Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Meeting the potential emergency global drug supply challenge of hydroxychloroquine for COVID-19

Tony Y. Zhang *, Boyu Zhong
Tyligand Bioscience Ltd. 3728 Jinke Road, Building 1, Zhangjiang Hitech Park, Shanghai, China

ABSTRACT

Article history: Received 4 April 2020 Received in revised form 6 April 2020 Accepted 6 April 2020 Available online 9 April 2020

This paper provides an overview of the current global market and manufacturing landscape for hydroxychloroquine (HCQ). The capacity and capabilities of global producers to meet the potential demand for treating patients infected with COVID-19 by the novel corona virus SARS-CoV-2, should HCQ's efficacy be established by more definitive clinical trials, is also assessed. Given the large existing manufacturing base and abundance of raw materials for HCQ, the supply challenge can be met with considerable efforts and international cooperation. Preemptive and coordinated emergency efforts among global governments, regulatory agencies, chemical and pharmaceutical industries are imperative for meeting the potential surge in demand.

© 2020 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

1. Introduction ................................................................ 1
2. Current Market and Production of HCQ .................................................... 2
3. Demand Projection for COVID-19 ....................................................... 2
4. Can the demand be met, why? and how? ................................................... 2
Conflict of Interest ................................................................ 5
Acknowledgment and disclaimer ................................................................. 5
CRediT author statement ................................................................ 5
References ................................................................ 5

1. Introduction

The pandemic caused by the novel corona virus SARS-CoV-2 is on the list of the biggest challenges that human beings have ever faced in modern history. The most effective means against viral diseases like COVID-19, and also one of the most impactful human inventions, i.e. vaccines, will take months if not years to develop and to prove safe and efficacious in clinical trials. Among the few options readily available for health care providers to treat this highly contagious and deadly disease is to repurpose an existing drug, especially if the drug has been exposed to a diverse patient population with known and acceptable safety outcomes. Hydroxychloroquine sulfate [1] (1, HCQ, Fig. 1) is the front runner fitting such a profile, as indicated by several very preliminary clinical trials, especially when combined with azithromycin [2]. While the efficacy of HCQ against COVID-19 still needs to be proved in larger randomized controlled clinical trials (RCT), several of which are underway [3], demand for HCQ has already skyrocketed in recent weeks due in part to the surprising virulence of the disease, yearning for cure from the populace, and some highly visible endorsements. This has propelled several states and pharmacy chains in the United States to implement allocation program, a measure to curb hoarding of the product so as to ensure a steady albeit limited supply chain [4]. Physicians are also urged not to prescribe the medicine for prophylactic use, since many patients rely on this drug for treating their debilitating chronic diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Meanwhile, several manufactures have responded by either pledging to donate a substantial number of tablets or promising to ramp up production [5].

On 28 March 2020, the US FDA issued an Emergency Use Authorization (EUA) to permit the emergency use of hydroxychloroquine sulfate (HCQ, 1), and its older chemical cousin chloroquine (di)phosphate (CQ, 2), to be
supplied from the Strategic National Stockpile to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible [6]. Clinically justifi ed or not, the current shortage for HCQ is acute. The situation could either be alleviated by an increase of global production, or exacerbated by further escalating demand, especially if HCQ's efficacy for treating COVID-19 is demonstrated unequivocally by RCT. This paper will focus on the supply and demand for hydroxychloroquine.

2. Current Market and Production of HCQ

Originally developed to treat malaria, hydroxychloroquine was invented by Alexander R. Surrey of the Sterling Drug Inc. of New York in 1949 [7]. It is generally considered to be less toxic and better tolerated than chloroquine, and has been approved in the US for RA and SLE, in addition to treatment and prophylaxis of malaria. As show in Fig. 1, HCQ differs from CQ (2) by an extra hydroxyl group and is a sulfate salt, vs a diphosphate salt for CQ.

According to various sources [8], in 2018, roughly 300 metric tons of HCQ sulfate was sold across the world, led by the United States which accounted for more than a quarter of the amount, followed by India and China, consuming 20% and 12%, respectively (Fig. 2). It should be noted that a majority of the prescriptions in the US were for chronic indications such as RA and SLE. In fact, HCQ is the second most prescribed medicine in the US after methotrexate. In 2019, over 5.8 million scripts have been dispensed in the US, equating to 478 million 200 mg tablets, or 97 metric tons of the active pharmaceutical ingredient (API).

