Review of Coronary Artery Stents (Guidance No. 71)

Response to Appraisal Consultation Document.

Cordis, Johnson & Johnson

Executive Summary

- The Evaluation Report and ACD do not take all relevant evidence into account with respect to DES price, absolute risk of repeat revascularisation, the risk reduction associated with DES and diabetes as in independent predictor of repeat revascularisation.

- Cordis believe that the price premium of £600 stated in the ACD is too high and its origin should be clarified. This appraisal has also failed to appreciate the price dynamics in the medical device market that NICE does not face when dealing with many pharmaceuticals.

- The absolute risk of revascularisation with BMS is understated at 11% for an unselected population. The true rate, based on the Scottish registry requested by the Appraisal Committee, is 12.9% in elective patients and 16.6% in those with acute coronary syndromes.

- The risk reduction used in the economic model is inconsistent with trial data. The trial-based risk reductions of 70% should be used.

- Diabetes is not off label for Cordis's Cypher stent and diabetes should, consistent with the literature, be considered as an independent risk factor for repeat revascularisation.

- New data show that

    - 70%, not 55% is the appropriate risk reduction.
    - The assumption of a common risk reduction across all DES is not valid.
    - There is a differential MI benefit, that is not fully captured in the current model due to an inappropriate time frame.

- Patients with acute coronary syndromes (ACS) should be investigated as a population in which DES would be cost effective. Using the trial-based risk reduction of 70%, ICERs range from £19,878 to DES being dominant in different risk-factor groups within the ACS population.

- The Decision Support Unit should be asked to ensure that all relevant and up-to-date information is taken into account and the economic model is updated accordingly.

1. Introduction

1.1. On 1 August 2007, the Institute issued an Appraisal Consultation Document on the use of coronary artery stents in ischaemic heart disease. In section 1.1 of the ACD, NICE indicated that drug-eluting stents are not recommended for use in percutaneous coronary intervention in patients with coronary artery disease. Cordis has a number of objections to the ACD, its recommendations, the Evaluation Report and the process upon which it is based.

1.2. On numerous occasions, Cordis and other consultees have raised concerns about what they believe to be a clear and significant conflict of interest within the Assessment Group. In a paper published shortly before this Technology Appraisal, members of the Assessment Group published an economic assessment of DES (Bagust et al 2005). It has become increasingly clear that this publication has influenced its methods, assumptions and the manner in which it has selected clinical effectiveness data. These have often been inconsistent with the Institute's policies and procedures as set out in the Institute's Guide to the Technology Appraisal Process and Guide to the Methods of Technology Appraisal. The Institute has therefore prepared an ACD that is perverse in the light of the evidence submitted.

1.3. Our detailed responses to the ACD are set out under five categories:

- Has all the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?
- Are the provisional recommendations sound and do they constitute a suitable basis for the preparation of guidance to the NHS?
- Are there any equality-related issues that may need special consideration?
- Major new meta-analyses published and in press.

2. Has all the relevant evidence been taken into account?

2.1. ***In short, not all of the relevant evidence has been taken into account.***

2.2. The numerous submissions in the Evaluation Report show that consultees have repeatedly demonstrated that LRiG have consistently failed to present all the available evidence pertaining to:

- The DES price
- The absolute risk of repeat revascularisation with BMS
- The risk reduction associated with DES
- The risk factors for repeat revascularisation

2.3. DES Price

2.3.1. ***Cordis believe that the price premium of £600 stated in the ACD is too high and its origin should be clarified. This appraisal has also failed to appreciate the price dynamics in the medical device market that NICE does not face when dealing with many pharmaceuticals.***

2.3.2. This factor has clearly had a profound impact on the draft guidance, the implication of which is to potentially completely remove from the NHS, DES technology that has been in use for five years. It is unclear why £600 has been chosen as a DES price premium given that DES prices have fallen sharply over recent times, but we note that the original Assessment Report identified a premium of approximately £600. LRiG's market price survey is cited as May/June 2005 and is clearly out of date and irrelevant to guidance that will apply from 2008 onwards. It would be

perverse for an inaccurate DES price to be used, particularly as experts have already given evidence that much lower prices are already available in the market.

