

CONFLICTS OF INTEREST – ANNUAL COMPLIANCE REPORT 2016

PURPOSE OF THIS REPORT

1. Under the Medicine and Healthcare products Regulatory Agency's ('the Agency') conflicts of interest (COI) policy there is a requirement for an annual compliance report to be prepared by both the National Institute of Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD) and for the report to be signed off by a subgroup of the Agency's Corporate Executive Team (CET). Under the policy, the report is subsequently considered by the Agency's Risk and Audit Committee (ARAC).
2. It was agreed at the ARAC meeting on 17 June 2016 that future reports should cover the calendar year. The previous report covered up to 30 April 2016 so this report covers the period 1 May – 31 December 2016.
3. This report was agreed by the CET COI sub-group and ARAC in March 2017.

BACKGROUND

4. A policy was developed to set out the approach to handling potential COIs arising out of the merger of NIBSC with the Agency in April 2013 and the launch of CPRD as a function of the Agency in April 2012. The policy was approved by the CET and the Board in April 2013 and reviewed in 2016 to assess if it remained fit for purpose. A revised policy that better took account of financial conflicts of interest, current activities carried out by CPRD, and the role of the Chief Executive in the COI process, was agreed by the CET COI sub-group and subsequently by the CET and Board at their May 2016 meetings.

PROCESSES THAT APPLY UNDER THE POLICY

5. The key arrangements that apply under the policy are as follows:
 - Both NIBSC and CPRD operate within clearly defined parameters in accordance with their operational guidance.
 - NIBSC and CPRD consider all new areas of business from the perspective of potential COI.
 - NIBSC and CPRD ensure that in taking on any new business appropriate strategies are in place to avoid any COI.
 - NIBSC and CPRD identify cases that fall outside the operational parameters but where there may be justification on public health grounds for undertaking those activities.
 - In those exceptional cases where NIBSC and CPRD consider there may be justification in undertaking activities that fall outside the restrictions of operational arrangements, a specific escalation process applies. This involves consideration of the specific case by a sub-

group of the Agency's CET which also includes an Agency non-Executive Director.

- In those exceptional cases, where the CET sub-group considers there is justification for undertaking activities that fall outside the parameters of operational arrangements, an arrangement is in place whereby the MHRA can call upon another EU regulatory authority to provide any independent regulatory oversight that may be required.
- NIBSC and CPRD are responsible for producing regular reports on the operation of the policy including the annual report.

The escalation arrangements in the policy are as follows:

- i. Where possible, potential COIs will be managed within NIBSC and CPRD at an operational level in accordance with the criteria and principles set out in the policy. This is anticipated to address the majority of potential COI cases and this has been the case since the policy came into operation.
- ii. NIBSC and CPRD are responsible for ensuring that their activities are carried out in accordance with the requirements laid down in operational guidance.
- iii. NIBSC and CPRD are responsible for considering any activities they carry out which may create a perceived or possible financial COI. For example, this includes cases where the Agency provides a service and receives a fee for provision of the service. (iv)
- iv. NIBSC and CPRD are responsible for considering cases where there might be a public health justification for undertaking activities that fall outside the restrictions of operational guidance.
- v. In those cases where NIBSC and CPRD consider 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, they will escalate to a group comprising representatives from the CET (Directors of the regulatory divisions, NIBSC, CPRD, Operations & Finance, a representative from Legal Services along with a non-executive representative from the Agency Board and chaired by the Director of Policy Division) for decision.
- vi. In those cases where there is a significant risk of reputational damage to the Agency, or where there is a risk of perceived or possible financial COI, the CET sub-group will provide advice to the Chief Executive, who will take account of that advice in deciding an appropriate course of action. Such cases might include services provided by either NIBSC or CPRD where there is a significant financial fee charged for provision of a service and where there is a possibility that MHRA may be required to undertake a regulatory function in the future .
- vii. The Chief Executive, taking into account the advice of the CET sub-group, may decide to escalate the issue to the Chairman or another member of the Agency Board for decision. To preserve separation and clarity of roles, there will not be overlap between NEDs on the

sub-group and those on the Agency's Audit, Risk and Assurance committee (ARAC).

viii. The CET sub-group will also have the option to call upon a person independent to the Agency for independent input.

