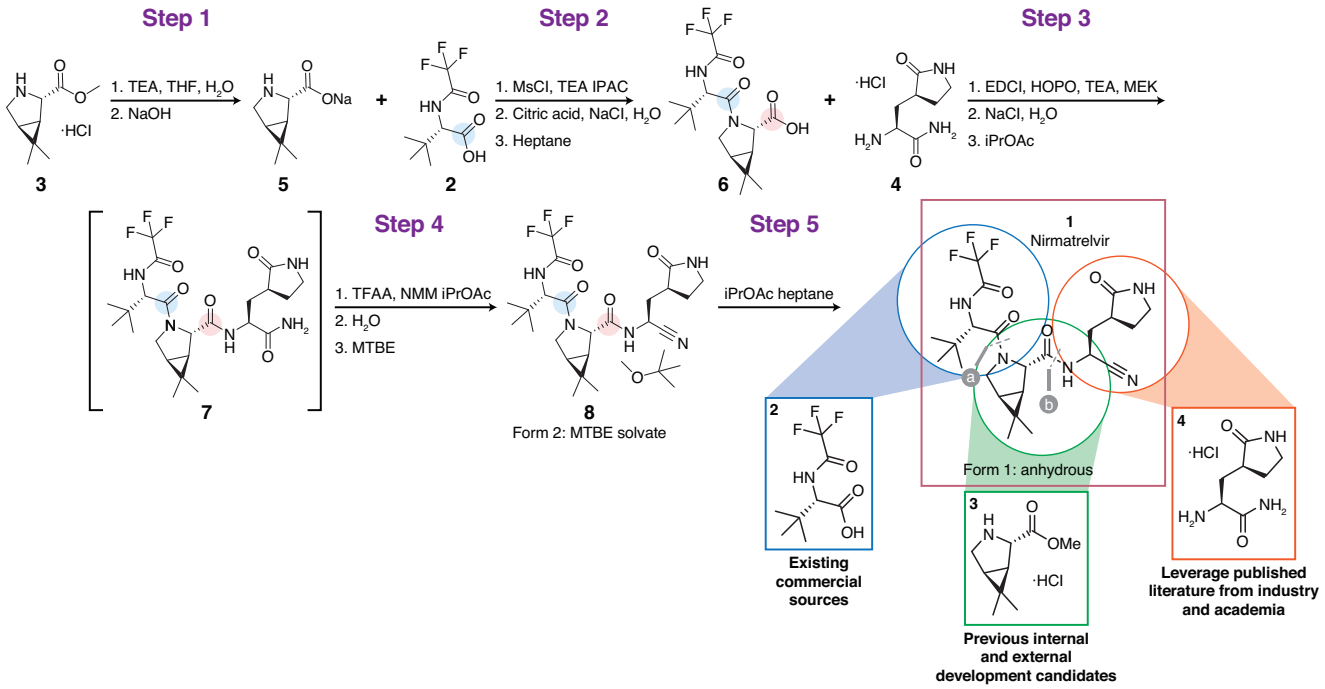

Fig. 2 | Key building blocks (compounds 1, 2, and 3) and synthetic steps required to convert the building blocks to nirmatrelvir (steps 1–5). EDCI 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt, HOPO 2-hydroxypyridine-N-oxide, IPAC isopropyl acetate, iPrOAc acetic acid isopropyl ester, MEK methyl ethyl ketone, NaCl sodium chloride, NaOH sodium hydroxide, NMM N-methylmorpholine, MsCl methanesulfonyl chloride, MTBE methyl tertiary-butyl ether, TEA triethylamine, THF tetrahydrofuran, TFAA trifluoroacetic anhydride.

An important component of the development process was determining commercial drug substance specifications, and the appropriate starting material specifications to meet them. Although standard protocol for any development program, the pace amplified the need for this approach for nirmatrelvir. Regulatory toxicology studies were therefore performed with drug substance batches of representative purity, anticipating that process-related impurities in these development batches may be present in the final drug substance specification.