2.3.3. The reference to national procurement of DES in section 4.3.13 of the ACD is surely misplaced, as the Institute would be exceeding its powers if such a statement were perceived to be advising a procurement policy.

2.3.4. The price issue is not straight forward, and raises a number of points unique to devices that the Institute does not often face with pharmaceuticals. Pharmaceutical prices tend to be reasonably constant over time during the period a drug has patent protection, and decrease only when generic competition is possible. Devices, on the other hand, do not benefit from long periods of market exclusivity. It is easier for a competitor to develop an alternative device to do the same job than it is for a drug company to find a new compound, and once the idea is in the public domain, the time to market is relatively short, compared with drugs. This results in much earlier competition, a shorter product life cycle, and greater market price competition. Average selling prices therefore fall more quickly than with drugs. This Review over-simplifies the market conditions for stents and a wider understanding of the market conditions is required.

2.3.5. When BMS were the novel technology, introduced in the mid-1990s, the list price was of the first BMS to market (produced by Johnson & Johnson) was approximately £1,500. The first DES (Cypher, Johnson & Johnson) was introduced in 2002 again with a list price of £1,500, in real terms lower than the original BMS list price. In 1998-99, the mean market price for BMS in five UK hospitals was £582 (range £750 to £500) (Sculpher et al, 2002). At the time of the first stent HTA in 2000 (TA number 4), Meads et al (2000) reported list prices for BMS ranging from £650 to £1,440 and average selling price appeared to be around £500. The stent review in 2002 (TA no. 71) reported a cost for BMS of £341 whilst Jenkins et al (2002) reported a cost of £380 in the same year, giving an average of £361. The current Assessment Report gave a market average of £278. Thus, market prices of BMS always fall within a wide range, but overall, have fallen dramatically over time. The reality of the situation today is that the NHS is now procuring DES, and where necessary Clopidogrel, for less than the cost of DES alone when the original guidance was produced in 2003.

2.3.6. This fall in BMS prices has taken place at the same time as, and as a result of, falling DES prices. The Institute's methods must take account of these dynamics because the ICER as a binary decision-making tool becomes unreliable in this situation, despite the fact that the effectiveness of DES, as stated in the ACD, has not diminished. If device price dynamics were not taken into account, there would potentially be regression to the least expensive therapy even if it had already been rendered clinically obsolete in many patients.

2.3.7. NICE needs to recognise that the market place for medical devices is different from pharmaceuticals, where patent protection does give market exclusivity and something closer to a monopoly supplier. To provide meaningful guidance to the NHS relating to medical devices NICE needs to recognise the difference between drug and device markets.

2.3.8. NICE may find an acceptable solution to be use of average selling prices, as was the case in the first DES appraisal in 2003, or to use list prices as per its own Guide to the Methods of Technology Appraisal "*Where the actual price paid for a resource may differ from the public list price (for example pharmaceuticals, medical devices), the public list price should be used*" (NICE 2004, section 5.6.1.1). We recognise the desire from the NICE to quote a price that all NHS hospitals can procure at, but NICE should also recognise that not all providers purchase BMS at the same price now. Furthermore, it would be inequitable to use list prices as a source of upper DES price certainty whilst at the same time using market prices for BMS.

[redacted]

2.4. The Absolute Risk of Repeat Revascularisation with BMS

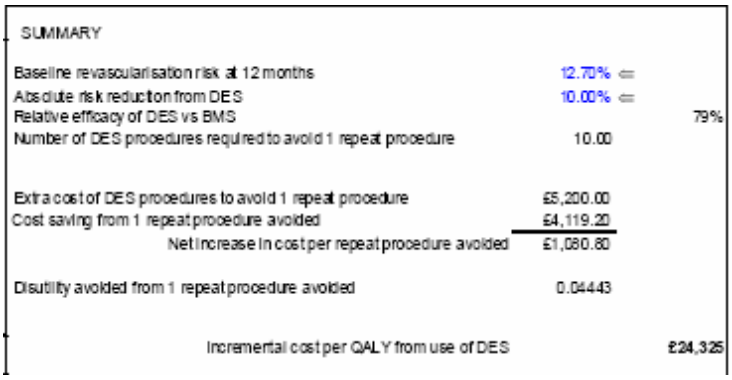
2.4.1. ***The absolute risk is understated at 11% for an unselected population. The true rates, based on the Scottish registry and requested by the Appraisal Committee, are 12.9% in elective patients and 16.6% in those with acute coronary syndromes.***

