CORPORATE CONFLICTS OF INTEREST
ANNUAL COMPLIANCE REPORT 2021

PURPOSE OF THIS REPORT

1. Under the Medicines and Healthcare products Regulatory Agency's ('the Agency') Corporate Conflicts of Interest (COI) Policy and Procedure there is a requirement for an annual compliance report to be prepared and for the report to be signed off by a Sub-Group of the Agency's Executive Team. Under the policy, the report should subsequently be considered by the Agency's Risk and Audit Committee (ARAC).

2. This report covers the calendar year 2021 and was agreed by the Corporate COI Sub-Group ('Sub-Group') in January 2022 and endorsed by ARAC in April 2022.

BACKGROUND

3. A policy was developed to set out the approach to handling potential COIs arising out of the merger of the National Institute for Biological Standards and Control (NIBSC) with the Agency in April 2013 and the launch of the Clinical Practice Research Datalink (CPRD) as a function of the Agency in April 2012.

4. The policy was approved by the Corporate Executive Team (CET, a pre-cursor to the current Executive Committee) in April 2013, reviewed in 2016 and then republished. A further review took place in late 2019 to provide assurance that the policy remained fit for purpose. A revised policy that better took account of current activities carried out by the whole Agency was approved by the Sub-Group in December 2019. The updated policy was approved by the CET in January 2020 and is published on both the Agency's intranet and external website.

PROCESSES THAT APPLY UNDER THE POLICY

5. The Agency will operate in accordance with the following principles when managing potential conflicts of interest:

    - transparency
    - impartiality
    - robustness
    - efficiency
    - maximising the Agency's contribution to public health.

6. The Agency's mission is to protect and improve public health while supporting innovation. Staff are therefore encouraged to progress new work, identifying any potential COIs and ways of mitigating them in a transparent way. This involves consideration of the specific case by the Sub-Group which also includes an Agency non-Executive Director.

7. NIBSC and CPRD operate within clearly defined parameters, set out in operational guidance to ensure that COIs are identified and then either managed or avoided.

8. While operating in the interests of public health and innovation, the Agency will take steps to avoid having a stake in the success of a product, company or organisation which it also regulates.

9. Where the proposed mitigation for a potential or perceived COI is to ask another regulatory authority, individual or organisation to review a decision or finding, or to carry out some work on behalf of the Agency, this should be approved by the Sub-Group in advance and all instances this mitigation will be recorded on the COI Tracker by the Sub-Group Secretariat.

10. The escalation arrangements in the policy are as follows:

    - Where possible, the majority of potential COIs will be managed within NIBSC, CPRD or the Regulator at an operational level in accordance with the principles set out above.

    - In those cases where
        - NIBSC and/or CPRD consider that there may be merit in undertaking activities that fall outside the restrictions of operational guidance - including activities that may create a perceived or possible financial COI, or
        - Part of the Regulator identifies something that may create a perceived or possible COI with another part of the Regulator or the rest of the Agency

        they will escalate to the Sub-Group for decision.

    - In exceptional cases, where it is felt particular work should proceed (such as for public health or scientific reasons) but where despite agreed mitigations there remains a risk of reputational damage to the Agency, the Sub-Group may decide to seek a Ministerial steer.

    - The Sub-Group has the option to call upon a person external to the Agency for independent input if required.

CONSIDERATION OF POTENTIAL COI CASES AND OTHER MATTERS

11. The Sub-Group met twice in the reporting period (March and August 2021). At these meetings, all cases identified during the year were reviewed.

12. The Sub-Group considered eight cases during the year in meetings, correspondence or both, as detailed below in paragraphs 13 to 44. These eight cases have been added to the tracker document (see Annex A) since the last compliance report.

Case 1

13. At the March meeting, the Sub-Group considered a case which involved performing 3 stability tests on multivalent meningococcal conjugate vaccine. The NIBSC stability data would be used to inform the administration of the vaccine to clinical trial volunteers and for a phase III clinical trial application. The data could then be reviewed by regulatory agencies in India, Europe and the UK. The NIBSC data would be confirmatory data to support data already produced by the customer. This proposal was brought to the Sub-Group as NIBSC was being asked to test a final medicinal product. The proposed mitigation was for customer to inform the Agency prior to submission in the event of a submission containing NIBSC data and that NIBSC data would be clearly highlighted.