CONSIDERATION OF POTENTIAL COI CASES AND OTHER MATTERS

6. The CET sub-group met once in the reporting period (November 2016). At this meeting a review was undertaken of all cases identified during the year. The sub-group also considered two cases in correspondence in June 2016.
7. Four NIBSC cases, and no CPRD cases, were added to the tracker document (see Annex A) since the last compliance report.
8. The first case considered in correspondence was where two companies had approached NIBSC to perform neurovirulence testing (to test the capacity of the vaccine to revert to infectivity) on the seed stock of a potential clinical trial batch of developmental inactivated polio vaccine (IPV). There was no potential/actual conflict of interest as regards submitting a Clinical Trial Application (CTA) because there is no intention to hold a clinical trial in the UK. NIBSC data would not be decision-critical because it would be testing the seed stock which would subsequently be inactivated as part of the manufacturing process for the final product. The inactivated IPV would have no capacity to revert, and therefore no neurovirulence testing was required. If the companies proceeded to a Marketing Authorisation Application, NIBSC's data was likely to be included as supporting information which would be reviewed by MHRA. Therefore it was agreed that NIBSC write into the contract that should any of their data be included the company must clearly mark this in the dossier and ensure the Agency is notified in advance.
9. The second case considered in correspondence was where two new potential Polio vaccines had been selected and were being further developed with the intended eventual indication of prevention of poliomyelitis disease caused by infection with poliovirus type 2 during an outbreak. In the future there may be a clinical trial in which NIBSC's involvement would be to contribute pre-clinical data to the regulatory submission, design clinical assays to assess the success of the trial, and to train the Contract Research Organisation who would carry out the assays and analyse the data with others. NIBSC and the other consortium members would have a data oversight role to comment on unexpected findings. Submission of a Clinical Trial Application would not give rise to a conflict of interest however, should there be a polio outbreak in Europe and a decision made to vaccinate the population with stockpiled mOPV2, MHRA may review the dossier relating to NIBSC's strains and potentially containing non decision critical data (NIBSC's data will have been superseded by the time this stage is reached). It was agreed that NIBSC should request that the potential vaccine producer(s) highlight any strains or data that are included in the submission.

10. At the November 2016 sub-group meeting, NIBSC highlighted that in carrying out Next Generation Sequencing on biological medicines, NIBSC's results may be used by a manufacturer to identify species or strains of interest. In order to avoid a conflict of interest, where the material may become a biological medicine, NIBSC would carry out analysis on early stage (pre-clinical trial) materials only or provide data for the customer's in house use only, except where there is an overriding public health interest in accordance with the agency's conflicts of interest policy. It was agreed that guidelines should be added to NIBSC's Operational Guidance to make clear the early stage work that can be undertaken and that work that falls outside of these guidelines must be escalated in line with the COI Policy.
11. Also at the November 2016 meeting, NIBSC explained that they had been approached by a UK company to assess cytokine release caused by their developmental therapeutic antibody. Should a Clinical Trials Application (CTA) be made in the UK, MHRA may review NIBSC's data when making a regulatory-critical decision and the data could be relied upon. There was a high likelihood that one or more clinical trials will have first been carried out outside the UK. It was agreed that guidelines should be added to NIBSC's Operational Guidance to make it clear the early stage and/or provision of data for the customer's in-house use only work that can be undertaken and that NIBSC should include wording in its contract to carry out this work that 'should the customer include any of NIBSC's data in a CTA submission to the UK, it must give the MHRA as much advance notification as possible'. It was also agreed that 'the MHRA, at its sole discretion, will have the right to consult with other European regulators NIBSC's data arising from this work' and that the European regulator would be the German (PEI) regulator or the Irish regulator (HPRA).
12. There were no CPRD cases in the time period although the sub-group did receive an update on the DECIDE study.

ONGOING REVIEW OF THE COI POLICY

13. The policy will be kept under active review to ensure it continues to fulfil its purpose, including taking account of any new issues that may emerge in the future including innovation and life sciences related work and any complaints from stakeholders about the Agency's COI process. To date, no such complaints have been received.