2.4.2. The ACD states that the absolute risk of repeat revascularisation with BMS have been chosen to be 11% for all patients, based on 10% for elective patients and 13% for non-elective patients. It is not clear how these rates have been determined because the submission to NICE by NHS QIS (dated 13th January 2006) states:

"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."

2.4.3. As the Appraisal Committee requested that the Scottish data be used to inform the base case scenario in the economic model (specification of additional work, February 2006), we would have expected this to be implemented. This is clearly a case where relevant evidence was identified by the Appraisal Committee, but is has not been taken into account in the economic model. It is perverse to specify use of a data input and then later ignore it.

2.4.4. It is also of note that the 2003 Appraisal employed a BMS revascularisation rate of 12.7% (LRiG 2003 Addendum B, page 35), but this evidence appears to have been omitted from this Review. As there is no evidence that BMS repeat revascularisation rates have fallen since 2003, how can a reduction in the base case rate in the model be justified in this review? A copy of the relevant section of the 2003 model is reproduced in Figure 1:



SUMMARY

Baseline revascularisation risk at 12 months	12.70% ⇐	
Absolute risk reduction from DES	10.00% ⇐	
Relative efficacy of DES vs BMS		79%
Number of DES procedures required to avoid 1 repeat procedure	10.00	
Extra cost of DES procedures to avoid 1 repeat procedure	£5,200.00	
Cost saving from 1 repeat procedure avoided	£4,119.20	
Net increase in cost per repeat procedure avoided	£1,080.80	
Disutility avoided from 1 repeat procedure avoided	0.04443	
Incremental cost per QALY from use of DES		£24,325

Figure 1. Baseline risk and absolute risk reduction used in the 2003 Appraisal of DES.

2.5. The Risk Reduction Associated with DES

2.5.1. ***The risk reduction used in the economic model is inconsistent with trial data. The trial-based risk reduction of 70% should be used.***

2.5.2. We welcome the fact that the Appraisal Committee have recognised that a 41% reduction in repeat revascularisation risk under-estimates the effectiveness of DES, but the use of 55% risk reduction is still an under-estimate of the true treatment effect shown by the randomised trials. The use of a trial-based effect is recommended by NICE's own Guide to the Methods of Technology Appraisal, which states *".....RCTs are therefore ranked first in the hierarchy of evidence for measures of relative treatment effect."* It would be procedurally unsound and produce a perverse outcome for NICE to fail to follow its own methods guide.

2.5.3. The model should be re-run using a 70% risk reduction, as shown in Section 6 (a value that confirms the trial-based treatment effects used in Cordis's original submission).

2.5.4. It is also notable that the 2003 Appraisal used 79% DES risk reduction (Figure 1), so it is unclear why the current economic model employs a risk reduction of 55%, given that the Appraisal Committee have recognised that the clinical benefit of DES has been sustained.

2.5.5. Whilst the Assessment Group has continued to assert that the protocol-mandated angiogram in some of the randomised trials increases the DES treatment effect, there is no evidence for this. Schömig et al (2007) investigated this very question and concluded:

> *"10 of the 16 trials included in this meta-analysis had a* ***protocol-mandated follow-up angiography****. This may exaggerate the risk of the occulo-stenotic reflex and lead to an increase in the number of reinterventions, although* ***no significant interaction could be found between this study design feature and treatment effect****. In addition, the fact that the difference in the risk of reintervention between the 2 DES types persisted even beyond the scheduled time for follow-up angiography (6 to 9 months)* ***does not support a***

significant impact of protocol-mandated follow-up angiography on the treatment effect *in favour of the SES observed in this meta-analysis.*

Thus, there is no need to dilute the trial-based risk reductions due to concerns over the impact of the trail angiogram.