By revenue, HCQ sales in the US is estimated to be well over $220 million annually, shared mostly by generic drug makers including Zydus Cadila 30% (India), Prasco Laboratories Ltd. 22% (India), Sandoz (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US). Innovator's brand Plaquenil dominates the European and Japanese market (Sano (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US). Innovator's brand Plaquenil dominates the European and Japanese market (Sano (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US). Innovator's brand Plaquenil dominates the European and Japanese market (Sano (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US). Innovator's brand Plaquenil dominates the European and Japanese market (Sano (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US). Innovator's brand Plaquenil dominates the European and Japanese market (Sano (Switzerland) 20%, Teva 7% (Israel) and Mylan 7% (US).

According to the news media in the last week of March 2020:
- Cadila is ramping up (5×) to produce 20 tons of HCQ per month, and said could go up to 40 tons/month if needed.
- Amneal Pharmaceuticals will ramp up and expects to produce ~20 M tablets by mid-April (4 tons).
- Laurus will ramp up HCQ production from mid-April from 5 to 15–20 tons/month.

3. Demand Projection for COVID-19

The following table (Table 1) attempts to compare the HCQ market prior to COVID-19 breakout, and the projected US and global need for HCQ supply, if the drug is indeed proven efficacious by larger and more definite clinical trials. We assume that a typical COVID-19 regimen would include 6 g of HCQ sulfate, or 30 tablets of 200 mg each.

Of note, the current worldwide need of 300 metric ton for HCQ was spread out across an entire year and was met steadily, mostly for chronic diseases. The COVID-19 demand, however, is an immediate surge. For example, if 2% of the US population needs treatment, 40 metric tons of HCQ would be needed in weeks. Globally, 2% treatment rate means a requirement of 1000 metric tons of the drug in weeks, or 3 times the current world annual production capacity. Can this be met within reasonable time?

4. Can the demand be met, why? and how?

To answer this question, let’s examine the following developments as reported by the news media in the last week of March 2020:
- Cadila is ramping up (5×) to produce 20 tons of HCQ per month, and said could go up to 40 tons/month if needed.
- Amneal Pharmaceuticals will ramp up and expects to produce ~20 M tablets by mid-April (4 tons).
- Laurus will ramp up HCQ production from mid-April from 5 to 15–20 tons/month.
Novartis intends to donate up to 130 million tablets (26 tons) by the end of May, including its current stock of 50 million 200 mg doses (10 tons).

Mylan said it has restarted production of its hydroxychloroquine sulfate tablets in West Virginia, United States, with plans to ramp up production to 50 million tablets, which could treat more than 1.5 million people (10 tons).

Teva is donating 16 million tablets to hospitals around the U.S. (6 million tablets by March 31st and more than 10 million within a month, 3.2 tons)

Bayer's announced donation of 3 million tablets of chloroquine to US hospital (0.6 ton)

Pankaj Patel, chairman of Cadila Healthcare, stated that India could make 100 tons per month immediately. “We are ramping up our capacity and are geared up to supply enough for the Indian market. There would be no shortage of this drug here. Moreover, most of the raw material used is fortunately available locally.”

Taking these events as a whole at face value, we can reasonably expect a surge of over 200 metric tons, or a billion tablets of HCQ, be made available within a month or two. Larger demand, however, would seriously challenge the manufacturing process for HCQ API, or hydroxychloroquine sulfate, is considered to be average in overall complexity, when compared with other marketed small molecule therapeutic drugs. Thus, the original procedure for making HCQ as disclosed by its inventor Surrey in 1950 [7] is still practiced by a majority of API manufacturers and regulatory agencies in order to mobilize and coordinate international collaboration between global governments, pharmaceutical manufacturers and regulatory agencies in order to mobilize and coordinate worldwide resources to meet the demand. Lessons can be learned from the success of penicillin production scaled up from milligrams to metric tons within two years during the World War II. This was achieved with leadership for being accountable, courage for taking risks, can-do attitude and ingenuity from scientists and engineers, and commitment of the governments and enthusiastic participation by more than 20 private companies.

The COVID-19 virus strikes and cares no national border. Country governments should also work together to lower bureaucratic barriers for drug supply while ensuring quality in innovative and efficient ways. The regulatory bodies can and have to work together to find creative solutions. When it comes to to saving lives, speed matters.

