Lysosomal Enzymes in fibroblasts

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Annual Report 2021
Version Number[1]: 2
Date of issue: 15 August 2022

Note: This annual report is intended for participants of the ERNDIM Lysosomal Enzymes in fibroblasts scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

The fact that your laboratory participates in ERNDIM schemes is not confidential. However, the raw data and performance scores are confidential and will only be shared within ERNDIM for the purpose of evaluating performance of your laboratory, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the terms and conditions in the EQA Schemes Catalogue and Participant Guide and the ERNDIM Privacy Policy on www.erndim.org.

1. Scheme Design
The scheme has been designed, planned and coordinated by Ms Marie Jackson (as Scientific Advisor) and Dr Eline van der Hagen as Scheme Organiser (sub-contractor on behalf of MCA Laboratory); both appointed by and according to procedures laid down by the ERNDIM Board.

1.1. Sub-contracted activities:
The fibroblasts used as the EQA materials were cultured by Centre de Biotechnologie Cellulaire, CHU de Lyon. The fibroblasts were prepared and aliquoted by MCA Laboratory, Netherlands, which also hosts and manages the results submission website (www.erndimqa.nl) on behalf of ERNDIM.

2. Samples
All EQA materials are lyophilised samples of human fibroblasts. All samples were obtained following local ethical and consent guidelines.

Table 1: Samples included in the EQA scheme

Sample	Disorder	Enzyme Defect	Reporting deadline
LEFB2021.01	Control	All normal	28 May 2021
LEFB2021.02	MPS VI (maroteaux Lamy)	Arylsulphatase B	
LEFB2021.03	Tay Sachs disease	Hexosaminidase A	
LEFB2021.04	Mucolipidosis II (I-cell)	Multiple enzyme deficiencies	27 August 2021
LEFB2021.05	GM1 gangliosidosis	Beta-galactosidase	
LEFB2021.06	Alpha-mannosidosis	Alpha-mannosidase	

3. Shipment
One shipment of six samples was dispatched 9th February 2021, to the 69 laboratories, from 28 countries, which registered for the scheme.

4. Receipt of results
There were two submission deadlines for the 2021 scheme: (LEFB2021.01, 02 & 03 on 28th May) and (LEFB2021.04, 05 & 06 on 27thAugust).

[1] **If this Annual Report is not Version 1 for this scheme year, go to APPENDIX 2 (page 15) for details of the changes made since the last version of this document.**

Laboratories were asked to submit results for each EQA sample by the relevant submission deadline using the results website www.erndimqa.nl. All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting.

Laboratories were asked to report the total protein in mg/vial and the activities for 10 enzymes in:

- Absolute units
- As the percentage of activity in sample *LEFB 01*.

See Table 2 for details. Laboratories could submit results for as many, or as few, of these 10 enzymes as they wished and were asked to select an 'interpretation' of the results from a dropdown list on the results website.

Table 2: Analytes to be measured

Analyte	Parameter 1	Parameter 2
Protein	mg/vial	-
Arylsulphatase B	nmol/h/mg protein	% of sample LEFB 01
Sphingomyelinase	nmol/h/mg protein	% of sample LEFB 01
α -Galactosidase	nmol/h/mg protein	% of sample LEFB 01
α -Glucosidase	nmol/h/mg protein	% of sample LEFB 01
α -Mannosidase	nmol/h/mg protein	% of sample LEFB 01
β -Galactosidase	nmol/h/mg protein	% of sample LEFB 01
β -Glucosidase	nmol/h/mg protein	% of sample LEFB 01
β -Hexosaminidase (A+B)	nmol/h/mg protein	% of sample LEFB 01
β -Hexosaminidase A	nmol/h/mg protein	% of sample LEFB 01
α -Fucosidase	nmol/h/mg protein	% of sample LEFB 01

5. Reports

All data-transfer, the submission of data as well as request and viewing of reports is via the interactive website www.erndimqa.nl which can also be reached through the ERNDIM website (www.erndim.org). The results of each laboratory are confidential and only accessible by password protected laboratory accounts. The anonymised mean results of all labs are accessible to all participants. Statistics of the respective reports are explained in the general information section of the website.

Short-term reports on the six individual specimens are available two weeks after the submission deadline and provide up-to-date information on analytical performance. Although it is technically possible to produce reports immediately there is a delay of 14 days to enable the scientific advisor to inspect the results and add comments to the report when appropriate.

A second important characteristic of the website is the different levels of detail of results which allows individual laboratories the choice of fully detailed and/or summarised reports.

