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The Breakfast Club "Bottom Line"

Summary of Key Points from the 4th Blue Matter Breakfast Club™ Meeting

Virtual Meeting, 13th May 2020

Guest speaker: Dr. Thomas Lönngren, Strategic Advisor and Former Executive Director, European Medicines Agency (EMA)

The Breakfast Club virtual meeting of 13th May 2020 was a multi-faceted session with Dr. Thomas Lönngren, Strategic Advisor and Former Executive Director of the European Medicines Agency (EMA). The session included two main components:

1. An interview with Thomas, conducted by Dirk Moritz, who works with the Blue Matter team in Zurich

2. A question and answer session with the audience

The summary below is intended to capture the "bottom line" of the meeting in a concise, well-organized manner. Key themes from the session are captured here as notes for attendees and other interested readers. These notes are intended to provide a general overview.

Strategic Impact of the Coronavirus Pandemic on Biopharma Companies: R&D, Clinical, and Regulatory

Executive Summary *(Key Themes and Takeaway Messages)*

Biopharma Company Impact

- Companies are significantly affected by COVID-19: R&D activities have been disrupted and a large number of clinical trials have been stopped.
- Key priorities for companies are to ensure patient safety and continued drug supply, protect study integrity, and ensure the well-being of biopharma staff members.
- Companies of all sizes are being impacted, but smaller companies will feel the most burden.
- Companies need to plan for long-term effects from the current crisis and continue to adapt.
- Relentless focus on putting the patient first and effective collaboration with key stakeholders—including regulators—will be key.

What is the Blue Matter Breakfast Club?

As a strategic consulting firm serving the life science industry, Blue Matter works to remain on the leading edge of commercial strategy in biopharmaceuticals.

Blue Matter Breakfast Club meetings are 1.5 to 2 hours long and provide ideal opportunities to network and interact with senior leaders and colleagues from other organizations. They are by invitation, and they offer a private, engaging environment for networking and discussion.

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Regulatory Impact

- Regulators have learned from previous epidemics, such as the 2009 H1N1 "swine flu" outbreak and have put special processes and procedures in place that are being used now.
- Close collaborations between regulators and companies are critical to overcome barriers, and there is great willingness on the side of the regulators to be flexible

Treatment & Vaccine Development

- Currently, there are more than 1,000 studies for the development of coronavirus treatments and vaccines.
- A large part of the therapeutic studies is focusing on the repurposing of drugs; curiously, the vast majority of them are sponsored by hospitals and academic institutions.
- There are about 8 vaccine studies ongoing. The most optimistic scenario is a vaccine approval by H1 2021.
- Given the very large number of individuals that would have to be treated with a vaccine, regulators will likely remain conservative and require solid evidence for safety and efficacy, even when experiencing political pressure.

Positive Aspects of the COVID-19 Pandemic

- Companies reacted very quickly and creatively to this crisis and adapted well to that challenging situation.
- Significant collaborative efforts (e.g. between companies and regulators) are ongoing to overcome obstacles and find solutions.
- In general, there are high levels of resilience: Productivity has generally been preserved, as novel ways of working remotely seem to work well.
- Companies have a major opportunity to re-invent procedures—such as virtual site-visits—to leverage new technologies to streamline trial design and continue to drive digitalization.
- The biopharma industry has an opportunity to boost its public reputation as it focuses on patients, works to provide new testing methodologies, and develops and provides innovative coronavirus treatments and vaccines.

Introduction to Dr. Thomas Lönngren

1. Thomas is the former Executive Director of the European Medicines Agency (EMA).
   a. He served as Executive Director in London from 2001 to 2010.
   b. Under his leadership, the EMA developed into the world-leading regulatory agency it is today.
2. He currently lives in Uppsala, Sweden.
3. Professionally, he splits his time equally between two roles:
   a. Strategic Advisor for the NDA Group, a leading regulatory and drug development consultancy that helps companies secure approval for new medicinal products in the EU and US
   b. Non-executive board member for biotech/med-tech companies and a venture capital advisor

Interview Questions

A. Personal Impact and Thoughts on COVID-19

1. How have you been personally affected by the current situation and how do you deal with it?

a. I belong to one of the higher-risk groups, but I'm isolated in my country house outside of Uppsala, far away from the areas of the coronavirus.

b. I've been working from home for the NDA Group and working remotely to fulfill my board responsibilities for biotech firms.

c. My daughter is a frontline doctor in a hospital in London. It was challenging for her a few weeks ago when the crisis was at its peak in the UK. This was a bit of a reality check for me to hear my daughter's experience treating COVID-19 patients and sadly seeing many of them die. Coronavirus has not been a disaster for me personally, but it is a major health crisis and all of us need to contribute and collaborate to solve it.