Under extreme circumstances, such as a global demand surge for 10,000 metric tons of HCQ to treat over up to 20% of the world population as illustrated on the far right column in Table 1, vitally necessary is the close international collaboration between global governments, pharmaceutical manufacturers and regulatory agencies in order to mobilize and coordinate worldwide resources to meet the demand. Lessons can be learned from the success of penicillin production scaled up from milligrams to metric tons within two years during the World War II. This was achieved with leadership for being accountable, courage for taking risks, can-do attitude and ingenuity from scientists and engineers, and commitment of the governments and enthusiastic participation by more than 20 private companies.

For reference, we listed a few of the most common synthetic processes of hydroxychloroquine in schematic form (Fig. 4). As illustrated, the HCQ active ingredient can prepared in relatively straightforward manner from feedstocks including benzene, ethylene, acetic acid, butane, ethylene and ethanol. These are commodity chemicals with abundant and stable supply as far as pharmaceutical manufacturing is concerned. Many of the intermediates...
Fig. 4. Common Synthetic Processes of Hydroxychloroquine and supply Chain Illustration.
within the scheme are also enjoying multiple uses within the chemical and pharmaceutical industries, so the supply chain is relatively robust. Unit operations are considered within the normal ranges other than one or two steps requiring high temperature conditions. Cycle time and regulatory considerations are the most critical factors for bringing up emergency supply.

In conclusion, we remain cautiously optimistic with the global manufacturing capability to ramp up production, meeting the demand for HCQ should it be proven efficacious by randomized clinical trials. Cycle time and regulatory considerations are the most critical factors for bringing up emergency supply. Considering that there is significant lead time to ramp up production at this scale, cost of API production is relatively small, starting materials are readily available, and the potential benefits and probability of HCQ being eventually proven efficacious [11] to help patients inflicted with COVID-19, immediate ramping up of production at risk as a contingency before definitive clinical trials conclude appears to be justifiable.

Conflict of Interest

Recommendations and opinions presented therein are those of the authors and do not represent that of any organizations. Data presented are for informational purposes only and should not be considered or construed as medical advice or financial analysis and is not intended to be a substitute for professional advice, diagnosis, or treatment. Always seek the advice of a qualified health provider with any questions you may have regarding a medical condition.

Acknowledgment and disclaimer

The authors wish to thank Vincent Xiang, Alex Zhang, Doris Jiang, Keith DeVries and Wenjun Tang for their valuable input. Recommendations and opinions presented therein are those of the authors and do not represent that of any organizations. Data presented are for informational purposes only and should not be considered or construed as medical advice or financial analysis and are not intended to be a substitute for professional advice, diagnosis, or treatment. Always seek the advice of a qualified health provider with any questions you may have regarding a medical condition.

CRediT author statement

Tony Zhang: Conceptualization, Data curation, Writing. Original draft preparation.
Boyu Zhong: Analysis, Writing- Reviewing and Editing.

References

[1] For product monograph including patient medication information of hydroxychloroquine. see: http://products.sanofi.ca/en/plaquenil.pdf. For US label, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/009768Orig1s051lbl.pdf.
[2] (a) https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1.full.pdf, (b) Gautret et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI: https://doi.org/10.1016/j.ijantimicag.2020.105949; (c) https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf.; (d) https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa237/5801998.
[3] For clinical trials registered with clinicaltrials.gov involving hydroxychloroquine against COVID-19. see https://www.clinicaltrials.gov/ct2/results?cond=COVID&term=hydroxychloroquine&cntry=&state=&city=&dist=.
[4] For a recent report, see https://khn.org/news/why-hoarding-of-hydroxychloroquine-needs-to-stop/.
[5] For a recent report, see https://www.rheumatologynetwork.com/news/hydroxychloroquine-production-surges-covid-19https://news.bloomberglaw.com/pharma-and-life-sciences/maker-of-trumps-unproven-virus-cure-boosting-capacity-10-times.
[6] For HCQ EUA issued by FDA. see https://www.fda.gov/media/136537/download.
[7] A. Surrey, US Patent 2,546,658, 1950.
[8] Data from multiple sources, including marketing research, prescription statistics, import/export data, analyst reports, security filing and company annual reports, were used to cross-corroborate for the best estimates to ensure directionally correctness.
[9] https://www.bloomberg.com/news/articles/2020-03-23/fda-lifts-import-curbs-on-maker-of-unproven-virus-drug-in-india.
[10] https://www.fiercepharma.com/manufacturing/chinese-apis-flowing-but-indian-hindrances-u-s-approval-hydroxychloroquine.
[11] For report on the lack of evidence of significant clinical benefit of HCQ and azithromycin combination when treating patients with severe COVID-19 Infection. See https://www.sciencedirect.com/science/article/pii/S0399077X20300858.