14. The Sub-Group agreed that this project could proceed with the proposed mitigations

Case 2

15. At the March meeting, the Sub-Group considered a request from a company for the UK Stem Cell Bank (UKSCB) at NIBSC to produce and store a master bank of 50 vials of Clinical Grade Embryonic Stem Cells for sole use by the company. The Clinical Grade Embryonic Stem Cells had been deposited in the UKSCB by a UK University.

16. This would be the first time that the UKSCB has been approached to undertake contract banking. The Opportunity Assessment Group (OAG)[1] had assessed this project, discussed with Agency Inspectorate and Biologics colleagues and had established that the master bank of cells could be produced and managed under the existing HTA license because the cells would be just expanded and not manipulated.

17. The conflict of interest for the provision of EUTCD-Grade cell lines as starting materials for the generation of cell-based products had been examined by the Sub-Group in 2019. There remained a possibility that, as the master bank supplied by NIBSC could be used by the company in the development of starting materials for Phase1 clinical trials, the data created by UKSCB could therefore end up in a regulatory submission. This could result in the situation where the regulator could be assessing starting materials provided by UKSCB. It was noted that the data generated would form a small part of the data and would not be decision critical data.

18. The Sub-Group agreed that this project could proceed with the proposed mitigations.

1: The Opportunity Assessment Group (OAG) identifies, triages and progresses opportunities for business/income generation at NIBSC, as well as providing governance to identify potential Conflicts of Interest or operational challenges with proposed new projects at an early stage.

Case 3

19. At the March meeting, the Sub-Group considered a request from a clinical-stage biotech company for NIBSC to perform some contract testing in the Hamster model. Testing would be for 2 therapeutic antibody treatments to SARS-CoV-2 which were in the development phase. The company had indicated that if successful they would want to use the efficacy data generated by NIBSC in the documents provided to regulators. The antibodies would also be tested by other centres/institutes in different animal models and the data that NIBSC produce would be additional data to support a large body of efficacy data generated so far in the other studies.

20. Although NIBSC would be the only centre testing the materials in hamsters if the product proves effective, the NIBSC efficacy data could be included in a regulatory submission (in either a Clinical Trial Application and/or Market Authorisation Application). The NIBSC efficacy data would be a small part of any regulatory submission. There was an important public health need for the development of new treatments for SARS-CoV-2 and NIBSC was one of the few centres with access to the appropriate facilities to be able to run this testing effectively. NIBSC has access to the hamster model, within containment facilities and also access to the emerging SARS-CoV-2 variants.

21. It was noted that NIBSC would be involved in the submission of data only and not the analysis of which product would go forward.

22. The Sub-Group agreed that this project could proceed with the proposed mitigations.

Case 4

23. In correspondence in July and at the August meeting, the Sub-Group considered a case concerning a request by a company for NIBSC to produce a reference material to be used for development of a product.

24. The perceived COI was that the company would be paying NIBSC to produce a reference material. If in the future the product was likely to be reviewed by the Regulator for possible license the Agency could be open to a claim it was paid by the company it to produce this supporting material.

25. The Sub-Group noted that:

    - There is a public health requirement for laboratories to have access to a stable reference material to set up assay methods that will accurately measure this product.

    - Once the material is licenced, it is anticipated that IVD manufacturers will produce plasma calibrators for day to day clinical monitoring and it would be beneficial to produce such a reference material to which these calibrators are traceable.

    - The production of a NIBSC reagent for this product was in line with the

Agency's product life cycle strategy

- This would be beneficial to clinical laboratories as the reference material would be available for verification of monitoring assays as soon as the product is licenced.

- NIBSC regularly accepts donations of materials from manufacturers to produce reference materials.

26. In this situation, the production of the material would be carried out under a Contract Filling Agreement, with the subsequent donation of the produced materials to NIBSC under a separate Material Transfer Agreement (MTA). The MTA would include a clause on what should be done with the material should the product not be licenced. NIBSC would make it transparent that the company had funded the work on the information sheet provided with the reference material.

27. The Sub-Group agreed that this project could proceed as proposed.

Case 5

28. In correspondence in July and at the August meeting, the Sub-Group considered a case concerning a grant funded project to undertake preclinical evaluation of an experimental SARS CoV-2 vaccine designed to address the issues of spike variability in the current vaccine. The project would result in production of an experimental vaccine for SARS CoV-2.

