Court File No. T-1786-16

FEDERAL COURT

BETWEEN:

SWEDISH ORPHAN BIOVITRUM AB (publ)

Applicant

- and -

MINISTER OF HEALTH

- and -

MENDELIKABS INC.

Respondents

NOTICE OF APPLICATION

TO THE RESPONDENT:

A PROCEEDING HAS BEEN COMMENCED by the applicant. The relief claimed by the applicant appears on the following page.

THIS APPLICATION will be heard by the Court at a time and place to be fixed by the Judicial Administrator. Unless the Court orders otherwise, the place of hearing will be as requested by the applicant. The applicant requests that this application be heard at Toronto, Ontario.

IF YOU WISH TO OPPOSE THIS APPLICATION, to receive notice of any step in the application or to be served with any documents in the application, you or a solicitor acting for you must file a notice of appearance in Form 305 prescribed by the *Federal Courts Rules* and serve it on the applicant's solicitor or, if the applicant is self-represented, on the applicant, WITHIN 10 DAYS after being served with this notice of application.

Copies of the *Federal Courts Rules*, information concerning the local offices of the Court and other necessary information may be obtained on request to the Administrator of this Court at Ottawa (telephone 613-992-4238) or at any local office.

IF YOU FAIL TO OPPOSE THIS APPLICATION, JUDGMENT MAY BE GIVEN IN YOUR ABSENCE AND WITHOUT FURTHER NOTICE TO YOU.

October 20, 2016

Issued by: SHERRI ALLY
REGISTRY OFFICER
AGENT DU GREFFE

Address of local office: 180 Queen Street West
Toronto, Ontario
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TO: **THE ADMINISTRATOR**
Federal Court

AND TO: **THE DEPUTY ATTORNEY GENERAL OF CANADA**
Ontario Regional Office
Department of Justice Canada
The Exchange Tower
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c/o Federal Court Registry
(pursuant to Rule 133)

AND TO: **THE MINISTER OF HEALTH**
Therapeutic Products Directorate
Address Locator: 0201A1
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Ottawa, ON
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AND TO: **MENDELIKABS Inc.**
4601 rue de Tonnancour
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APPLICATION

This is an application pursuant to section 18.1 of the *Federal Courts Act* for judicial review of the decision by the Minister of Health (**Minister**) to issue a Notice of Compliance (**NOC**) to Mendelikabs Inc. (**MDK**) in respect of its MDK-nitisinone 2, 5 and 10 mg capsules for oral administration (**MDK Product**) on September 20, 2016.

The Minister's decision to issue this NOC appears to be a *de facto* decision to refuse a request from the applicant, Swedish Orphan Biovitrum AB (publ) (**Sobi**) to add ORFADIN® (nitisinone) to the Register of Innovative Drugs, pursuant to section C.08.004.1 of the *Food and Drug Regulations.* Therefore, Sobi's legal rights are directly affected by the Minister's decision to issue the NOC to MDK for the MDK Product, and Sobi is directly and prejudicially affected by this decision.

The only clinical data demonstrating the safety and efficacy of nitisinone sufficient to support a regulatory filing is Sobi's proprietary data, some of which is confidential. MDK must have relied on Health Canada's Guidance Document "Submissions Relying on Third Party Data" (**SRTD Guidance Document**) when it sought approval for the MDK Product, and the "third party data" that was relied upon must be Sobi's data. This abbreviated process is only available when a sponsor cannot assemble a conventional drug submission, and accordingly, was not available to Sobi because it has the exclusive rights to the data demonstrating the safety and efficacy of nitisinone.

Sobi submitted a conventional New Drug Submission (**NDS**) seeking approval for ORFADIN. Sobi's NDS was being considered by Health Canada at the same time as MDK's abbreviated submission. Health Canada requested additional data from Sobi to

supplement the extensive and proprietary data that it had already submitted as part of its NDS. This request delayed the review of Sobi's submission. In the meantime, the Minister issued a NOC to MDK on the basis of publicly available, third party data. These third party data must belong to Sobi, since the only relevant clinical data belongs to it.

