**SUPPLEMENTAL DOCUMENT SD-7**
**FOR PART IIIB - Methods of Analysis/Analytical Scheme for Identification of Drugs or Chemicals**

## Construction of an Analytical Scheme

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**Purpose**
The purpose of this supplemental document is to provide guidance on the construction of appropriate analytical schemes as required by SWGDRUG Recommendations Part IIIB.

**Definition**
An ***analytical scheme*** is a combination of selected techniques used to reach a scientifically supported conclusion.

**Introduction**
The following minimum requirements are necessary for a scientifically supported conclusion:

- If a Category A technique is used, then at least one other technique from either Category A, B or C is required;
- If a Category A technique is not used, then at least three separate techniques are required, two of which must be from Category B to achieve a sufficiently high degree of selectivity.
- The chosen techniques must achieve the appropriate level of selectivity for their respective categories (see Figure 1)

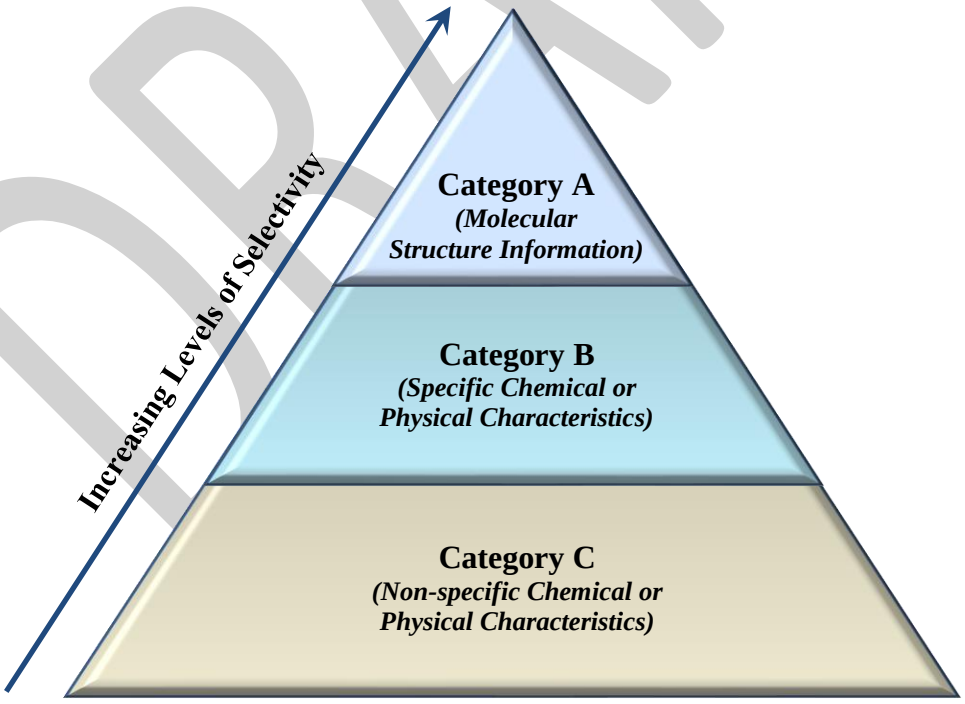


Figure 1 – Levels of Selectivity

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A hyphenated technique (e.g. gas chromatography-mass spectrometry, liquid chromatography-ultraviolet/visible spectroscopy) may be considered as two separate techniques within the analytical scheme provided the criteria for positive results are fulfilled for both techniques. When using a hyphenated technique, the analyst is not precluded from using only one of the two results produced. When only two tests are performed and the results originate from the use of a hyphenated technique, quality practices such as those described in PART IIIB.5.2 are required.

Where any selected technique does not achieve the intended level of selectivity, then the analytical scheme may require additional techniques in order to provide a scientifically supported conclusion.

*Note: Throughout the following examples, it is assumed that the laboratory is utilizing validated methods and employing quality practices to ensure the results correspond to the sample tested. Examples of these practices include:*

- *removing two aliquots from the sample and testing them independently;*
- *employing sample identification procedures such as bar-coding and witness checks;*
- *using good laboratory practices (e.g., positive and negative controls, one sample opened at a time, procedural blanks).*

**Examples of Selected Schemes**

**Question #1: Does the sample contain heroin?**
**Selected Scheme #1: GC-MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | GC | Retention time ($t_R$) of analyte peak is consistent with heroin reference material | Consistent with heroin | B |
| A | MS (EI) | Spectrum of analyte is consistent with heroin reference material | Heroin | A |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. The scheme of GC (Category B) and MS (Category A) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains heroin.

