SUPPLEMENTAL DOCUMENT SD-7
For Part III B - 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 III B.

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

Introduction
The minimum requirements for constructing an analytical scheme are put forth in Part III B *Methods of Analysis/Analytical Scheme for Identification of Drugs or Chemicals*. For convenience of the reader, the Levels of Selectivity (Figure 1) and Categories of Analytical Techniques (Table 1) are included here as a reference.

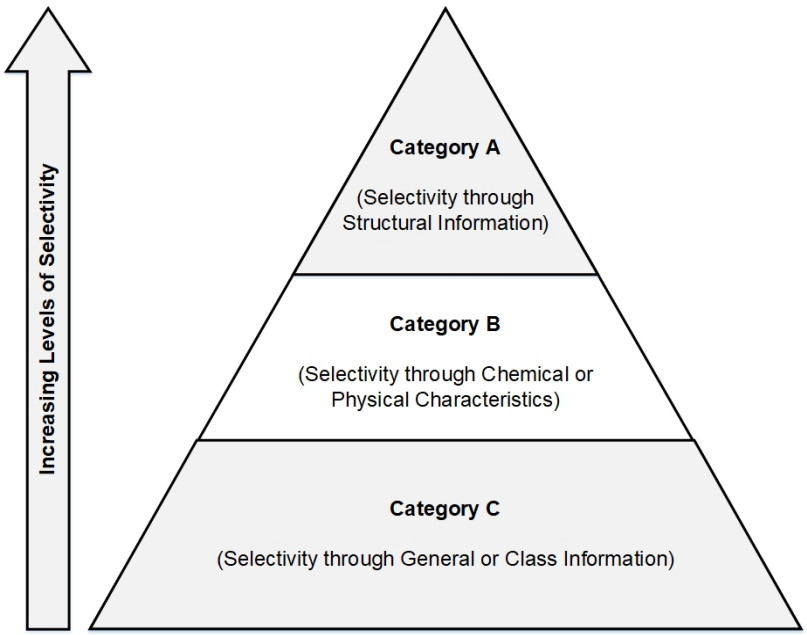

Figure 1 – Levels of Selectivity

Category A (Selectivity through Structural Information)	Infrared Spectroscopy
	Mass Spectrometry
	Nuclear Magnetic Resonance Spectroscopy
	Raman Spectroscopy
	X-ray Diffractometry
Category B (Selectivity through Chemical and Physical Characteristics)	Capillary Electrophoresis
	Gas Chromatography
	Ion Mobility Spectrometry
	Liquid Chromatography
	Microcrystalline Tests
	Supercritical Fluid Chromatography
	Thin Layer Chromatography
	Ultraviolet/Visible Spectroscopy
	Macroscopic Examination (Cannabis only)
	Microscopic Examination (Cannabis only)
Category C (Selectivity through General or Class Information)	Color Tests
	Fluorescence Spectroscopy
	Immunoassay
	Melting Point
	Pharmaceutical Identifiers

Table 1 – Categories of Analytical Techniques[1]

When constructing an analytical scheme, the achieved selectivity of the technique in the context of the particular analysis must be considered. 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.

These example analytical schemes are not intended to be all inclusive. Each of these analytical questions have multiple options for analytical schemes that would achieve a correct answer. These examples were selected to demonstrate different ways techniques can be used within a particular scheme. A discussion of considerations follows each example.

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;*

[1] Techniques within categories are listed in no particular order or ranking.

- *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?
Scheme Selected #1: GC-MS (Category B + A)

Category	Technique	Result	Assessment
B	GC	Retention time (t_R) of analyte peak is consistent with heroin reference material	Information provides Category B selectivity and the result is consistent with heroin
A	MS (EI)	Spectrum of analyte is consistent with heroin reference material	Information provides Category A selectivity and the result is consistent with heroin

Discussion: Each technique achieves the level of selectivity required 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.