COIs Considered by the COI Sub-Group May 2016 – December 2016

NIBSC

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
1	<p>Two companies have approached NIBSC to perform neurovirulence testing (to test the capacity of the virus used for vaccine production [vaccine] to revert to infectivity) on the seed stock of a potential clinical trial batch of developmental inactivated polio vaccine (IPV).</p> <p>There is no potential/actual conflict of interest as regards submitting a Clinical Trial Application because there won't be a clinical trial in the UK.</p> <p>NIBSC understands that its data would NOT be decision-critical because NIBSC will test the seed stock which will subsequently be inactivated as part of the manufacturing process for the final product. The inactivated IPV will have no capacity to revert, and therefore no neurovirulence testing is required</p>	<p>If all goes well for each polio vaccine and the companies proceed to a Marketing Authorisation Application (MAA), NIBSC's data is likely to be included as supporting information (therefore in a dossier which may be reviewed by MHRA).</p>	<p>NIBSC will write into the contract that, should any NIBSC data be included in the MAA, the company must ensure that we are notified in advance and that any NIBSC data should be clearly marked as such in the dossier.</p>	<p>Agreed with the approach.</p>
2	<p>Two new potential Polio vaccines have been selected and are now being further developed with the intended eventual indication of prevention of poliomyelitis disease caused by infection with poliovirus type 2 during an outbreak.</p>	<p>There is no potential/actual conflict of interest as regards submitting a Clinical Trial Application because there won't be a clinical trial in the UK.</p>	<p>Given that only NIBSC non decision-critical data would be involved, should a submission be made to the MHRA, NIBSC should request the potential vaccine producer(s) to highlight any NIBSC strains or data that are</p>	<p>Agreed the mitigating action and asked NIBSC to put in writing that the MHRA must be given advance</p>

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
	In the future there may be a clinical trial in which NIBSC's involvement would be to contribute pre-clinical data to the regulatory submission, design clinical assays to assess the success of the trial, and to train the CRO who will carry out the assays and analyse the data with others. NIBSC and the other consortium members will have a data oversight role to comment on unexpected findings. NIBSC will continue to be grant funded to carry out further development work.	However, should there be a polio outbreak in Europe and a decision is made to vaccinate the population with stockpiled mOPV2, MHRA may review the dossier relating to NIBSC's strains and potentially containing non decision critical data (NIBSC's data will have been superseded by the time this stage is reached).	included in the submission.	warning if NIBSC's strains or data are included in the submission.
3	In carrying out Next Generation Sequencing on biological medicines, NIBSC's results may be used by a manufacturer to identify species or strains of interest	To avoid a conflict of interest, where the material may become a biological medicine, NIBSC intends to carry out analysis on early stage (pre-clinical trial) materials only or provide data for the customer's in house use only, except where there is an overriding public health interest in accordance with the agency's conflicts of interest policy	Guidelines to be added to NIBSC's Operational Guidance to make clear the early stage work that can be undertaken and that work that falls outside of these guidelines must be escalated in line with COI Policy.	Agreed the guidelines.
4	NIBSC has been approached by a UK company to assess cytokine release caused by their developmental therapeutic antibody.	The potential actual or perceived conflict of interest is that, should a CTA be made in the UK, Licensing Division may review NIBSC's data when making a regulatory-critical decision and the data may be relied upon. In mitigation, there is a high likelihood that one or more clinical trials will have first been carried out in the US.	It was agreed that guidelines should be added to NIBSC's Operational Guidance to make it clear the early stage and/or provision of data for the customer's in house use only work that can be undertaken and for NIBSC to include in its contract to carry out this work that 'should the customer include any of NIBSC's data in a CTA submission to the UK, it must give the MHRA as much advance notification as possible. It	Agreed the mitigations and the working assumption that in this case the other European Regulator would be the German regulator.

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			was also agreed that 'the MHRA, at its sole discretion, will have the right to share with other European regulators NIBSC's data arising from this work.	

CPRD – No cases in this period

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
	N/A			