Furthermore, Sobi has no knowledge that MDK ever undertook comparative bioavailability studies, as required per subsections C.08.002(2)(g) and (h) of the *Food and Drug Regulations* and the SRTD Guidance Document.

It is our understanding that Sobi is now *de facto* precluded from receiving eight years of data protection for ORFADIN as an "innovative drug". Data protection is intended to reward innovators for investing in the data required to bring new, safe and effective drugs to the Canadian market. ORFADIN would have been eligible for data protection had the Minister not unreasonably delayed review of SOBI's NDS and incorrectly and unreasonably issued a NOC for the MDK Product.

THE APPLICANT MAKES APPLICATION FOR:

One or more Orders in accordance with sections 18, 18.1 and 18.2 of the *Federal Courts Act*, in particular:

1. Interim relief pursuant to section 18.2 of the *Federal Courts Act* in the form of an Order requiring the Minister to stay the NOC issued to MDK on September 20, 2016 pending resolution of this Application;

2. An Order requiring the Minister to classify ORFADIN as an "innovative drug" in accordance with section C.08.004.1 of the *Food and Drug Regulations*, such that it is eligible for inclusion on the Register of Innovative Drugs when a NOC for ORFADIN issues;

3. An Order requiring the Minister to add ORFADIN to the Register of Innovative Drugs when a NOC for ORFADIN issues;

4. An Order quashing and setting aside the Minister's final decision dated September 20, 2016 to issue a NOC to MDK for the MDK Product;

5. An Order requiring the Minister to revoke or suspend the NOC issued on September 20, 2016;

6. A declaration that the Minister did not meet its duty of procedural fairness when it considered Sobi's NDS for ORFADIN, and issued a NOC for the MDK Product first;

7. An Order requiring the Minister to issue Sobi's NOC for ORFADIN within 10 days of this Court's Judgment, to the extent that it has not yet issued; and

8. Such further and other relief as counsel may advise and this Honourable Court may deem just.

THE GROUNDS FOR THE APPLICATION ARE:

Sobi and its Innovative Drug, ORFADIN

9. Sobi is an international specialty biopharmaceutical company dedicated to bringing innovative therapies and services to improve the lives of patients with rare diseases and their families. In 2015, Sobi set up a Canadian affiliate, Sobi Canada, Inc., and began preparations to seek marketing authorization for ORFADIN in Canada.

10. Sobi manufactures ORFADIN for the treatment of hereditary tyrosinemia type 1 (**HT-1**). HT-1 is a rare genetic disorder where the patient is unable to breakdown tyrosine, a common amino acid. Tyrosine accumulation leads to the build up of toxic substances in the blood and over time, can cause liver failure, kidney dysfunction and neurological problems, and without treatment can result in death.

11. Sobi, as an innovative manufacturer, has spent considerable time, effort and expense working with healthcare professionals and patients to understand and meet the medical needs of HT-1 patients. Sobi has developed several ORFADIN formulations to improve treatment of HT-1 and improve these patients' experience.

12. ORFADIN is marketed by Sobi in other jurisdictions worldwide, and market approval has consistently been based on Sobi's submission of a full dossier of clinical and non-clinical data demonstrating the safety and efficacy of ORFADIN.

Clinical Trials for ORFADIN

13. Sobi has exclusive rights to use the data from the single, pivotal clinical trial that demonstrates the safety and efficacy of ORFADIN in the treatment of HT-1, namely the "**NTBC Study**".

14. The NTBC Study was an investigator-initiated, double-blind, multinational, Phase III clinical study comprised of 207 patients who were diagnosed with HT-1. The study began in 1991 and ran for over 9 years.

15. The NTBC Study is the only pivotal clinical study (worldwide) that demonstrates the safety and efficacy of nitisinone for the treatment of HT-1. Sobi has not authorized the release of the data from the NTBC Study. Further, Sobi has no knowledge that these data have been disclosed, other than as part of confidential submissions to federal health agencies for drug approval and for inclusion in product monographs. Certain details of the NTBC study have never been disclosed in product monographs.