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

Category	Technique	Result	Assessment
B	GC	t_R of analyte peak is consistent with pseudoephedrine reference material	Information provides Category B selectivity and the result is consistent with ephedrine, pseudoephedrine, or a mixture of both
A	MS (EI)	Spectrum of analyte is consistent with pseudoephedrine reference material	Information provides Category A selectivity and the result is consistent with ephedrine, pseudoephedrine, or a mixture of both

Discussion: 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	Assessment
B	GC	t_R of analyte peak is consistent with ephedrine reference material but is indistinguishable from pseudoephedrine reference material	Information provides Category B selectivity and the result is consistent with ephedrine, pseudoephedrine, or a mixture of both, but does not provide sufficient separation to answer the question; need another technique
A	MS (EI)	Spectrum of analyte is consistent with ephedrine reference material. Structural information is provided, but it is indistinguishable from pseudoephedrine reference material	Information provides Category A selectivity and the result is consistent with ephedrine, pseudoephedrine, or a mixture of both
Additional Technique: LC (Category B)			
B	LC	t_R of analyte peak is consistent with ephedrine reference material and distinguishable from pseudoephedrine reference material	Information provides Category B selectivity and the result is consistent with ephedrine

Discussion: 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 (with inclusion of the additional technique) 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	Assessment
A	ATR-FTIR	Spectrum consistent with methamphetamine HCl reference material	Information provides Category A selectivity and the result is consistent with methamphetamine HCl

C	Color Test	Positive color change consistent with methamphetamine HCl reference material	Information provides Category C selectivity and the result indicates methamphetamine or related compounds

Discussion: 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	Assessment
A	ATR-FTIR	Mixed spectrum with few significant peaks attributable to methamphetamine	Information does not provide Category A selectivity since there are insufficient identification features; need another technique
C	Color Test	Positive color change consistent with methamphetamine HCl reference material	Information provides Category C selectivity and the result indicates methamphetamine or related compounds
Additional Technique(s): GC-MS (Category B + A)			
B	GC	t_R of analyte peak is consistent with the methamphetamine HCl reference material, but inconsistent with the phentermine reference material	Information provides Category B selectivity and the result is consistent with methamphetamine
A	MS (EI)	Spectrum of analyte is consistent with methamphetamine HCl reference material	Information provides Category A selectivity and the result is consistent with methamphetamine

Discussion: The selected scheme of the ATR-FTIR (Category A) and Color Test (Category C) was insufficient to identify methamphetamine within the mixture, 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: Raman (Category A) + Color test (Category C)

Category	Technique	Result	Assessment
A	Raman spectroscopy	Spectrum consistent with cocaine HCl reference material	Information provides Category A selectivity and the result is consistent with cocaine HCl
C	Color test	Positive color change consistent with cocaine HCl reference material	Information provides Category C selectivity and the result indicates cocaine or related compounds

Discussion: Each technique achieves the level of selectivity required of its category and the positive test results corroborate each other**.** The scheme of 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 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, for Raman to be considered a Category A technique, it is required to have reviewable spectral data (see Part III B.5.1).

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	Assessment
A	MS (DART-TOFMS)	$[M+H]^+$ ion (no fragmentation) consistent with methcathinone	Molecular ion and molecular formula information are consistent with methcathinone, but does not achieve Category A due to lack of structural information
B	GC-FID	t_R of analyte peak is consistent with methcathinone reference material	Information provides Category B selectivity and the result is consistent with methcathinone

Additional Technique: GC-MS (Category B + A)			
B	GC	t_R of analyte peak was not compared with a reference material	No inconsistent information was obtained
A	MS (EI)	Spectrum of analyte is consistent with methcathinone reference material	Information provides Category A selectivity and the result is consistent with methcathinone

Discussion: 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), necessitating further testing with either Category A, B or C. 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 + A)

Category	Technique	Result	Assessment
B	GC	t_R of analyte peak is consistent with methcathinone reference material	Information provides Category B selectivity and the result is consistent with methcathinone
A	FTIR	Spectrum consistent with methcathinone reference material	Information provides Category A selectivity and the result is consistent with methcathinone

Discussion: 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	Assessment
C	Pharmaceutical identifier	Appearance consistent with a pharmaceutical-grade amphetamine sulfate tablet	Information provides Category C selectivity and indicates amphetamine sulfate tablet
B	GC-FID	t_R of analyte peak is consistent with amphetamine reference material	Information provides Category B selectivity and the result is consistent with amphetamine
B	TLC	R_f of analyte is consistent with amphetamine reference material	Information provides Category B selectivity and the result is consistent with amphetamine

Discussion: 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	Assessment
C	Pharmaceutical identifier	OC80 markings consistent with known pharmaceutical product containing oxycodone	Information provides Category C selectivity and indicates oxycodone tablet
B	GC	t_R of analyte peak is not consistent with oxycodone reference material, but is consistent with fentanyl reference material	Information provides Category B selectivity and the result is consistent with fentanyl
A	MS (EI)	Spectrum of analyte is too weak to provide sufficient information	Did not achieve Category A selectivity due to lack of structural information/low abundance