2.6. **Risk Factors for Repeat Revascularisation**

2.6.1. ***Diabetes is not off label for Cordis's Cypher stent and diabetes should, consistent with the literature, be considered as an independent risk factor for repeat revascularisation.***

2.6.2. We recognise that the Appraisal Committee has accepted long lesions and small vessels as risk factors for repeat revascularisation.

2.6.3. The ACD suggests in section 4.3.4 that there is still some doubt over diabetes as an independent risk factor for repeat revascularisation. This conclusion is perverse in the light of evidence submitted. Cordis's response to the Assessment Report Addendum presented seven studies not cited by LRiG, five of which identified diabetes as an independent predictor, along with two others previously identified. Of the 14 literature sources identified, diabetes was the second most commonly occurring independent risk factor (in 7 out of 14 datasets). It is remarkable that this evidence from the entire literature has not prompted a clear statement that diabetes is an independent predictor of repeat revascularisation.

2.6.4. In the latest cost effectiveness analysis (Addendum 6') LRiG have used an unusually low relative risk (RR) for diabetes (1.19). This results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients (Addendum 4'). It is notable that the British Cardiovascular Intervention Society (BCIS) have adopted a more reasonable approach in their response to Addenda 3" and 4', in deriving relative risks from the wider literature. BCIS identify a RR of 1.52 for diabetes (range 1.34 to 1.81) and LRiG should have noticed that in comparison, the CTC dataset has produced an apparently spurious result that is driven by the peculiar RR of 0.90 for non-elective patients. It is most odd to quote a RR of <1 for a risk factor that has been shown to increase the relative risk and is perverse in the light of the other evidence submitted. This is a clear example of LRiG failing to take all the relevant evidence into account and it would be more reliable to run the economic used to produce Addendum 6' (that informed the ACD) using the BCIS mean relative risk of 1.52. LRiG's relative risks for the individual risk factors of small vessels and long lesions are within the ranges in the wider literature and on that basis, although somewhat low for long lesions, seem reasonable.

3. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?**

3.1. ***The summaries of clinical and cost effectiveness are not reasonable on the following grounds:***

3.1.1. The source of the DES price information is unclear, but appears to be 2 years out of date. It is therefore an unreasonable interpretation of the resource impact for the NHS.

3.1.2. The absolute risk of repeat revascularisation has been unreasonably reduced compared with the rates submitted from the Scottish registry and that used in the original DES appraisal.

3.1.3. The risk reduction associated with DES has been unreasonably reduced compared with the rates from the randomised trials.

3.1.4. Removal of DES from the NHS will have an undoubted effect on NHS service provision in that some patients who may currently be treated by PCI with DES will in future need to be referred to CABG because the restenosis risk with BMS will simply be too great. The potential impact can be estimated as follows:

3.1.4.1. 58,576 PCIs in England and Wales in 2005 (Ludman 2006) models to 67,809 PCIs in 2008, assuming a conservative growth of 5% per year. If 20% of these patients are referred back to CABG, surgical capacity has to increase by 13,562 procedures from a standing start in 2008. Bearing in mind that there were 22,724 CABG procedures in 2005 and CABG has not shown growth, this equates to a potential demand for a 40% increase in CABG.

3.1.4.2. In addition, the CABG reference cost, at weighted average of £8,198, is 2.54 times than PCI with DES at £3,231. This cost differential means that the NHS will have to pay an extra £67.4 million to achieve the same number of revascularisation procedures. In addition, the NHS will also have to fund an additional 4,231 repeat revascularisation procedures (based on the current LRiG model) at a cost of £16.2 million. Thus, the gross cost would be approximately £83.5 million.

3.1.4.3. Assuming current DES usage of 60% and an incremental cost of £870 per DES procedure (LRiG model), the cost avoided if this draft guidance becomes final would be £28.3 million. The net cost to the NHS is therefore likely to be £55.2 million in 2008 alone. The ACD does not take these costs and service implications into account and this estimate takes a conservative view of the potential shift back to surgery.