16. Sobi is the only company that has been approved to market nitisinone based on its proprietary safety and efficacy data. At most, any other nitisinone products could only have been approved as "subsequent entry" products by way of an abbreviated submission relying on Sobi's data, market experience with ORFADIN and/or studies demonstrating comparative bioavailability between ORFADIN and the subsequent nitisinone product.

Sobi's Canadian Regulatory Submission for ORFADIN

17. Sobi has sold ORFADIN in Canada through Health Canada's Special Access Program. These sales were doctor-requested and provided access to this important treatment for Canadian patients.

18. While establishing its Canadian presence, Sobi attended a pre-submission meeting with Health Canada in relation to its proposed NDS for ORFADIN. This pre-submission meeting took place in June 2015, and Sobi presented the non-clinical and clinical data packages that would be included in its NDS.

19. In the pre-submission meeting, Sobi asked whether Health Canada agreed that the clinical package was sufficient to approve nitisinone for use in the treatment of HT-1. Health Canada advised that the clinical data were sufficient for filing, but also discussed that additional information be submitted with the NDS, including the most current cumulative Periodic Safety Update Reports, and carcinogenicity study data, information which is not otherwise available in the public domain.

20. Sobi advised Health Canada in the pre-submission meeting, that it intended to file its NDS within the next few months.

21. In December 2015, Sobi requested Priority Review of its NDS. On January 15, 2016, Health Canada confirmed that Sobi's NDS met the requirements in the *Priority Review of Drug Submissions* Guidance Document, and would be granted priority review.

22. Sobi filed its NDS on March 15, 2016.

23. On April 29, 2016, Sobi received a Screening Deficiency Notice requesting additional data on the batch records from the NTBC Study. Sobi worked diligently to gather the required information and responded as soon as possible on June 15, 2016.

24. Sobi expects its NOC for ORFADIN will issue by January 9, 2017.

25. The Minister's review of Sobi's NDS was unreasonable in light of MDK's simultaneous submission that relied on Sobi's proprietary (and possibly its confidential) data. The Minister's review was particularly unreasonable since Sobi's rights to data protection were vulnerable and indeed, now appear to be lost as against MDK, if not entirely.

Data Protection for ORFADIN

26. On May 6, 2016, the Office of Patented Medicines and Liaison (**OPML**) advised Sobi by letter that:

> At this time, ORFADIN appears to be an "innovative drug" and is therefore eligible for data protection. At the time the submission receives a notice of compliance ("NOC"), the Office of Patented Medicines and Liaison ("OPML") will conduct a final review to determine if any other nitisinone-containing drug has been approved. If no other nitisinone-containing drug has been approved, ORFADIN will be added to the Register of Innovative Drugs for a term of eight years from the date of the issuance of the NOC....

27. The OPML also noted that there was a submission for another nitisinone product that was concurrently under review by Health Canada.

The MDK Product

28. At the same time Health Canada was reviewing Sobi's NDS, it also was reviewing MDK's submission for the MDK Product. As stated previously, MDK's submission must have been filed pursuant to the SRTD Guidance Document, and reviewed using this abbreviated process. Since the only clinical data in respect of ORFADIN is proprietary (and confidential, at least in part) to Sobi, Sobi's data must be the "third party data" that was relied upon by MDK and by Health Canada. This abbreviated process was not available to Sobi, because, as the only company entitled to use the data demonstrating the safety and efficacy of nitisinone, Sobi could not justify filing anything other than a conventional NDS.

29. The Minister issued a NOC to MDK for the MDK Product on September 20, 2016.

30. Health Canada allowed MDK's submission to proceed using the abbreviated SRTD Pathway and at least a subset, if not all, of Sobi's proprietary (and in part, confidential) data.

31. Indeed, the Product Monograph for the MDK Product (**MDK Product Monograph**) does not include any data other than information contained on the foreign labels for ORFADIN, and even refers to the NTBC Study in the "clinical trials" section.