2. Have you been surprised by (the extent of) this pandemic?

a. I personally experienced the H1N1 influenza ("swine flu") pandemic in 2009 while at the EMA.

b. It was expected that approximately 10 years later we could get another epidemic or pandemic. However, I have been surprised at how much more severe the COVID-19 pandemic is compared to the 2009 pandemic.

c. It seems that governments around the world were not prepared for it.

B. Impact on Biopharma Companies

1. What do you think are the biggest immediate impacts of COVID-19 on biotech companies?

a. We need to think about the biopharma staff members. This can have significant consequences for them. Isolation can be a problem, especially as the lockdowns continue. Safety in the workplace also needs to be taken into account. Each company needs to develop processes to protect their people, as well as engage with them.

b. In addition, many clinical trials are on hold for 6 months or more. That has a major impact on development timelines. Lab work has also stopped for the moment.

c. Overall, the impact is likely to be higher on small companies with single assets.

d. Again, for smaller companies, the financial impacts could be immediate, especially if they were in the process of raising money to continue their operations. Considering the huge costs associated with running trials, maintaining a business, paying salaries, and so on, it can be extremely challenging when capital streams dry up, even for a limited time. This environment also makes it more difficult for them to raise money.

e. There could be long-term financial consequences for small, mid-size, and large companies. We are already seeing "big pharma" revenues going down, and this will have repercussions on the financial markets.

f. Also, thinking a little longer-term, countries are spending a huge amount of money dealing with COVID-19 and its various impacts. This will probably make it even more difficult for biopharma companies to get premium reimbursement for expensive products In the future.

2. From what you have seen, how are current R&D activities affected and in particular, what is the impact on clinical trials and ongoing studies (for example, an estimated 1,000+ studies world-wide are affected, and IQVIA says that more than 80% of their sites are paused)?

a. For life-threatening diseases such as cancer or rare diseases, it is difficult to put clinical trials on hold. However, some companies are constrained and had to stop patient recruitment.

b. The EMA, European Commission, and FDA came out with very good guidance on how to manage through the situation.

c. Their emphasis has been on coming up with solutions to continue trials wherever possible while putting patient safety first. Regulators are accepting deviations from study protocols to adjust to the new reality, as long as they are safe and protect data integrity. Some solutions include remote monitoring, telemedicine, getting drugs at home, and so on.

d. To move through this, we need to find some smart new ways to run clinical trials. Regulators are willing to adapt, and all decisions should be made in close collaboration and alignment with them.

3. How should companies best respond to the current challenge? What are some key things companies should do, based on your experience?

a. First, we are all in this together! Companies need to think about how to effectively collaborate with each other, share data and "lessons learned", and put patients first and foremost, and before shareholders' interests.

b. Companies must also remember that their people are their most important "assets". They need to take care of their staffs in terms of safety and engagement.

c. The biopharmaceutical industry needs to realize that this pandemic presents a golden opportunity to regain people's confidence and improve its reputation. It's no secret that the industry's reputation used to be relatively low. Now, as companies seek COVID-19 treatments and vaccines, they have the opportunity to improve their public standing, and I think it has been rising lately because of that.

d. Companies should also do what they can to support the healthcare system during this time. Examples of this include Roche, which is offering new coronavirus testing kits, and GSK, which is supporting lab testing work in the UK.

e. Ensuring a strong, uninterrupted supply of drugs and medicines is a huge responsibility for pharma. There are ongoing initiatives from government agencies to ensure a continued supply of medicines to patients, and companies need to remain focused on this.

f. Finally, companies will need to be very strategic about how they reprioritize resources away from areas such as clinical trials that have been put on hold. For small companies, it's vitally important to plan for the future and set themselves up for success.