The process shown in Fig. 2 was developed while keeping sustainability in mind by continuously improving yield and reducing solvent and reagent quantities. Process intensification efforts were necessary to make this synthesis viable as a long-term commercial process to support the 100 MT quantities of drug substance needed for a global pandemic. Table 1 shows utilization factor improvements made over a 15-month timespan. This reflects yield improvements in each drug substance synthesis step arising from a combination of reagent and solvent optimization based on process understanding and performance on scale, process optimization via study designs, computational modeling of mixing effects and kinetics to optimize reaction conversions. This improvement represents a substantial reduction in starting material input requirements.

Table 1 | Process intensification from March 2021 to May 2022

Input (compound # from Fig. 2)[a]	Utilization factor (kg of input/kg drug substance)[b]		
	March 2021	September 2021	May 2022
3	1.2	0.87	0.69
2	1.5	0.90	0.81
4	1.1	0.72	0.60

[a]Key building blocks of Nirmatrelvir drug substance as illustrated in Fig. 2.
[b]Utilization factor is defined as kg input/ kg drug substance. A lower utilization factor implies generally an improvement in efficiency with respect to the input material. In this case the authors are using the utilization factor of the three key building blocks to show gains in efficiency over time through process optimization efforts.

Shortly after EUA, drug substance production substantially increased, from 6.7 MT manufactured within ~1 month after EUA to 44.6 MT within ~3 months. This scale and pace required multiple global sites and key strategic partners. The latter was used for manufacture of the 3 drug substance building blocks (**3**, **2**, **4**), which went to 8 distinct manufacturing sites for drug substance.

Challenge 3: accelerated commercial dosage-form design using predictive science to supply pivotal clinical studies with proposed commercial formulation. After completion of the FIH study, phase 2/3 pivotal trials were initiated within 2 months. The drug product team set a breakthrough goal to have the final commercial dosage form and manufacturing process ready to supply these clinical studies, which if successful, would eliminate a need for a pivotal bioequivalence study.

Drug product stability, bioperformance, and manufacturability were key elements in designing the potential commercial drug product dosage form. To meet the accelerated development timeline, predictive tools, including material-sparing experimental approaches and computational predictions, were leveraged for risk assessment and decision-making.

Adequate long-term drug product stability is paramount for commercial dosage form design. Early identification and selection of the most stable crystalline nirmatrelvir polymorph used crystal structure