The "Analyte in Detail" is the most detailed report and shows the results of a specific analyte in a specific sample. Thus, for the 10 enzymes in the year 2021 cycle, 6 x 10 (60) such Analyte-in-Detail-reports can be requested.

The "Cycle Review" summarises the performance for all enzymes in a specific sample (6 such Cycle Reviews can be requested in 2021).

6. Scoring scheme and Poor performance policy

It was approved by the Scientific Advisory Board at their meeting in November 2019 that scoring of interpretation would be formally introduced for the 2020 scheme onwards.

For the 2021 Scheme and subsequent years, the %CV for each enzyme will no longer be provided.

If the interpretation of a result is incorrect for a specific enzyme a performance support letter may be issued, but only **for that particular enzyme assay**. This is to initiate a dialogue between us, the EQA scheme advisor/organiser and you, the participating laboratory, to solve any particular analytical problems and to help you improve performance.

***Comments box*:** Participant comments may be taken into account by the Scientific Advisor. Please use this box to note any issues noted regarding the sample or assay, or to note further relevant information.

The **diagnostic proficiency** was scored for each enzyme: i.e. is the interpretation correct or incorrect. One point was awarded for a correct diagnosis.

For the protein value a maximum of 2 points could be scored depending on the %CV.

Table 3: Scoring criteria

	Criteria		Score
Protein	**CV**	CV<35%	2
		CV= 35%<CV<60%	1
		CV>60%	0
Enzymes	**Diagnosis**	Diagnosis correct	1
		Diagnosis incorrect	0
	CV	Not scored from 2020 onwards	

Laboratories could participate in as many of the ten enzymes offered in the scheme plus the protein assay as required. Each enzyme is assessed individually, the emphasis being on the correct interpretation of the result. Making the correct interpretation / diagnosis for each enzyme/ sample is the priority: i.e. identifying a deficiency in an affected patient and reporting normal activity in unaffected samples.

If a laboratory misinterprets a result, then a performance support letter is sent relating to **that specific enzyme only**. The letter is intended to instigate dialogue between the EQA Scientific Advisor and the participating laboratory in order to solve any particular analytical problems in order to improve quality of performance of labs in the pursuit of our overall aim to improve quality of diagnostic services in this field.

6.1. Diagnosis

The participants must select an interpretation from the dropdown list on the results website.

Diagnosis correct: correct interpretation and correct measurement of enzyme activity level.

Diagnosis incorrect: incorrect interpretation and incorrect enzyme activity level.

6.2. Coefficient of variation

From 2020 CV results for enzymes included in the scheme will **not** be determined or contribute to the scoring. *Only CV for proteins will contribute to scoring: from 2021 this will be calculated from median results for all labs.*

6.3. Appeals

If your laboratory has been sent a performance support letter for the 2021 scheme and you wish to appeal against this classification please email the ERNDIM Administration Office (admin@erndim.org) , with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal against poor performance are included in the Performance Support Letter sent to poor performing laboratories.

7. Results

Sixty-nine laboratories were registered in the 2021 scheme. Sixty-four laboratories (93% of registered laboratories) submitted sufficient results for their performance to be assessed.

Five laboratories (7.2% of registered laboratories) did not submit enough results for their performance to be assessed.

There were no non-submitting labs in the 2021 scheme and also no labs registered as educational participants.

Table 4: Results returns for the 2021 scheme

	Submission Deadline					
	28th May 2021			27th August, 2021		
Sample Numbers:	**2021.01**	**2021.02**	**2021.03**	**2021.04**	**2021.05**	**2021.06**
No. of labs that submitted results:						
By the submission deadline	68	68	68	68	69	*69*
Within 7 days of the submission deadline	0	0	0	0	0	0
Within 2 weeks of the submission deadline	0	0	0	0	0	0
Did not submit	1	1	1	1	0	0

The results for each sample were published on the results website 14 days after the relevant submission deadline.

Full details of the results for each participant's results (for labs that submitted results) are given in Appendix 1 but summaries are presented here:

- 89% of all laboratories submitted results for 5 or more enzymes, see Table 5.
- The proficiency per analyte is given in

- Table 6.
- The majority of participants made the correct interpretation.
- **84.4% of laboratories achieved >90% of their maximum possible score (i.e. of enzymes plus proteins). See Table 7 which shows the percentage of the maximum possible score for the laboratories that submitted results.**

Table 5: Number of enzymes for which laboratories submitted results (excluding non/partial submitters)

Number of Enzymes for which results were submitted	Number of laboratories
0	0
1	0
2	2
3	3
4	2
5	2
6	4
7	5
8	7
9	7
10	32
Total number of labs	**64**