29. The lead university would be submitting an application for this project to Coalition for Epidemic Preparedness Innovations (CEPI) for grant funding, and wanted to include pre-clinical evaluation of the experimental vaccine at NIBSC using the specialist high containment facilities and existing scientific expertise with the hamster challenge model of SARS-CoV-2. The perceived conflict of interest was that NIBSC would undertake pre-clinical evaluation of the experimental vaccine in the hamster model using different SARS CoV-2 variants. The data from these experiments could be included in documents submitted to the Agency's Clinical Trials Unit for Phase 1 clinical trial approval.

30. The data that NIBSC generate would not be safety data, it would be efficacy data only. The proposed mitigation included the data being published in a peer reviewed journal and the NIBSC data being clearly identified if it is submitted to the Agency's Clinical Trials Unit to enable the implementation of additional steps to ensure impartiality if required.

31. The Sub-Group agreed that this project could proceed with the proposed mitigations.

Case 6

32. In correspondence in July and at the August meeting, the Sub-Group considered a case concerning the expert and research group, a multidisciplinary group set up to look into the mechanisms of the observed

thrombotic adverse events with some Covid-19 vaccines. This expert and research group was funded by the Vaccine Task Force and administered by the National Institute of Health Research.

33. A member of staff from the Vigilance and Risk Management of Medicines Division (VRMM) and the NIBSC Director were asked to be members of the group. The NISBC Director[1] nominated a NIBSC expert in coagulation, to also be on the group, as the experimental work of the consortium would benefit from NIBSC knowledge of standardisation. That expert would likely be involved in actual projects and experiments and the generation of data which may be part of future decision making.

34. There was potential for a perceived conflict of interest with the Agency's safety and surveillance function where the scientific findings could guide regulatory decision-making such as varying or amending product authorisation. Therefore, membership/observership and/or generation of data needed to be adequately governed in order to enable this important work whilst maintaining independence of regulatory decision-making.

35. The Sub-Group agreed that there was a clear, overriding public health interest in the NIBSC expert being a member of this group and that her involvement was crucial to the success of the project. It was agreed that the NIBSC expert could be involved in the creation of data but would not be involved directly in any decision-making unless asked for objective advice (e.g. if results required expert input); otherwise, decision-making would be in Safety and Surveillance.

36. With regard to safety and surveillance, there was strong case for the Agency to be represented as an observer (rather than member), to ensure that any future decisions would be made in the possession of full information. The VRMM staff member, or a nominated alternative, would not be part of decision making but could answers questions put to them by the Chair and/or point out any inaccuracies raised in discussions. Their observer status would be noted in the minutes of all meetings for transparency.

37. It was agreed, as guiding principles, that involved staff should avoid 1) doing analysis and then advising on whether that analysis should be accepted 2) being involved in group discussions and then taking regulatory decisions.

38. The Sub-Group agreed with the proposed mitigations for participation in this project and in addition that the VRMM staff member would keep a log of who attended as observers.

Case 7

39. At the August meeting, the Sub-Group considered whether there were any potential COIs created by providing advice for the Innovation Service. By

[1] The NIBSC Director left the Agency, and therefore this group, at the end of July 2021.

contributing to the service, the Agency is supporting innovators in their development of novel innovative medical devices for the UK market which aligns with the Agency's goal to support scientific innovation.

40. The Sub-Group heard that some innovators who go through the Innovation Service may subsequently come to the Agency in the future about other regulatory matters, and this could cause the perception of a COI where regulatory action was required by the Agency on that innovator. In mitigation, it was proposed that enquiries dealt with through the service would be treated in exactly the same way and with the same timelines for enquiries received directly by the Agency. Also, the Agency would limit engagement to answering specific regulatory enquiries (e.g.: advice) rather than providing general regulatory support and that this would be set out in Terms of Use or similar documentation for clarity.

41. The Sub-Group agreed that this proposal could proceed managing the mitigations as proposed.

Case 8

42. In correspondence in September, the Sub-Group considered a proposal for a new distribution model for the UK Stem Cell Bank (UKSCB) human Embryonic Stem Cell lines (hESC). This proposed new income-generating activity built upon the existing supply of human Embryonic Stem Cell lines (hESC) for research use only (with a certificate of analysis), with a request to consider enabling the UKSCB to broaden the potential uses of the hESC lines, with a tiered pricing structure according to the intended use of the cells and the level of documentation / data accompanying the cell lines.

