AUDIT & RISK ASSURANCE COMMITTEE (ARAC)
17th June 2016 10.30 - 12.30
151 Buckingham Palace Road
Room 410

CONFLICTS OF INTEREST – ANNUAL COMPLIANCE REPORT 2015/16

PURPOSE OF THIS REPORT

1. Under the Agency's 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 would subsequently be considered by the Agency's Risk and Audit Committee (ARAC).

2. This report has been agreed by the CET COI Sub-group.

3. **It is proposed that in future this report cover the reporting year 1 April to 31 March and be submitted to ARAC at the first available meeting following the end of that period.**

BACKGROUND

4. In 2013, a new policy was developed to set out the approach to handling potential COI arising out of the merger of NIBSC with MHRA in April 2013 and the launch of CPRD as a function of the MHRA in April 2012. The policy was approved by the CET and Agency Board (AB) in April 2013.

5. That policy was reviewed following the CET meeting in December 2015 to assess if it remained fit for purpose, and a revised policy was agreed by the CET COI subgroup and subsequently by the CET and Board at their May 2016 meetings. The updated policy takes account of:
   - Financial conflicts of interest (including issues raised in Autumn 2015 about the DECIDE study)
   - Current activities carried out by CPRD; and
   - The role of the Chief Executive in the COI process.

PROCESSES THAT APPLY UNDER THE POLICY

6. 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 subgroup of the Agency's CET which also includes an Agency non-Executive Director.
- In those exceptional cases, where the subgroup of the Agency's CET 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 revised 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) 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.
iv. 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.
v. 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 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 .

vi. The Chief Executive, taking into account the advice of the CET 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 subgroup and those on the Agency's Audit, Risk and Assurance committee (ARAC).

vii. The 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

7. The group met twice in the year (September 2015 and April 2016) and also received an update in correspondence in February 2015. At each meeting a review was undertaken of all cases that were identified during the year.

8. Two cases, one NIBSC and one CPRD, were added to the tracker document since the last compliance report – see **Annex A** for full information on both cases and the mitigating action that was agreed.

9. The first case arose after the WHO approached NIBSC to test an Oral Polio Vaccine type 2 manufactured by Sanofi Pasteur who were unable to test it themselves. There were two potential COIs that could occur: - first that NIBSC could be regarded as acting as the manufacturer's QC laboratory rather than an independent confirmatory OMCL laboratory, which could present a perceived or actual conflict of interest with its OMCL role, and second, in the unlikely event that there was a polio outbreak in Europe and a decision was made to vaccinate the population with the stockpiled vaccine, Licensing Division may review NIBSC's data when making a regulatory- critical decision, and the data may be relied upon.

10. The second case arose because CPRD was contracted to conduct a commercially funded study: "Pragmatic Randomised 104 Week Multicentre Trial to Evaluate the Comparative Effectiveness of dapagliflozin and Standard of Care in Type 2 Diabetes ('The DECIDE Study'). The Sponsor is Astra-Zeneca. A COI could occur in this case as MHRA approval for the study through the Trial Notification System was required.

11. A further potential COI case arose in February 2016 that the group was asked to consider. NIBSC referred to Devices Division a manufacturer advertising in vitro diagnostic materials which seemed to meet the definition of a medical device and yet appear not to be CE marked as such. It was noted that an MHRA investigation could lead to the company changing or removing their product leaving NIBSC with a greater market

share as a result. The group agreed that Devices Division should proceed with the investigation and their proposed mitigating action be considered depending on the outcome. The proposed mitigating action is as follows:

- To adhere to the 'Policy of handling conflicts of interest' by inform the Irish Competent Authority, Health Products Regulatory Authority (HPRA) of the background and protocol in investigating medical device cases involving compliance to the regulations.
- In the event that major / serious issues arise from the investigation, HPRA independently review the process and outcome of the investigation.
- To treat NIBSC as any other complainant in relation to confidentiality of the investigation.

The investigation is ongoing.