32. Further, the MDK Product Monograph does not contain any comparative bioavailability studies, or any information on efficacy or safety studies. These data

should have been included in the MDK Product Monograph, pursuant to sections 4.2.1 and 4.2.2, respectively, of Health Canada's Product Monograph Guidance Document. In fact, Sobi has no knowledge that MDK ever undertook comparative bioavailability studies, as required per subsections C.08.002(2)(g) and (h) of the *Food and Drug Regulations* and the SRTD Guidance Document.

33. Therefore, it appears that MDK's submission is deficient. Health Canada has allowed MDK to rely on Sobi's proprietary (and possibly confidential) data to Sobi's detriment.

Improper Reliance on the SRTD Pathway

34. SRTDs are defined as NDSs and Supplements to NDSs that substantially rely on literature and market experience.

35. The SRTD Pathway was adopted on March 20, 2015 and came into effect on May 1, 2015. The SRTD Guidance Document sets out submission criteria for relying on third-party data and in particular, the evidentiary standards for proposed commercial products.

36. The SRTD Guidance Document states that:

> ...Health Canada has developed applicable criteria for cases where sponsors seek to satisfy the evidence requirements [namely, C.08.002(2)(g) and (h)] by way of a reference product (as reported in the literature) and its domestic and/or foreign market experience. **To satisfy evidentiary standards, sponsors are expected to demonstrate (in a coherent and consistent manner) the comparative safety and efficacy profile of the proposed commercial product to the reference product**. [emphasis added]

37. Pursuant to subsections C.08.002(2)(g) and (h) of the *Food and Drug Regulations,* an NDS must include:

> (g) detailed reports of the tests made to establish the safety of the new drug for the recommended purpose and conditions of use; and
>
> (h) substantial evidence of the clinical effectiveness of the new drug for the purpose and the conditions of use recommended.

38. The SRTD Guidance Document states that "…it is of primary importance that it meets the same standards for approval as a conventional submission, i.e., substantial evidence of safety and efficacy, as stipulated in subsections C.08.002(2)(g) and (h) for NDSs."

39. In addition, SRTD submissions should only be allowed when all of the following conditions and requirements are adequately addressed by the sponsor:

1. A rationale supporting SRTD filing to explain why a conventional drug submission was not assembled;
2. A complete chemistry and manufacturing data package for the proposed commercial drug product;
3. In accordance with requirement C.08.002(2)(m) of the Regulations, **evidence, based on comparative pharmaceutical and/or comparative bioavailability data, to establish that the product used in studies reported in the literature (i.e. reference product) is representative of the proposed commercial product** (see details further below); [emphasis added]
4. Evidence of extensive current foreign market experience with the same medicinal ingredient (for a minimum of 10 years under the same conditions of use), or evidence that the same medicinal ingredient is currently or has previously been marketed in Canada (under the same conditions of use);
5. For the published literature-based evidence, sponsors are expected to provide a systematic review using the methodology outlined in the Cochrane Handbook

for Systematic Reviews of Interventions and presented in the form as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement;

6. Copies of all documents, as detailed in Health Canada's Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format;

7. The most complete and current evidence-based information for the development of a Canadian Product Monograph;

8. A Canadian Risk Management Plan as described in the Health Canada Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E; and

9. A pre-submission meeting with Health Canada to discuss the safety and efficacy evidence required to support market authorization and the data requirements to bridge the proposed product to the reference product."

40. The SRTD Guidance Document also states that:

> The sponsor should provide... appropriate data to establish that the reference product used in those pivotal studies is representative of the proposed commercial product, based on comparative pharmaceutical and/or bioavailability characteristics.
>
> **Clinical studies reported in the literature and included in the submission will not be considered sufficient to establish the clinical safety and efficacy required by the Regulations unless it is demonstrated that the proposed commercial product will have the same in vivo performance as the reference product used in the studies reported in the literature**... For other drug products (e.g., solid oral dosage forms), demonstration of comparative bioavailability between the proposed and the reference products would be required.