4. **<u>Are there any equality-related issues that may need special consideration</u>**

4.1. Diabetic patients are not 'off label' for the Cypher stent in Europe. Diabetes is not a contra-indication on the Instructions for Use. [redacted] Section 4.1.24 of the ACD should be removed as it constitutes unfounded inequality towards diabetic patients on the basis and the Institute is exceeding its powers in pronouncing diabetics to be off label. We believe diabetic patients should be mentioned as a specific high-risk group who should benefit from DES.

5. Recommended Solutions

5.1. The economic model should be updated to addresses all the concerns identified above. At a minimum, it must incorporate and address:

5.1.1. An accurate absolute risk of repeat revascularisation from the Scottish registry. The NHS QIS submission dated 13th January 2006 (in the Evaluation Report) shows this to be 12.9% (elective) and 16.6% (ACS patients) for unselected populations without protocol-mandated angiographic follow up.

5.1.2. A literature-based relative risk of 1.52 for diabetes. LRiG's relative risk of 0.90 for non-elective patients is clearly unrepresentative and makes their relative risk for all diabetics unrealistically low (outside the range seen in the wider literature quoted by BCIS).

5.1.3. A repeat revascularisation risk reduction of 70%, based on the randomised trials – see Section 6.

5.1.4. An extended time horizon as the current 1-year time does not capture the full benefit of the Cypher stent, particularly in the light of the new data on MI benefit shown in Section 6. The Institute's Guide to the Methods of Technology Appraisal requires the selection of a time horizon "sufficient to reflect important cost and benefit differences between the technologies being compared" (section 5.2.1.1), thus the time horizon should be extended to capture the full impact of the MI benefit.

5.1.5. Acute coronary syndromes (ACS) as a patient sub-group. Whilst clinical experts have advised that 'elective' and 'non-elective' are not appropriate term to distinguish between patient groups, patients with ACS are a recognised sub-group and this is alluded to in section 4.3.5 of the ACD. This is also recognised in the Institute's recent announcement of the development of a clinical guideline for patients with ACS. The Appraisal Committee should be mindful that DES would be cost effective in at least some ACS patients because there is no additional Clopidogrel cost. The Appraisal Committee should also note that the repeat revascularisation rate in an unselected population is 16.6% at 1 year according to the NHS QIS submission. Non-elective costs, resource use and relative risks are most appropriate for this group of patients, as they tend to present as non-elective PCI. This issue deserves some exploration, but correct and representative data should be used as model inputs, as outlined by consultees throughout this process.

5.2. Table 1 shows the impact of substituting a trial-based risk reduction of 70%, relative risk of 1.52 for diabetes and DES price premium of £390 into a reproduction of LRiG's model for ACS patients. Even using the £600 price premium, with which we profoundly disagree, most of the risk factor groups are cost effective for ACS patients.

Risk Factors	ICER
No risk factors	£33,140
Long lesions	£19,878
Diabetes	7,166
Small vessels	DES dominant
Long lesions + diabetes	£32,640*
Long lesions + small vessels	DES dominant
Small vessels + diabetes	DES dominant
Long lesions + small vessels + diabetes	DES dominant
Overall	£30,790

Table 1. ICERs by risk factor for patients with acute coronary syndromes. *ICERs calculated using a reconstruction of the LRiG model but with risk reduction of 70%, literature based relative risk of 1.52 for diabetes and DES premium of £390. * = unreliable result due to use of LRiG relative risk for patients with combined risk factors of long lesions and diabetes, where LRiG's diabetes risk is spurious.*

5.3. The Evaluation Report shows that consultees have repeatedly demonstrated LRiG 's failure to present the Appraisal Committee with all the relevant evidence on many occasions. These failures may well be due to the LRiG's unwillingness to contradict their pre-formed opinion on the cost effectiveness of DES, published prior to the deadline for submissions by consultees. Given the clear and documented problems that this has created throughout, we call for this Review to be referred to the **Decision Support Unit** to ensure that all relevant and up-to-date information is taken into account.