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**Question #2: Does the sample contain ephedrine or pseudoephedrine?**
**Scheme Selected #2: GC-MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | GC | $t_R$ of analyte peak is consistent with pseudoephedrine reference material | Consistent with ephedrine, pseudoephedrine, or a mixture of both | B |
| A | MS (EI) | Spectrum of analyte is consistent with pseudoephedrine reference material | Ephedrine, pseudoephedrine, or a mixture of both | A |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. Even though the scheme does not allow the discrimination between ephedrine and pseudoephedrine, the data from GC (Category B) and MS (Category A) provide a scientifically supported conclusion to the question asked and, therefore, the scheme is fit for purpose.

**Conclusion:** The sample contains ephedrine/pseudoephedrine.

**Question #3: Does the sample contain ephedrine?**
*Note the difference from Question 2 above: now, ephedrine specifically has to be identified, rather than identification of ephedrine/pseudoephedrine.*

**Scheme Selected #3: GC-MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | GC | $t_R$ of analyte peak is consistent with ephedrine reference material and indistinguishable from pseudoephedrine reference material | Consistent with ephedrine, pseudoephedrine, or a mixture of both | B, selectivity for stereoisomer not achieved |
| A | MS (EI) | Spectrum of analyte is consistent with ephedrine reference material. Structural information is provided, but it is indistinguishable from pseudoephedrine reference material | Ephedrine, pseudoephedrine, or a mixture of both | A, selectivity for stereoisomer not achieved |
| B | LC | $t_R$ of analyte peak is consistent with ephedrine reference material and distinguishable from | Consistent with ephedrine | B |

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|---|---|---|---|---|
| | | pseudoephedrine reference material | | |

**Assessment:** The selected scheme of GC-MS (Category B + Category A) was sufficient to identify ephedrine/pseudoephedrine, but did not specifically identify ephedrine as required. Although the mass spectrum provided structural information, the information was insufficient to differentiate between stereoisomers. Another test (LC - Category B) was necessary to obtain the selectivity to differentiate the two compounds in question.

The enhanced scheme provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains ephedrine.

**Question #4: Does the crystalline sample contain methamphetamine?**

**Scheme Selected #4: ATR-FTIR (Category A) + Color test (Category C)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| A | ATR-FTIR | Spectrum consistent with methamphetamine HCl reference material | Methamphetamine HCl | A |
| C | Color Test | Positive color change consistent with methamphetamine HCl reference material | Indicates methamphetamine or related compounds | C |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. The scheme of ATR-FTIR (Category A) and color test (Category C) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose. In addition, the ATR-FTIR provided salt form information, which was not part of the question.

**Conclusion:** The sample contains methamphetamine.

**Question #5: Does the powder sample contain methamphetamine?**

**Scheme Selected #5: ATR-FTIR (Category A) + Color test (Category C)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| A | ATR-FTIR | Mixed spectrum with few significant peaks attributable to methamphetamine | Inconclusive | Did not achieve the required level of selectivity/structural information |

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|---|---|---|---|---|
| C | Color Test | Positive color change consistent with methamphetamine HCl reference material | Indicates methamphetamine or related compounds | C |
| B | GC | $t_R$ of analyte peak is consistent with methamphetamine HCl reference material | Consistent with methamphetamine | B |
| A | MS (EI) | Spectrum of analyte is consistent with methamphetamine HCl reference material | Methamphetamine | A |

**Assessment:** The selected scheme of the ATR-FTIR (Category A) and Color Test (Category C) was insufficient to identify methamphetamine, but did provide information on the class of compounds (an amphetamine). The ATR-FTIR did not provide suitable structural information, so another test (MS - Category A) was chosen. In addition, the hyphenated GC-MS test provided retention time information to further support the conclusion.

The enhanced scheme provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains methamphetamine.

**Question #6: Does the powder sample contain cocaine?**

**Scheme Selected #6: High-resolution Raman (Category A) + Color test (Category C)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| A | High-resolution Raman spectroscopy | Spectrum consistent with cocaine HCl reference material | Cocaine HCl | A |
| C | Color test | Positive color change consistent with cocaine HCl reference material | Indicates cocaine or other related compounds | C |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other**.** The scheme of high-resolution Raman spectroscopy (Category A) and color test (Category C) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose. In addition,

the high-resolution Raman spectroscopy provided salt form information, which was not part of the question.

