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# No news equals bad news for Nabriva and Heron

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**Manufacturing issues prompt the US regulator to knock back projects from Nabriva and Heron Therapeutics, both of which insist that the problems are easily solvable.**

Crossing the regulatory finishing line is never a dead cert, and Nabriva and Heron show that, when a small company is involved, the odds are even longer. A day after the PDUFA date had passed for their respective applications, both groups announced the receipt of complete response letters.

Manufacturing problems were blamed in both instances, and on conference calls this morning executives stressed that no new clinical data had been requested. The possibilities of substantial delays were largely played down but, with expectations high for green lights all round, investors were disappointed. Nabriva shares were 21% lower in early trade, with Heron down 13%.

The two companies' projects look very different on the surface. Nabriva is trying to bring a new intravenous antibiotic, fosfomycin, to the US; this is to be branded Contepo, and has been available in most other markets around the world for many years. Heron, meanwhile, has developed a non-opioid-based painkiller currently called HTX-011; the extended-release formulation of bupivacaine plus the anti-inflammatory meloxicam is being aimed at the post-operative market.

The candidates do have one notable thing in common, however: both were assessed under expedited pathways. Suggestions were made on both calls that a short review period could have contributed to the need to issue a CRL; presumably the inference is that the FDA ran out of time to clear up outstanding issues.

Barry Quart, chief executive of Heron, expressed this most forcibly. HTX-011 had fast-track and breakthrough therapy designation, and received priority review on acceptance of the NDA at the end of December.

"This was a very fast review period. I don't think that's a good excuse – but it's the only explanation I have," he said, adding that the agency had requested only a "small amount of information", with no verbal or written questions related to clinical data.

"We believe we understand the issues that have been raised … and we can respond very quickly. We are extraordinarily disappointed that these issues were not brought up by the agency during the review period. We will make our displeasure known," he said.

No firm details were released as the exact nature of the problem, though such a robust defence of the company's application will raise hopes for a relatively short delay.

| Outlook for Heron sales | | | |
|---|---|---|---|
| | Global sales ($m) | | |
| **Product** | **2019e** | **2021e** | **2023e** |
| HTX-011 | 35 | 310 | 569 |
| Cinvanti | 97 | 145 | 179 |
| Sustol | 22 | 98 | 144 |
| **Total** | **154** | **553** | **893** |
| *Source: EvaluatePharma.* | | | |

Nabriva is a slightly different case, as the issues raised by the FDA relate to problems at the company's contract manufacturer, which supplies most fosfomycin globally, executives said on a conference call, adding that European regulators had recently inspected the facility without raising any issues.

Again, few specific details were released, though Ted Schroeder, chief executive of Nabriva, said the company hoped to launch "in a reasonable time frame. I want to emphasise that these are not fundamental issues with the manufacturing of the compound, these are more manufacturing operations types of concerns that are addressable."

Importantly, the company confirmed that there was no supply chain overlap with another Nabriva antibiotic the FDA is reviewing, lefamulin, which is thought to hold much greater commercial potential.

Contepo was accepted for review in the opening days of 2019 and was initially given a June 30 PDUFA date, but the FDA brought this forward to April 30 after reclassifying the filing. This gave the agency only four months to complete its review.

Notably, the 35-day US government shutdown occurred over the period that Contepo and HTX-011 were accepted, at least according to company press releases. At the time, the agency said applications already in process would not be affected, and neither company raised this as a factor on their conference calls.

It is impossible to know whether the shutdown played a role here. It should also be remembered that small companies are more prone to regulatory missteps, as a previous *Vantage* analysis has shown (*Are small companies carrying the complete response letter can?, May 24, 2018*).

Drug developers will have to hope that the FDA is not struggling to meet expedited timelines. However, hints of problems at the regulator will provide little comfort to Nabriva and Heron investors, who must trust that these hold-ups are as inconsequential as executives have described.

| Outlook for Nabriva sales | | | |
|---|---|---|---|
| | Global sales ($m) | | |
| **Product** | **2019e** | **2021e** | **2023e** |
| Lefamulin | 8 | 73 | 204 |
| Contepo | 3 | 24 | 65 |
| **Total** | **10** | **98** | **269** |
| *Source: EvaluatePharma.* | | | |

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