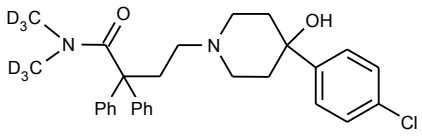
BDG SYNTHESIS

Certificate of Analysis

BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

Neil Beare, PhD, Director
11 April 2017

Name:	**Loperamide-d_6**
CAS Number:	53179-11-6 (unlabelled)
Structure:	
Molecular Weight:	$C_{29}H_{27}D_6ClN_2O_2$ = 483.07
Lot Number:	BDG 4660
Appearance:	White, crystalline solid
Corrected Purity:	99.7 % (HPLC) - 1.2 % (2-propanol) - 1.8 % (water) = 96.7 %
Isotopic Purity:	Under 0.5 % d_0
Re-test Date:	11 April 2022
Storage and Handling:	Temperature: refrigerate for prolonged storage; may be handled and shipped at ambient temperature.
	Humidity: not believed to be hygroscopic; may be handled in normal laboratory atmosphere.
	Light: protect from strong sunlight.
	Caution: only experienced laboratory personnel should handle the material.

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Identity and Purity

Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration are absent, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: a small amount of 2-propanol (1.2 % *w/w*) is observed.
Impurities: no significant impurities are evident in the spectrum.

Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the site of deuteration are obscured by the signal for the NMR solvent.

High-resolution Mass Spectrum (ESI+)

Found *m/z* 483.2693. $C_{29}H_{28}D_6ClN_2O_2$ $[M+H]^+$ requires *m/z* 483.2685. The deviation of 1.6 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for d_0 material was seen (detection limit about 0.5 %).

HPLC

A sharp, symmetrical peak is observed (99.7 %). Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

Elemental Analysis

	Found:	C 70.63, H 5.78, D 2.57, N 5.56 %
$C_{29}H_{27}D_6ClN_2O_2{\cdot}0.5H_2O$	Requires:	C 70.78, H 5.74, D 2.46, N 5.69 %, H_2O 1.83 %
$C_{29}H_{27}D_6ClN_2O_2$	Requires:	C 72.10, H 5.63, D 2.50, N 5.80 %

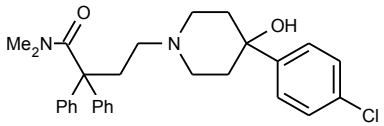
The elemental analyses fall substantially outside those expected for anhydrous material; the presence of water is reasonably expected from the method of purification and/or the type of material, and the “best-fit” hydrated molecular formula is given. In the absence of a Karl-Fischer water analysis, we recommend that the “best-fit” water content be used when determining corrected purity.

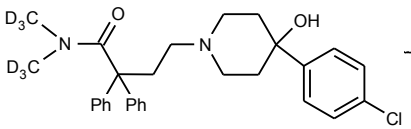
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration. Structures are shown with relative stereochemistry unless otherwise specified.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

BDG SYNTHESIS

Proton NMR Spectrum of Loperamide (top) and Loperamide-d_6 (bottom) in Methanol-d_4