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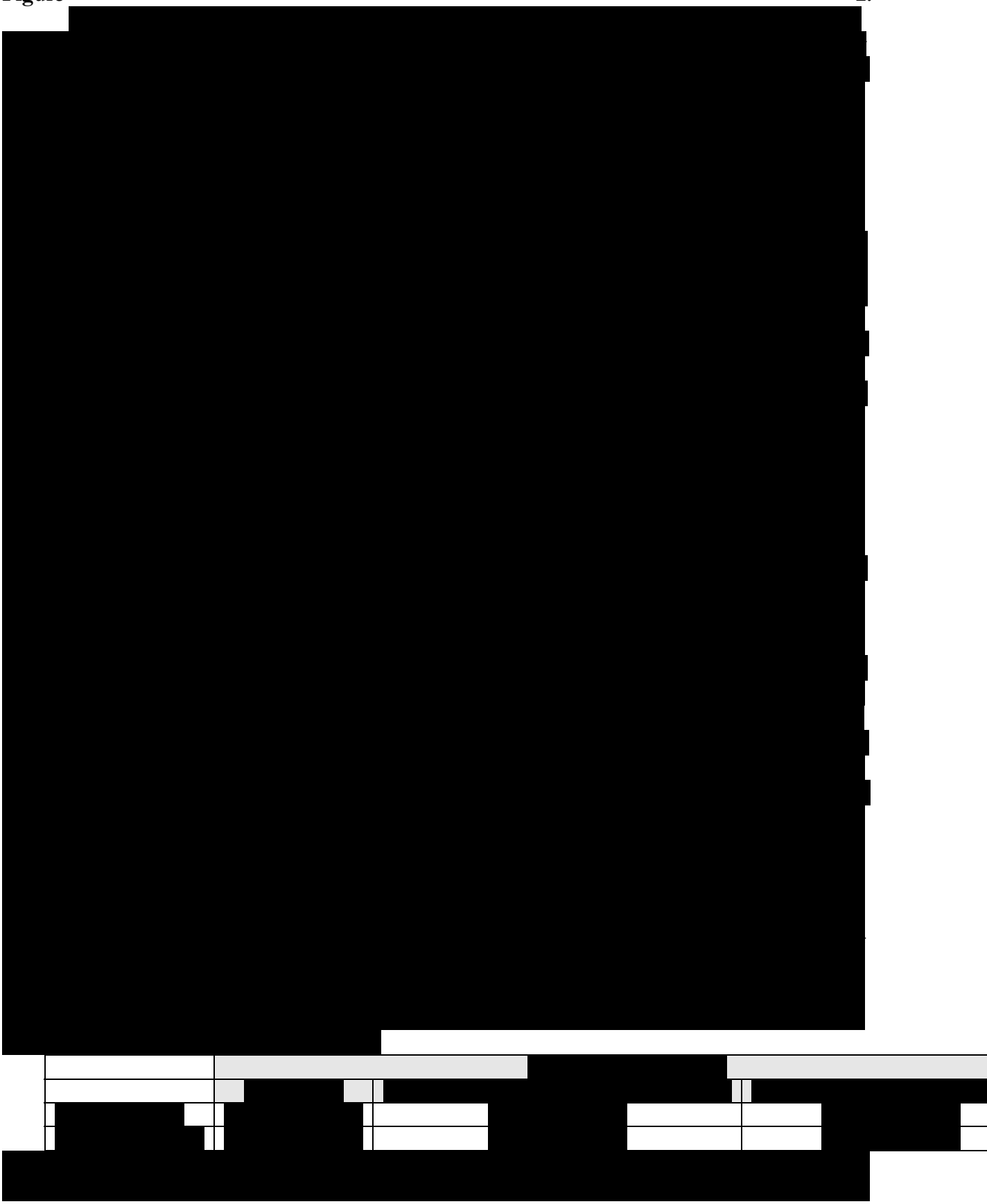
Figure 2.



[redacted]

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