**Conclusion:** The sample contains cocaine.

### Question #6A: Can I use a handheld Raman as a Category A test in Question 6?

**Answer:** Yes, but the handheld Raman would have to be assessed and validated for this purpose to ensure that the resolution and spectral range provide sufficient structural information to achieve the selectivity requirement of a Category A technique. In addition, Category A techniques are required to have reviewable data.

### Question #7: Does the sample contain methcathinone?

### Scheme Selected #7A: Time-of-flight mass spectrometry with Direct Analysis in Real Time ionization (DART-TOFMS) (Category A) + GC-FID (Category B)

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| A | MS (DART-TOFMS) | $[M+H]^+$ ion (no fragmentation) consistent with methcathinone reference material | Consistent with methcathinone | Does not achieve the required level of selectivity/structural information |
| B | GC-FID | $t_R$ of analyte peak is consistent with methcathinone reference material | Consistent with methcathinone | B |
| A | GC-MS (EI) | Spectrum of analyte is consistent with methcathinone reference material | Methcathinone | A |

**Assessment:** The selected scheme of MS (DART-TOFMS) (Category A) and GC-FID (Category B) was insufficient to identify methcathinone. The GC-FID provided retention time information, but the DART-TOFMS did not provide fragmentation (structural information). The MS (DART-TOFMS) test only provides the selectivity of a Category B technique (based on separation by mass) and further testing with either Category A, B or C is required. In this example, a Category A (GC-MS (EI)) technique was chosen. The retention time from the hyphenated GC-MS test was not used.

The enhanced scheme provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains methcathinone

**Question #7A: Would a DART-MS/MS have the same limitations as the DART-TOFMS in Question 7?**

**Answer:** No. DART-MS/MS has the potential for increased selectivity by allowing for a selected precursor ion to be isolated and then individually fragmented, providing structural information for the analyte. The DART-MS/MS would have to be assessed and validated for this purpose to ensure that the fragmentation provides sufficient structural information to achieve the selectivity requirement of a Category A technique. DART-MS/MS differs from DART-TOFMS with in-source fragmentation. In DART-TOFMS with in-source fragmentation, the precursor ion cannot be selected in advance and the resulting fragmentation spectrum is a mixture of fragments of simultaneously generated precursor and fragment ions.

**Scheme Selected #7B: GC-FTIR (Category B + Category A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | GC | $t_R$ of analyte peak is consistent with methcathinone reference material | Consistent with methcathinone | B |
| A | FTIR | Spectrum consistent with methcathinone reference material | Methcathinone | A |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other**.** The scheme of GC (Category B) and FTIR (Category A) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains methcathinone.

**Question #8: Does the pharmaceutical preparation contain a controlled substance?**

**Scheme Selected #8A: Pharmaceutical identifier (Category C) + GC-FID (Category B) + TLC (Category B)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| C | Pharmaceutical identifier | Appearance consistent with a pharmaceutical-grade amphetamine sulfate tablet | Indicates amphetamine sulfate tablet | C |
| B | GC-FID | $t_R$ of analyte peak is consistent with amphetamine reference material | Consistent with amphetamine | B |

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| | | | | |
|---|---|---|---|---|
| B | TLC | $R_f$ of analyte is consistent with amphetamine reference material | Consistent with amphetamine | B |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. The scheme of pharmaceutical identifiers (Category C), GC-FID (Category B), and TLC (Category B) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains a controlled substance identified as amphetamine.

**Scheme Selected #8B: Pharmaceutical identifier (Category C) + GC-MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| C | Pharmaceutical identifier | Not consistent with any known pharmaceutical product | Inconclusive | - |
| B | GC | $t_R$ of analyte peak is consistent with fentanyl reference material | Consistent with fentanyl | B |
| A | MS (EI) | Spectrum of analyte is too weak to provide sufficient information | Inconclusive | Did not achieve the required level of selectivity/structural information |
| A | MS (EI) Concentrate sample | Spectrum of analyte is consistent with fentanyl reference material | Fentanyl | A |

**Assessment:** The selected scheme of pharmaceutical identifier (Category C), GC-MS (Category B + A) was insufficient to identify fentanyl. The pharmaceutical identifier proved inconclusive, the mass spectrum did not provide sufficient sensitivity to obtain structural information, but the GC provided retention time information. The MS test was repeated after resampling and concentrating the sample.

The enhanced scheme provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains fentanyl.