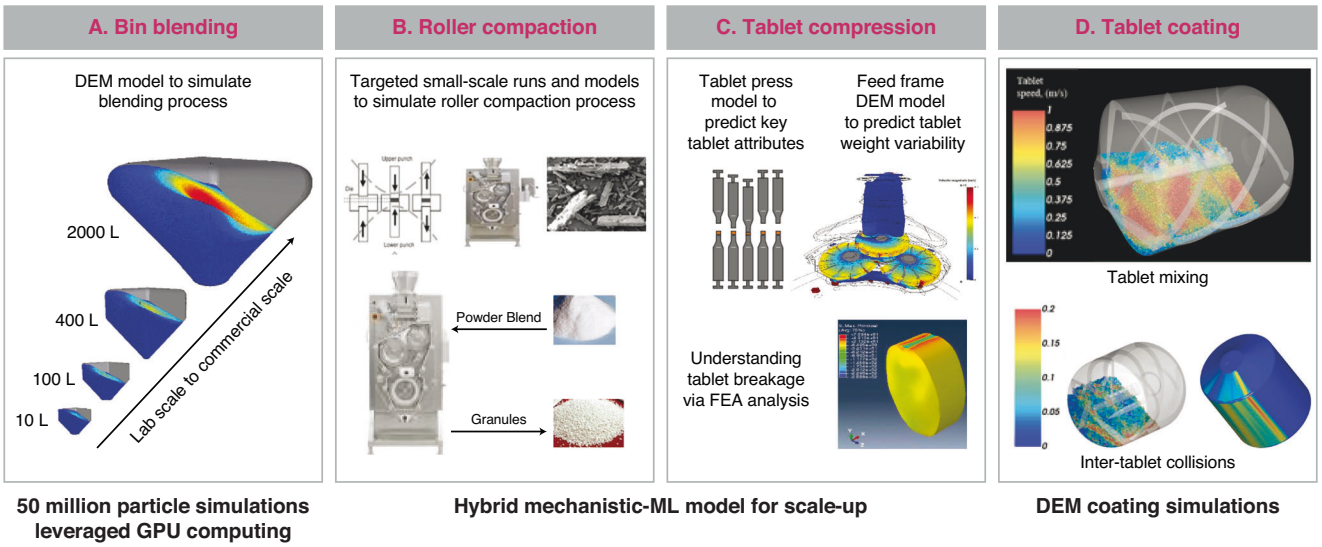

Fig. 3 | Accelerating tablet development: end-to-end digital design with highlights of predictive models used for process development and scale-up that resulted in ~500 kg drug substance (in this case, nirmatrelvir) savings, which was leveraged for clinical and commercial use. A Bin blending; **B** roller compaction; **C** tablet compression; **D** tablet coating. DEM discrete element method, FEA finite element analysis, GPU graphics processing unit, ML machine learning.

prediction tools and provided the basis for commercial dosage form design. Accelerated chemical and physical stability assessment approaches enabled rapid selection of commercial drug product formulation composition and packaging configuration prior to regulatory stability batch manufacture.

The initial prototype formulation from the rBA study was optimized for enhanced manufacturing robustness alongside adequate bioperformance. Continued pharmacokinetic model optimization provided key insights into the potential impact of drug substance and drug product characteristics on bioperformance, enabling rapid identification of key attributes and targeted development of a suitable control strategy for drug substance and drug product.

Given the lightspeed development, the scale-up of the drug product manufacturing batch process from development (<1 kg) to commercial scale (750 kg) with a limited drug substance supply was challenging. Timelines did not permit running processes to collect data and identify an appropriate operational space for drug product manufacture. Instead, state-of-the-art predictive computational and machine-learning models were used, which helped reduce risks in process development and subsequent scale-up to multiple commercial manufacturing sites. Nirmatrelvir film-coated tablets were manufactured using a dry granulation batch process comprising several key unit operations, which were each developed using computational tools shown in Fig. 3A–D. For blending, computational models investigated mixing behavior and blend homogeneity across development to commercial blender scales, providing vital understanding of mixing dynamics. Hybrid computational models combining mechanistic and machine-learning methods were developed to transfer the roller compaction process from development laboratories to commercial manufacturing sites. A suite of models was developed to optimize and scale-up the tablet compression process to predict key tablet attributes and virtually test and eliminate tablet fracture and breakage risk. Thermodynamic principles were used to determine suitable process conditions for commercial-scale coating. Simulations estimated mechanical stress on the tablets during coating to ensure physical integrity.

The process modeling of each of these unit operations was verified through rigorous quality testing of drug product batches manufactured at multiple sites and scales and was key to delivering Paxlovid global supplies.

Challenge 4: establishing a Paxlovid commercial supply chain. Rapidly scaling the manufacturing process to deliver millions of high-quality Paxlovid doses relied on the experience and capability within the network of manufacturing sites and key strategic partners. As the commercial manufacturing process and anticipated demand became clear, unprecedented agility and coordination among manufacturing site operations and supply chain professionals were needed to replan existing production across the network and to support Paxlovid supplies. Critical to these efforts were colleagues at those facilities and testing sites and across all supportive manufacturing functions, coupled with close collaboration with the research and development team.

Early in development, with lead times exceeding 7 months, scale-up within the existing manufacturing facility network was recognized as only part of the solution to supplying Paxlovid. Another critical consideration was production scale-out to multiple existing external suppliers and forging new supply relationships, which included all supply chain elements. With 25 supply nodes, including internal and partner sites across 10 countries, Paxlovid supply relies on a complex, global supply chain (Fig. 4). A component within this supply chain is ritonavir, which needs to be co-administered with each nirmatrelvir dose[7]. Although ritonavir is widely available from multiple suppliers, any appearance, size, shape, and physical and chemical specification variations limited the number of viable sources. Capacity and availability of sufficient quantities were challenging. Uncertainty in the initial forecasted volumes of finished, packed Paxlovid and varied regulatory status of each ritonavir source added to the complexity. With potential volumes of >100 million finished Paxlovid packs required by the end of 2022, a substantial increase in ritonavir supply was needed to avoid disrupting its existing global availability. As with all key materials sourced externally, incremental ritonavir production by suppliers was

Fig. 4 | Pfizer global supply network map. Pfizer leveraged numerous manufacturing sites to deliver Paxlovid globally. EU European Union, ROW rest of world, UK United Kingdom, US United States.

funded at risk to ensure sufficient stock availability for final packing operations.