43. There was potential for conflict of interest for the provision of hESC lines for clinical/commercial use if customers produced a material which would be submitted to the Agency for regulatory approval and also with the provision of Cell Line Dossier submission to the regulator which could lead to colleagues assessing, as part of a submission from a customer, a dossier where part of the information had been created by the UKSCB, NIBSC.

44. The Sub-Group agreed that there was public health justification for carrying out this work and agreed the proposed mitigations (see Annex A).

Other matters

Revised CPRD annex

45. In January, the Sub-Group considered and agreed proposed amendments to the annex in the Corporate COI Policy and Procedure on how CPRD COI cases are managed*.* The revised policy and procedure was published on the Agency's intranet and external website in March.

General management of cases

46. At the March meeting, the Sub-Group agreed that cases that were similar, and with the same COI mitigations as previously agreed, should come to the Sub-Group for information in future rather than for agreement. An amendment was made to the paper format so that it was clear to the Sub-Group whether the case was for information or for agreement**.**

47. There was discussion about standard clauses that should be included in contracts, such as always alerting the Agency when submitting an application including data or information on which the Agency had been involved.

48. For some cases in the past, the Sub-Group had approved the potential involvement of another regulator to review the Agency's decision/s where there were potential COIs. It was agreed that, for low risk activities, the preferred route in future should be to go to the Commission on Human Medicines first, since this would provide the necessary independent oversight. Where another regulator's input was required, the Sub-Group agreed that, in future, the Agency might wish to approach a regulator within the Access Group.

Future of the Corporate COI Sub-Group

49. There was discussion about the positioning and future of the Sub-Group within the Agency's new structure following the completion of the transformation programme in early 2022. It was agreed that the reporting lines, membership and remit of the Sub-Group would need to be reviewed.

ONGOING REVIEW OF THE COI POLICY

50. The next review of the Policy and Procedure is due in January 2023; however, it will need to be reviewed and updated in 2022 following the restructure of the Agency.

51. Since the last annual compliance report, no complaints or suggestions had been received.

Annex A

COIs Considered by the COI Sub-Group in 2021

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
1	**Stability Testing Project** - multivalent meningococcal conjugate vaccine. Stability Testing of Meningococcal Vaccine - Performing 3 stability tests on multivalent meningococcal conjugate vaccine	The NIBSC stability data would be used to inform the administration of the vaccine to clinical trial volunteers and for a phase III clinical trial application. The data could then be reviewed by regulatory agencies in India, Europe and the UK. This proposal was brought to the COI subgroup as NIBSC was being asked to test a final medicinal product.	The NIBSC data would be confirmatory data to support data already produced by the requesting organisation. The customer will inform the Agency prior to submission in the event of a submission containing NIBSC data and that NIBSC data will be clearly highlighted.	Agreed that this work could proceed, managing the potential COIs as proposed.
2	**UK Stem Cell Bank (UKSCB) - Contract Banking** Request by company for the UKSCB at NIBSC to produce and store a master bank of 50 vials of Clinical Grade Embryonic Stem Cells for sole use by the company.	Possibility that, as the master bank supplied by NIBSC could be used by the company in the development of starting materials for Phase1 clinical trials, the data created by UKSCB NIBSC could therefore end up in a regulatory submission. This could result in the situation where the Agency could be assessing starting materials provided by UKSCB	The data generated would form a small part of the data and would not be decision critical data. The legal contract would also contain clauses to ensure that the customer alerts the Agency ahead of any regulatory submission containing NIBSC data or concerning the use of NIBSC starting materials, and that they make it clear what the NIBSC data or contribution to the submitted material is. This will enable the Agency to seek review by an alternative regulator if required.	Agreed that this work could proceed, managing the potential COIs as proposed
3	**Contract Testing in the Hamster model for 2 therapeutic antibody treatments to SARS-CoV-2**	If the product proves effective, the NIBSC efficacy data could be included in a regulatory submission to the Agency in the future.	It was noted that NIBSC would be involved in the submission of data only and not the analysis of which product would go forward.	Agreed that this work could proceed, managing the potential COIs as