12. In addition to consideration of potential COI cases, in September 2015 the group considered NIBSC's review of its operational guidance and the implementation of the COI policy. This review had concluded that the policy was achieving an appropriate balance between protecting the agency's regulatory role as well as enabling NIBSC deliver its public health mission. One of the questions that had been raised under the review was whether NIBSC's policy about not accepting funding from individual manufacturers for developing assays or reference materials in furtherance if its general public health duties, outside what was agreed in the current operational guidance, was too cautious. It was agreed that the key principle that should apply to funding of NIBSC's core activities was one of non-exclusivity. A second question was raised around use of NIBSC's data in patent applications. It was agreed that in cases where NIBSC had contributed to an invention with another organisation, the proposed approach was not to ascribe patent data to NIBSC, however publication of the work was encouraged. A log of patents (to which NIBSC had contributed) was agreed in the interests of transparency and to ensure that there is oversight should a regulatory submission materialise in the future.

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.

Annex A

COIs Considered by the COI Sub-Group June 2015 – May 2016

NIBSC

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
1	NIBSC was approached by the WHO to test an Oral Polio Vaccine type 2 (OPV2) bulk manufactured by Sanofi Pasteur (SP) as SP are unable to test it themselves. This batch is intended as a monovalent OPV2 (mOPV2) bulk to help secure a global stockpile of mOPV2 to be used in the event of a polio outbreak after the globally synchronised withdrawal of OPV2 from routine immunisation.	NIBSC could be regarded as acting as the manufacturer's QC laboratory rather than an independent confirmatory OMCL laboratory, which could present a perceived or actual conflict of interest with its OMCL role. Second, in the unlikely event that there is a polio outbreak in Europe and a decision is made to vaccinate the population with stockpiled mOPV, MHRA colleagues (Licensing Division) may review NIBSC's data when making a regulatory- critical decision, and the data may be relied upon.	**NIBSC's OMCL role:** • All information shared by SP with NIBSC, and all NIBSC's results, to be shared with the WHO. • Normal OMCL process for batch release of polio vaccine testing to be followed, as far as possible. • To mitigate against the potential liability to NIBSC should the mOPV2 vaccine we test cause harm, SP to closely monitor and sign off each step of initial batch testing (normally carried out at their facility), to provide evidence that they take full responsibility for the results. SP also to be fully responsible for interpreting the results. The process for sign off by SP of NIBSC's batch testing to be set out in a technical agreement. • Batch testing to be carried out under a legal agreement which will mitigate NIBSC's liabilities as far as possible, except in the case of NIBSC's wilful misconduct or gross negligence. SP contractually obliged to pay for the work, regardless of whether the bulk passes or	Agreed to the work subject to the mitigating action being put in place. Should a regulator need to be called upon, this should be the German regulator.

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
			fails or needs re-testing. **MHRA's regulatory role.** If a regulatory submission is submitted that will require review of NIBSC's data by MHRA colleagues, it is proposed that the MHRA: • submits the application for review to the Commission on Human Medicines • seeks the opinion of another regulator on part of the submission that includes NIBSC's data. Should this situation arise, it is suggested that the MHRA could request the opinion of the RIVM in the first instance. • To enable NIBSC seek the opinion of other European regulators, NIBSC to include in its contract to carry out this work: • Should the customer include any of NIBSC's data in a MAA, it must give the MHRA as much advance notification as possible, and the submission must identify which data is from NIBSC. • The MHRA, at its sole discretion, will have the right to share with other European regulators NIBSC's data arising from this work.	

CPRD

#	Issue	Potential COI	Proposed mitigating action	CET COI subgroup decision (including any required mitigating action)
1	CPRD was contracted to conduct a commercially funded study: “Pragmatic Randomised 104 Week Multicentre Trial to Evaluate the Comparative Effectiveness of dapagliflozin and Standard of Care in Type 2 Diabetes. The DECIDE Study. The Sponsor is Astra-Zeneca. This study is considered Low Risk and is based upon a single intervention namely randomisation at point of care to second line treatments for T2DM either Standard of Care or Dapagliflozin (an AZ developed and marketed medication). The First Patient In target date is June 2016.	MHRA approval for the study through the Trial Notification System was required.	(1) Submission was made by Quintiles on behalf of the sponsor; (2) The trial met Low Risk criteria; (3) MHRA submitted the trial decision for review by the Irish regulatory body (who do not have the trial notification procedure) who concurred with the MHRA decision; (4) this approach has been included in new policy as the future approach.	N/A