Lot Number: BDG 4660

HOD

NMR Solvent

$2xCH_3+6xCH_2$ 18.1 H

↑ ↑ $2xCH_3$

14xCH 14.0 H

2-propanol

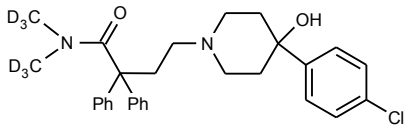
$6xCH_2$ 11.9 H

2-propanol 1.2 % *w/w*

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

BDG SYNTHESIS

Carbon-13 NMR Spectrum of Loperamide-d_6 in DMSO-d_6



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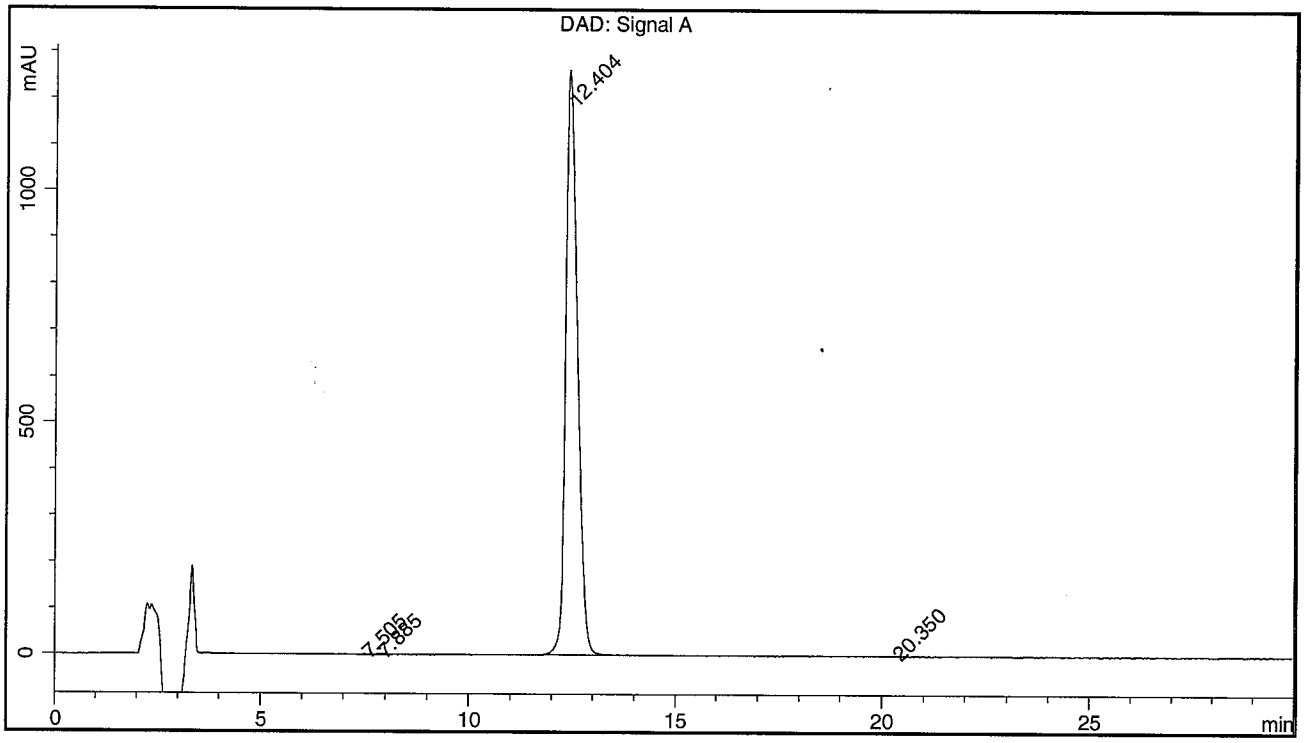
BDG - Analysis of Loperamide-d6

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase : 64:36 25 mM Tetrapropylammonium Hydroxide pH=2.0 (H2SO4) : Acetonitrile
Flow Rate : 1.0 mL/min
Sample Solvent : Methanol
Column Temperature : 30 C
Injection Volume : 10 uL
Detection : UV at 210 nm

Sample Name	BDG 4660	Instrument	AnalyticalLC01
Acquisition	11/04/2017, 18:45:05	Method (rev.)	LC10386c (7)
Sequence	BDG_11Apr2017g - Reprocessed	Vial Position	1
Operator	solvation010\cerityadmin	Injection	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	7.50 min	1.6725	20.9030	0.1778 min	0.083 %
2	7.89 min	2.2045	38.4234	0.2433 min	0.153 %
3	12.40 min	1261.8858	25076.0901	0.3118 min	99.651 %
4	20.35 min	1.1938	28.5771	0.3113 min	0.114 %