C. Regulatory Actions and COVID-19 Treatment / Vaccine Development

1. How are / will regulators such as the FDA and the EMA react to the current situation?

a. Procedures and plans for handling a pandemic were already in place in 2009. Those plans have been operationalized, rehearsed and updated in front of this crisis. We can see now the outcomes with FDA and EMA as new guidelines are swiftly being issued from the agencies, (e.g. accelerated pathways):

   i. FDA created a special Coronavirus Treatment Acceleration Program (CTAP)

   ii. FDA issued emergency use authorization for Gilead's remdesivir

   iii. EMA has similar compassionate use-like mechanisms

b. As a key learning from 2009, we saw the impact of collaborating between different national regulatory agencies. I was involved in the creation of an international collaboration of the leading authorities, such as EMA, FDA, and WHO. They are now meeting on a regular basis with involvement from WHO to discuss guidelines on the development of treatments and vaccines. As an outcome, the WHO developed harmonized protocols for vaccine development.

c. Regulatory bodies will remain focused on their established key message to drug developers: There is a very clear ongoing requirement to demonstrate efficacy and safety with well-controlled randomized trials.

d. Regulators will keep their doors open to provide sound scientific advice to guide and to collaborate with industry in a timely manner.

2. When do you think we will have the first therapeutics & vaccines approved?

a. The FDA created two guidelines and the EMA has done a similar program, an emergency use program.

b. Since January 2020, there are 1,115 ongoing trials in therapeutics and vaccines for COVID-19; mostly for therapeutics. More than 900 of them are hospital or academically sponsored. A mere 190 are from industry players.

c. The majority of clinical trials are focused on repurposing existing treatments (e.g. existing antivirals or anti-inflammatory compounds).

d. We need to clearly separate vaccines from therapeutics. Examples for therapeutics include immuno-modulators and anti-viral compounds, mainly repurposed drugs. This is positive, as we already know a lot about CMC (chemistry, manufacturing, and controls), the clinical experience, and importantly, also the safety profiles. The key objective for therapeutics is to conduct proper randomized trials to draw sound conclusions on the effectiveness of those treatments, as the existing data comes mostly from open-label studies.

e. As an example, much more data is required for Gilead's remdesivir to fully understand its therapeutic value. A huge number of clinical trials are currently ongoing, but usually not randomized and mostly exploratory. I think that regulators could be ready to make some shortcuts for treatments, depending on the public health needs and the initial results.

f. The story is not the same for vaccines. Currently, there are only 8 vaccines in clinical trials. Regulatory agencies won't be ready to make shortcuts here. They would like to see robust evidence on efficacy (possibly 50-60% effect size) in patient settings with infections. If some regulators are ready to move on and take some risks while evidence is still pending, the shortcut will likely be a consequence of public and political pressure. This discussion will probably happen in autumn when we will get the first phase 2/3 studies. I'm not sure if regulatory authorities would be ready give conditional approvals based on only surrogate endpoints (neutralizing antibodies) As vaccines will be given to a very large number of people, agencies will insist on robust efficacy data but even more important, on robust safety profiles. If all goes well, current timelines suggest that the earliest approval of a vaccine is likely to come late in the first half of 2021.

3. How reactive do you think regulators might be to political pressure?

a. Assuming there is an approval already after phase 2 results (e.g., through an emergency approval), then it would be impossible to conduct a proper placebo-controlled phase 3 study. Who would like to take that risk, as the real safety and efficacy would have not been established? And if there are any issues with the vaccine, this could have huge consequences on the belief in vaccination worldwide. Regulators would always like to be sure about the outcomes. But the EMA and FDA are two different agencies, so it will be really interesting to see in the autumn the results of the phase 2 studies and the agencies' reactions to it.

D. Conclusion and Outlook

1. The extent of the COVID-19 pandemic is rather unprecedented. During your 10 years at the EMA, you saw the SARS coronavirus (2002, with a relatively small number of people infected but a 10% mortality rate), AIDS/HIV (which peaked from 2005-2012), and H1N1 (2009, with 1 billion infected but 0.03% mortality). Given all that experience, what are the key learnings for us today?

a. The biggest learning from previous epidemics resulted in the EMA plans for emerging health threats that now have been activated and special procedures and guidelines are now in place to manage the pandemic from a regulatory perspective.

b. We also learned a lot from MERS, SARS, etc. Core dossiers that would be ready to get a vaccine approved in about 5 months was a successful initiative that lead to the availability of a vaccine for the 2009 influenza pandemic.

c. Unfortunately, this is not the case for COVID-19, as it is a new virus and we had very limited information upfront on this particular virus.

d. The WHO had warned countries and governments but sadly, this resulted in very little preparation for a new pandemic.