41. Contrary to Health Canada's Product Monograph and SRTD Guidance Documents, there is no comparative bioavailability data in the MDK Product Monograph to establish that the product used in studies reported in the literature (i.e., ORFADIN) is representative of the MDK Product. Further, there is also no data in the MDK Product Monograph that the MDK Product will have the same *in vivo* performance as ORFADIN.

42. Therefore, it appears that without Sobi's NDS containing the clinical trial data, which was filed contemporaneously, the data submitted by MDK in its submission would not have been enough to support the issuance of a NOC for the MDK Product.

43. Further, MDK's submission did not meet the requirements of subsetcions C.08.002(2)(g), (h) and (m) of the *Food and Drug Regulations*, since it did not include information on efficacy, safety, or any evidence of comparative bioavailability.

44. The Minister thus erred when it issued a NOC for the MDK Product. This final decision is prejudicial to Sobi, and because it was based on insufficient data and information, is a concern for Canadian patients and prescribers.

45. As a direct consequence of the Minister's improper issuance of the NOC to MDK, it appears that Sobi is no longer entitled to data protection under section C.08.004.1 of the *Food and Drug Regulations.* Moreover, even if Sobi were listed on the Register of Innovative Drugs and granted data protection now, it would have no practical effect as against MDK and its MDK Product. Sobi's position in the Canadian market has been prejudiced and will be irreparably harmed if MDK's NOC is not revoked or suspended.

Procedural Unfairness to Sobi in MDK's Use of the SRTD Pathway

46. Sobi could not take advantage of the abbreviated SRTD Pathway as the only company entitled to use the data demonstrating safety and efficacy for ORFADIN, and not a third party. Other than seeking priority review, which it did and was granted, there was no process available to Sobi to abbreviate the review of its NDS based on its

own market experience. Sobi had to invest the time and expense to prepare a full regulatory dossier, rather rely than on third party data that was readily and publicly available.

47. Not only was Sobi required to prepare a complete NDS that contained public and proprietary confidential information, Health Canada requested that Sobi file additional information related to the NTBC Study via a Screening Deficiency Notice and further delayed the issuance of its NOC.

48. The data contained in the NTBC Study could not have formed part of MDK's submission since it is Sobi's proprietary confidential information. Therefore, the Minister conferred a benefit to MDK, through a breach of procedural fairness to Sobi, when it issued a NOC for nitisinone to MDK first, despite the absence of data and information in MDK's submission.

49. The Minister held Sobi to a much higher standard when it reviewed its submission for nitisinone, the same drug product. Sobi apparently cannot now be granted data protection for ORFADIN as a direct result of this procedural unfairness. Even if Sobi were listed on the Register of Innovative Drugs and granted data protection now, it would have no practical effect as against MDK and its MDK Product. This is in direct contravention to the purpose and intent of the data protection provisions of the *Food and Drug Regulations*, and Canada's international treaty obligations set out in NAFTA and TRIPS.

50. In addition, the Minister breached a duty of procedural fairness to Sobi when it relied on the proprietary clinical trial data filed in Sobi's simultaneous conventional NDS in reviewing the MDK submission.

The Priority Review Guidance Document

51. The Priority Review Guidance Document cannot contemplate a SRTD submission. Priority review of an NDS is available "for a serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness…"

52. The Priority Review Guidance Document further states that:

> In general, Health Canada views substantial evidence of clinical effectiveness as evidence consisting of at least two adequate and well controlled clinical studies, each convincing on its own to establish effectiveness of the drug involved…
>
> In some instances, clinical evidence consisting of a single, large-scale, adequate and well controlled study or one pivotal trial and additional clinical evidence may be deemed "substantial"…

53. Sobi is the only innovative manufacturer with rights to data from clinical trial studies demonstrating the clinical effectiveness of nitisinone sufficient to support a regulatory filing. Despite this, the Health Canada NOC Database indicates that the MDK Product was also approved according to a priority review.