Additional Technique: GC-MS(EI) (Category A)			
	GC		
A	MS (EI) Concentrated sample	Spectrum of analyte is consistent with fentanyl reference material	Information provides Category A selectivity and the result is consistent with fentanyl

Discussion: The selected scheme of pharmaceutical identifier (Category C), GC-MS (Category B + A) was insufficient to identify oxycodone or fentanyl. The pharmaceutical identifier was inconsistent with the instrumental data, the initial 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)

Category	Technique	Result	Assessment
C	Pharmaceutical identifier	OC80 markings consistent with a pharmaceutical-grade oxycodone tablet	Information provides Category C selectivity and indicates oxycodone tablet
B	LC	t_R of analyte peak is consistent with oxycodone reference material	Information provides Category B selectivity and the result is consistent with oxycodone
B	UV/Vis (DAD)	Spectrum consistent with oxycodone reference material	Information provides Category B selectivity and the result is consistent with oxycodone

Discussion: 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	Assessment
B	Macroscopic examination	Characteristic morphological features of cannabis observed	Information provides Category B selectivity and the result is consistent with cannabis
B	Microscopic examination	Characteristic microscopic features of cannabis observed	Information provides Category B selectivity and the result is consistent with cannabis
C	Color test	Positive color change consistent with cannabinoids (e.g., THC, CBD,CBN)	Information provides Category C selectivity and the result indicates THC or other cannabinoids

Discussion: 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.

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 or an analyst appropriately trained in botanical identification (where jurisdiction allows), 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 #9B: Would the analytical scheme in #9 need to be changed to identify Marijuana cannabis, in a jurisdiction where Marijuana does not include Hemp cannabis with a concentration of delta-9-THC less than 0.3% by weight?

Answer: Yes, since the jurisdictional definition of Marijuana cannabis includes a minimum THC concentration, a test that measures the concentration of THC or that semi-quantitatively measures for a concentration greater than 0.3% THC must be added to the analytical scheme.

Question #10: Can 4-methylmethcathinone (4-MMC) be identified in a sample without reference materials?

Note that known isomers of MMC include 2-MMC, 3-MMC and 4-MMC.

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

Category	Technique	Result	Assessment
B	GC	t_R of analyte peak was not compared with a reference material	No inconsistent information was obtained
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	Information provides Category A selectivity and the result is consistent with 2-, 3-, or 4-MMC; but does not provide sufficient selectivity to answer the question; need another technique
Additional Technique: NMR (Category A)			
A	NMR	Spectrum provides structural determination of 4-MMC from SWGDRUG monograph, and distinguishable from 2- and 3-MMC from SWGDRUG monographs	Information provides Category A selectivity and the result is consistent with 4-MMC

Discussion: The selected scheme of GC (Category B) and MS (Category A) was insufficient to identify 4-MMC. As no reference materials are available for contemporaneous 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 IV A 6.1.6 and IV C 2.2.2)

Question #11: Does the sample contain psilocin?

Scheme Selected #11: GC-MS (Category B + A) + Thin Layer Chromatography (Category B)

Category	Technique	Result	Assessment
B	GC	t_R of analyte peak is consistent with psilocin reference material	Information provides Category B selectivity and the result is consistent with psilocin. However, the source of the psilocin is unknown.

A	MS	spectrum consistent with psilocin reference material	Information provides Category A selectivity and the result is consistent with psilocin. However, the source of the psilocin (from the material or as a thermal degradation of psilocybin) is unknown, and another technique is needed.
B	Thin Layer Chromatography	R_f of analyte spot is consistent with psilocin reference material and is inconsistent with psilocybin reference material	Information provides Category B selectivity and the result is consistent with psilocin

Discussion: The selected scheme of GC-MS (Category B + Category A) and Thin Layer Chromatography (Category B) was sufficient to identify psilocin. The MS test provided the required Category A structural information, but it could not determine the source of the psilocin (whether from the material or as a thermal degradation of psilocybin). Therefore, the additional Thin Layer Chromatography technique was required.

The scheme of GC (Category B), MS (Category A), and a Thin Layer Chromatography (Category B) 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	Assessment
B	LC	t_R of analyte peak is consistent with psilocybin reference material	Information provides Category B selectivity and the result is consistent with psilocybin
A	MS/MS	Fragmentation spectrum consistent with psilocybin reference material	Information provides Category A selectivity and the result is consistent with psilocybin

Discussion: 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.