**Scheme Selected #8C: Pharmaceutical identifier (Category C) + LC–UV/Vis Diode Array Detector (DAD) (Category B + B)**

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| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| C | Pharmaceutical identifier | Appearance consistent with a pharmaceutical-grade oxycodone tablet | Indicates oxycodone | C |
| B | LC | $t_R$ of analyte peak is consistent with oxycodone reference material | Consistent with oxycodone | B |
| B | UV/Vis (DAD) | Spectrum consistent with oxycodone reference material | Consistent with oxycodone | B |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. The scheme of pharmaceutical identifier (Category C), LC (Category B), and ultraviolet/visible spectroscopy (full spectrum) (Category B) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains oxycodone.

**Question #9: Does the sample contain cannabis?**

**Scheme Selected #9: Macroscopic examination (Category B) + Microscopic examination (Category B) + Color test (Category C).** *Note that the laboratory does not have access to a trained botanist, so the identification will be conducted by a drug chemist.*

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | Macroscopic examination | Characteristic morphological features of cannabis observed | Consistent with cannabis | B |
| B | Microscopic examination | Characteristic microscopic features of cannabis observed | Consistent with cannabis | B |
| C | Color test | Positive color change consistent with cannabinoids (e.g., THC, CBD,CBN) | Indicates cannabinoids | C |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other. The scheme of macroscopic examination (Category B), microscopic examination (Category B), and color test (Category C) provides a scientifically supported conclusion to the question asked and is, therefore, fit for purpose.

**Conclusion:** The sample contains cannabis.

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**Question #9A: Would all of the tests in the selected scheme for Question 9 be necessary if the analysis was performed by a trained botanist?**

**Answer:** No. If the analysis was performed by a trained botanist, analysis of the morphological characteristics of cannabis following an established botanical analytical scheme is sufficient to provide a scientifically supported conclusion to the question asked. Therefore, the color test in Scheme 9 would not be necessary.

**Question #10: Can 4-methylmethcathinone (4-MMC) be identified in a sample without reference materials**?
*Note that known isomers of 4-MMC include 2- and 3-MMC.*

**Scheme Selected #10: GC-MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | GC | No comparison possible due to lack of reference materials | Inconclusive | - |
| A | MS (EI) | Spectrum consistent with MMC reference spectra in the SWGDRUG library. From the structural information provided, it is not possible to identify the positional isomer | MMC, although no isomer information | A |
| A | NMR | Spectrum consistent with 4-MMC from SWGDRUG monograph, and distinguishable from 2- and 3-MMC from SWGDRUG monographs | 4-MMC | A |

**Assessment:** The selected scheme of GC (Category B) and MS (Category A) was insufficient to identify 4-MMC. As no reference materials are available for comparison, the retention time from GC cannot be used toward the identification. Although the mass spectrum is consistent with the MMC reference spectrum in the SWGDRUG library, there is insufficient information to determine the specific isomer. Therefore, another test (NMR - Category A) was chosen to identify the isomer.

The enhanced scheme provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains 4-methylmethcathinone. (For reporting guidance, see PARTS IVA 6.1.6 and IVC 2.2.2)

**Question #11: Does the sample contain psilocin?**



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**Scheme Selected #11: LC-ESI-MS (Category B + A) + Color Test (Category C)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | LC | $t_R$ of analyte peak is consistent with psilocin reference material | Consistent with psilocin | B |
| A | MS (ESI) | $[M+H]^+$ ion (no fragmentation) consistent with psilocin reference material | Consistent with psilocin | Did not achieve the required level of selectivity/structural information |
| C | Color test | Positive color change consistent with psilocin | Indicates psilocin | C |

**Assessment:** The selected scheme of LC-ESI-MS (Category B + Category A) and Color Test (Category C) was sufficient to identify psilocin. The MS (ESI) test did not provide the required Category A structural information, but it did provide the selectivity of a Category B technique (based on separation by mass).

The scheme of LC (Category B), ESI-MS ($[M+H]^+$ only - Category B), and a color test (Category C) provided a scientifically supported conclusion to the question asked and, therefore, was fit for purpose.

**Conclusion:** The sample contains psilocin.

**Question #12:** Does the sample contain psilocybin?

**Scheme Selected #12: LC-MS/MS (Category B + A)**

| Category | Technique | Result | Conclusion | Assessment |
|---|---|---|---|---|
| B | LC | $t_R$ of analyte peak is consistent with psilocybin reference material | Consistent with psilocybin | B |
| A | MS/MS | Fragmentation spectrum consistent with psilocybin reference material | Psilocybin | A – sufficient structural information now available |

**Assessment:** Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other**.** The scheme of LC (Category B) and MS/MS (Category A) provides a scientifically supported conclusion to the question asked and, therefore, is fit for purpose.

**Conclusion:** The sample contains psilocybin.



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