2. If you could look into your crystal ball, how will the COVID-19 situation evolve and what might the permanent impact or long-term change be?

a. My biggest worry is the impact on the global economy. What will be the consequences? We will likely see increased poverty. Hopefully it doesn't lead to deep depression and social unrest.

b. It's also important to remember that we are in a "marathon" with the virus. Lockdowns are likely to continue in one form or another until we have a vaccine. We will have to learn to live with the virus and there will be a long-term impact.

3. Is there anything positive coming out from this?

a. For sure, this will be an opportunity to further leverage digital solutions. They can make us more efficient as a workforce. Technology has worked extremely well (for example, Zoom workshops with breakout features, interactive team building games, etc.). The efficiencies we can gain from virtual tools will never replace human interaction, but can be realized in a post-lockdown environment, too.

Question and Answer Session with the Audience

Question 1: A lot of companies are developing COVID-19 treatments. There will be a rush to get those treatments approved while treatments for other indications would also require approval. Will there be a prioritization on approval from EMA regarding COVID-19 submissions?

Thomas Lönngren: As already discussed, a pandemic task force was developed within the EMA to support the approval of those new pandemic treatments, so there are dedicated resources available that do not take resources from other regulatory work.

Comment from Audience: So far and in our experience, there has not been any difficulty in getting timely scientific advice. Currently, there is no indication of any direct guidance to prioritize COVID-19 vaccines or treatments. But, due to the gravity of the situation, individuals may make personal decisions to prioritize vaccines or treatments for COVID-19.

Question 2: What do you think will be the economic impact and the impact on reimbursement for specialty & rare diseases (RDs)? When governments realize the amount of funding spent to address the crisis—and the subsequent budget pressures—would you think the future investment would likely go more into primary care and general public healthcare versus specialty care & RDs?

Thomas Lönngren: Budget spending occurs at a national level and therefore, the EU member states are likely to be impacted differently. It will be hard to predict the outcome. Healthcare will remain a high priority for governments in the US and the EU, and cost effectiveness will still be a leading topic of discussion. Industry should be prepared for potential changes, for a push for lower drug prices. It's certainly possible but it's really too early to say now. I'm unsure if the NICE QALY algorithm will change to make it harder for medicines to get reimbursement. Orphan drug and ultra-rare medications would likely remain untouched due to the low number of patients and the low impact on the overall budget.

Question 3: In the current situation, how can regulators conduct site inspections? What would be the implications, and would they be longer term?

Thomas Lönngren: Regulatory protocols—including inspections—involve complicated processes that have been developed and validated over a long period of time. Regulators are not known to change or adapt very easily but maybe they'll adopt some of the current measures (e.g. remote monitoring) in the future world, especially given advancements in technology. Of course, these changes will need to be documented and validated to ensure that trials, etc. are not compromised. This is an opportunity for the industry to partner with regulators to innovate. One initiative is exploring how to run clinical trials in a different way using a certification scheme: ACRES (https://www.acresglobal.net). Regulators have also worked with regional agencies to communicate better on inspections.

Comment from audience: There are some examples of industry / regulator collaborations. Some companies have experienced examples of (unprecedented!) virtual visits and inspections by the Italian regulatory agency using iPads and cameras in Milan. Another example includes site visits in the UK and the US by the Russian authorities. Timelines were condensed from usually 4 weeks to 2 days! These site visits or inspections required a lot more upfront preparation from the team but worked really well.

Question 4: A study with an anti-cytokine agent that might work in COVID-19 was started in Northern Italy. The study was running over 8 weeks and during that time, the standard of care changed every day! Doctors and nurses had to work over-time. The reality of clinical trials for COVID-19 is that it's difficult to properly design a control arm and to conduct trials without a lot of protocol amendments. In view of this very challenging context, would this require a different approach for regulatory approval?

Thomas Lönngren: In the current situation, the healthcare system is less over-loaded and the numbers of infected patients are going down. So now, it may be easier to work after a standard protocol. Also, the standard of care is beginning to stabilize. For repurposed drugs (such as the anti-cytokine agent you mentioned), there is an existing safety database that can be leveraged. It is easier to do a conditional approval for these kinds of therapeutics. It would be a good approach for a company to run a small phase 2, then plan for phase 3 and work to get a conditional approval to get the medication into the healthcare system more rapidly.

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Blue Matter is a consulting firm serving the life sciences industry. We strive to bring a new approach to consulting with original ideas that deliver a meaningful impact.

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