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
	Request from a clinical-stage biotech company in another country for NIBSC to perform some contract testing in the NIBSC Hamster Challenge Model. Testing will be for 2 therapeutic antibody treatments to SARS-CoV-2 which are in the development phase.		The legal contract would include clauses to ensure that: • The customer informs the Agency ahead of any regulatory submission • NIBSC data is clearly indicated in the submission. • NIBSC data is part of a set of data created by other parties as well. Notice of a submission to the Agency would require a review of the submission by another regulator for transparency.	proposed. This work did not proceed as there was no further contact from the company.
4	**Product specific reagent** - request for NIBSC to produce a publicly available reference reagent to promote standardisation of monitoring methods and reduce the risk of inaccurate measurement in clinical laboratories.	The company would be paying NIBSC to produce a reference material. If in the future the product is reviewed by the Agency for a possible license could be open to a claim that someone has paid to produce this supporting material.	This reference reagent would be made publicly available for other companies. It will be made clear that company had funded the work on the reference material.	Agreed that this work could proceed, managing the potential COIs as proposed
5	**Experimental vaccine against SARS CoV-2** – A member of staff from the NIBSC Infectious Disease Diagnostics Division had been invited to participate in a grant funded project to undertake preclinical evaluation of an experimental SARS CoV-2 vaccine designed to address the issues of spike variability in	NIBSC would be undertaking pre-clinical evaluation of the experimental vaccine in the Hamster model using different SARS CoV-2 variants. The data from these experiments may be included in documents submitted to the Agency's Clinical Trials Unit for Phase 1 clinical trial approval.	The work at NIBSC is purely to establish the scientific principle and is not designed to assure the suitability of the experimental vaccine as fit for human use. NIBSC will not be directly responsible for developing the vaccine. The results will be published in a peer reviewed scientific journal before they are incorporated into any submission to the Agency's Clinical Trials Unit. NIBSC data will be clearly identified in any submission to the Agency, to enable any additional steps to be	Agreed that this work could proceed, managing the potential COIs as proposed. This work did not proceed as grant funding was not secured by the collaborator.

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
	the current vaccine		implemented to ensure impartiality, if required.	
6	**Thrombotic Thrombocytopenia Expert and Research Group** - An expert and research group (set up by the Chair of the CHM) that will look into the mechanisms of the observed thrombotic adverse events with some Covid-19 vaccines	A NIBSC expert in coagulation was invited to sit on group with a VRMM staff member or another representative from VRMM as observer. There is potential for a perceived conflict of interest where the scientific findings may guide regulatory decision-making	The NIBSC expert may be involved in the creation of data but will not be involved directly in any decision-making unless asked for objective advice and must not be being involved in group discussions and then taking decision on regulatory or licensing decision. She would leave the room before decisions were made. The VRMM staff member or a representative of Safety and Surveillance would be observers on the group only. They would not be part of decision making but may answers questions as put to them by the Chair and/or point out any inaccuracies raised in discussions. This will be noted in the minutes of a future meeting for transparency. The Agency would maintain a log of who attended each meeting	Agreed that this work could proceed, managing the potential COIs as proposed
7	**Innovation Service – Provision of advice by Devices** The Innovation Service will be a portal for the research community. The Agency will have accessor status providing regulatory advice. This service has both a devices and medicines element as Advanced Therapy Medicinal	Risks around the ability to take impartial action in the future. Providing advice through this service could introduce bias where regulatory action is required by the Agency on that innovator	Limiting the Agency's engagement to answering specific regulatory enquiries (i.e.: advice) rather than providing general regulatory 'support' (such as other accessor organisations will be doing) – and this will be set out in Terms of Use or similar documentation for clarity. Ensuring that enquiries through the Service are handled with the same process and timelines as enquiries received directly.	Agreed that this work could proceed, managing the potential COIs as proposed

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
	products are included.			
8	**UK Stem Cell Bank (UKSCB) - Proposed new distribution model for human Embryonic Stem Cell lines (hESC)** Proposal to enable the UKSCB to broaden the potential uses of the hESC lines, with a tiered pricing structure according to the intended use of the cells and the level of documentation / data accompanying the cell lines.	Provision of hESC lines for clinical / commercial use - customers could produce a material which would be submitted to the Agency for regulatory approval, then the Agency will be assessing data on the starting materials which may have been produced or advised on by UKSCB.	If part of a clinical trial, another regulator to inspect study if UKSCB is required to provide / demonstrate operational management. IE&S and Licensing to be consulted, and mitigating steps documented and presented to COI Subgroup for approval of activity prior to study agreement. Alternate Regulator to process Licencing application required if UKSCB is providing operational management VRMM / Sponsor and UKSCB to be notified if safety issues arise throughout course of study. Third party to notify UKSCB to stop distribution due to safety issues or other COIs as a result of incorporation into an IMP for clinical use.	Agreed that application to do this work could proceed, managing the potential COIs as proposed