54. The Minister erred when it granted priority review for the MDK Product since MDK could not establish substantial evidence of clinical effectiveness. First, the Priority Review Guidance Document does not contemplate a SRTD submission.

Second, it was procedurally unfair to grant MDK priority review on the basis of Sobi's data and information.

55. In addition, the Minister breached a duty of procedural fairness to Sobi in reviewing Sobi's NDS at the same pace as MDK's NDS with the knowledge that there were significant intellectual property considerations at issue, in particular, that fact that Sobi would be apparently precluded from inclusion on the Register of Innovative Drugs while a third party relied on its information.

56. Therefore, the Minister's decision to issue a NOC to MDK for the MDK Product, before issuing a NOC to Sobi, the innovative manufacturer of the same drug product, was incorrect and unreasonable. MDK could not meet the requirements of the Product Monograph or SRTD Guidance Documents, or Health Canada's Priority Review Policy. The fact that the Minister simultaneously delayed Sobi's submission by requesting additional proprietary confidential data, while it appears to have approved a submission for the same drug allegedly on far less data and information, is a breach of the Minister's duty of procedural fairness towards Sobi. Therefore, Sobi requests that this Court should quash the Minister's decision, and revoke or suspend the NOC that was issued to MDK for the MDK Product.

Apparent Loss of Data Protection to Sobi on the Basis of an Improperly Issued NOC

57. Sobi appears to now be precluded from obtaining data protection for its innovative product, ORFADIN, pursuant to section C.08.004.1 of the *Food and Drug Regulations*, because MDK's submission was approved according to the abbreviated

SRTD Pathway and MDK was issued a NOC for nitisinone first. Even if Sobi were listed on the Register of Innovative Drugs and granted data protection now, it would have no practical effect as against MDK and its MDK Product.

58. The Minister's decision to issue a NOC to MDK for the MDK Product appears to be a *de facto* decision not to grant Sobi data protection under the *Food and Drug Regulations*. Unless the Minister's decision is quashed and MDK's NOC revoked or suspended, Sobi will suffer irreparable harm by loss of market exclusivity, which it would otherwise have been entitled to under the data protection provisions of the *Food and Drug Regulations,* for a product it has expended significant time and expense to develop and make available to patients suffering from HT-1.

THIS APPLICATION WILL BE SUPPORTED BY THE FOLLOWING MATERIAL:

59. Affidavit(s) to be filed;

60. Material as may be received from the Minister of Health pursuant to the Rule 317 request made herein.

61. The *Food and Drug Regulations*;

62. The *Federal Courts Act*, sections 18.1, 18.2 and 18.4;

63. The *Federal Courts Rules*; and

64. Such further and other material as counsel may advise and this Honourable Court may permit.

Pursuant to Rule 317 of the *Federal Courts Rules,* the applicant requests that the Minister send a copy of the following material that is not in the possession of Sobi but is in the possession of the Minister of Health to the applicant and to the Registry:

All letters, files correspondence, opinions, memoranda, minutes records, summaries, email communications, forms, briefing materials, notes, documents or any other materials, media or device upon which such information is stored:

i. that pertains to representations made by MDK to the Minister during the regulatory review of its NDS seeking a NOC for the MDK Product with references to Sobi or ORFADIN, or MDK's regulatory obligations that are relevant to Sobi or ORFADIN;

ii. that were prepared or generated for the purpose of making the decision to issue the NOC for the MDK Product, as well as a copy of the Minister's decision under review;

iii. which discusses, references, pertains to, underpins or is otherwise relevant to the decision set for in the decision to issue the NOC for the MDK Product;

iv. any and all written submissions made to Health Canada after September 20, 2016 pertaining to the decision to issue the NOC for the MDK Product;

v. any and all notes or recordings reflecting any verbal submissions made to or discussions with Health Canada by anyone regarding the decision to issue the NOC for the MDK Product; and

vi. that pertain to the decision whether to grant data protection for ORFADIN, including but not limited to, the review, assessment and eligibility of ORFADIN with respect to data protection and listing on the Register of Innovative Drugs.

October 20, 2016

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