Real-time packaged product stability was on the critical path to support the maximum duration of shelf life at launch. Supportive bulk stability and modeling tools were important to supplement the limited real-time data available. Packaging configurations that could be quickly scaled but also maximized ease of administration and patient compliance-focused technical solutions to a few options.

Paxlovid was launched in a patient pack configuration containing 5 blister cards per carton. With a 5-day dosing duration[7], each treatment course contained 30 tablets within the patient pack. Because each blister card was configured with morning and evening doses, each with 2 nirmatrelvir 150-mg tablets and 1 ritonavir 100-mg tablet, each dose needed to be convenient and unambiguous. The limited time to have commercial-ready packaging also dictated the use of foil/foil blisters, which provide the most protective barrier material configuration. This meant that the primary pack would be opaque; it was therefore critical to ensure each cavity contained the correct tablet before lidding. The packaging equipment included a high-resolution camera inspection system, which utilizes an AI-driven algorithm to distinguish between the ritonavir and nirmatrelvir tablets and therefore, confirm that all tablets are in the correct position during high-speed packaging operations.

Before the US EUA for Paxlovid on December 22, 2021[7], the first shipments were delivered for immediate availability upon this authorization. This would be repeated across the globe as other countries granted EUAs. In mid-November 2021, within weeks after announcing positive interim results in the pivotal EPIC-HR study, Pfizer and the Medicines Patent Pool (MPP), a United Nations-backed public health organization working to increase access to life-saving medicines for low- and middle-income countries (LMICs), announced a licensing agreement. This agreement enabled the MPP to grant sublicenses to other companies for the manufacture and sale of their generic nirmatrelvir equivalent with technical support from Pfizer. Combined with ritonavir, this generic equivalent can be supplied to 95 LMICs comprising ~53% of the world's population.

Concluding remarks

The COVID-19 pandemic impelled discovery and development of the novel antiviral therapy nirmatrelvir. To meet the urgent demand for a safe and effective oral treatment, a lightspeed development paradigm was deployed to take Paxlovid from lab-scale synthesis to commercial-scale production in record time. The unprecedented pace of development and manufacture of large drug substance quantities, millions of drug product units, and uniquely packaged medicine was made possible using institutional knowledge and experience, predictive science, and smart experimental design. Along with deploying required resources, global connectivity, and supply chain logistics, the ability to make timely and risk-balanced decisions contributed to the pace of development.

Successful rapid transformation of the nirmatrelvir molecule into a safe, effective medicine was primarily due to the collaboration of scientists across countries and continents. Their ingenuity combined experimental and predictive science, resulting in innovative tactics to address the global medical needs arising from the pandemic. The use of experimental and predictive science for drug substance and drug product manufacture was developed through years of precompetitive industrial collaborations, alongside industry–academic and industry–government partnerships. These strategies will be shared in greater scientific detail through

publications in peer-reviewed, discipline-specific journals to facilitate future rapid medicine development by the industry.

For brevity, only a few specific advances are highlighted here. First, the decision to invest at risk, before results from definitive clinical trials were completed, highlights the credibility of structural biology and AI-guided design of antiviral molecules. Second, an adaptive design for the FIH study enabled rapid dose selection for phase 2/3 trials and the inclusion of ritonavir to maximize nirmatrelvir exposure and prevent resistance. Third, implementing a flexible and diversified global supply chain to minimize geographic, regulatory, and economic risks and ensure adequate production to meet the immense global need was crucial for managing pandemic waves. Finally, the development of Paxlovid highlights the value of effective incorporation of experimental investigations in conjunction with existing and bespoke modeling tools in building confidence in decision-making, scaling up manufacturing processes, and enabling global regulatory acceptance. The deep institutional knowledge and close collaborations across multi-disciplinary teams were key to defining and executing a sound digitally integrated strategy. The knowledge and experience gained will further accelerate development of future life-saving medicines, speed therapies to patients, and support pandemic preparedness.

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Author contributions

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Competing interests

The authors declare the following competing interests: The authors are Pfizer employees.

Additional information

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