Table 6: Proficiency per analyte

Analyte	No of returns	Participants with CV < 35	Correct interpretation* (diagnostic proficiency)
Protein	69	83.3%	-
Arylsulphatase B (ASB)	54	-	90.7%
Sphingomyelinase	45	-	93.3%
α -Galactosidase	65	-	89.2%
α -Glucosidase	56	-	91.1%
α -Mannosidase	54	-	81.5%
β -Galactosidase	64	-	90.6%
β -Glucosidase	65	-	92.3%
β -Hexosaminidase (A+B)	61	-	91.8%
β -Hexosaminidase A	58	-	89.7%
α -Fucosidase	57	-	93.0%

*** = percentage of maximum possible score (for laboratories that submitted results)**

Table 7: Percentage of maximum possible scores for laboratories that submitted results (excluding partial submitters)

%age of maximum possible score	No of submitting labs	%age of submitting labs
0% – 9%	0	0%
10% – 19%	0	0%
20% – 29%	0	0%
30% –39%	0	0%
40% – 49%	0	0%
50% –59%	0	0%
60% –69%	1	1.6%
70% –79%	2	3.1%
80% –89%	7	10.9%
90% –99%	7	10.9%
100%	47	73.4%
Total	**64**	**100%**

Table 8: Number of enzymes for which laboratories had satisfactory performance

Anon Lab No.	No of enzymes for which:	
	results were submitted by lab	lab had satisfactory performance
1	10	10
2	6	6
3	10	10
4	10	10
5	9	9
6	4	4
7	0	0
8	8	8
9	10	10
10	10	10
11	10	10
12	3	3
13	10	7
14	10	10
15	10	10
16	10	10
17	10	10
18	0	0
19	10	10
20	9	9
21	10	9
22	2	2
23	10	8
24	5	5
25	10	10
26	10	10
27	10	10
28	10	10
29	10	10
30	7	7
31	10	10
32	10	10
33	6	6
34	10	10
35	6	6
36	10	10
37	10	10
38	2	2
39	8	8
40	9	9
41	0	0

Anon Lab No.	No of enzymes for which:	
	results were submitted by lab	lab had satisfactory performance
42	10	10
43	8	8
44	7	7
45	9	9
46	7	7
47	10	10
48	0	0
49	10	10
50	7	7
51	10	10
52	6	5
53	6	6
54	10	10
55	9	9
56	10	10
57	4	3
58	8	8
59	0	0
60	10	10
61	3	3
62	4	4
63	10	10
64	9	9
65	10	10
66	10	10
67	8	8
68	8	8
69	10	10

8. Certificates of Participation

As for other schemes, the performance for this scheme is summarised in the annual Certificate of participation. The certificate lists the total number of enzymes in the scheme, the number for which results have been submitted and the number for which satisfactory performance has been achieved. It is important to bear in mind that the certificate must be backed up by the laboratory's individual on-line reports in the case of internal or external auditing.

9. Comments on Overall Scheme Performance.

The majority of participants made the correct interpretation: that is, the correct enzyme deficiency was observed in the samples from affected patients and normal activity was observed in the unaffected samples.

Further information on the affected samples provided for testing can be found in Table 9 below.

Table 9: Cultured fibroblast samples included in the EQA scheme:

Sample	Diagnosis & enzyme deficiency	Age at diagnosis	Clinical information	Other information
LEFB2021.01	Normal control			All 10 enzymes in 2021 scheme were assayed prior to distribution and confirmed to have normal levels of enzyme activity
LEFB2021.02	MPS type 6 (Maroteaux Lamy). Deficiency of arylsulphatase B activity.	Sample collected at 18 years	No further information available.	
LEFB2021.03	GM2 gangliosidosis – Tay Sachs variant. Deficiency of hexosaminidase A activity.	Male aged 11 months.	Psychomotor regression, global hypotonia, myoclonus.	
LEFB2021.04	Mucolipidosis type II – I cell disease. More than one enzyme deficiency observed.	Male aged 1 month		
LEFB2021.05	GM1 gangliosidosis. Deficiency of beta-galactosidase activity	Female aged 7 months	Psychomotor delay, hypotonia, nystagmus, hepatomegaly.	
LEFB2021.06	Alpha mannosidosis. Deficiency of alpha-mannosidase activity.	Female aged 37 years	Cerebellar atrophy, thickening of the cranial vault, demyelination, psychomotor delay since childhood, facial dysmorphia, dorsolumbar gibbus.	

LEFB 01 was included as a control to enable an improved comparison of overall results from all participants, and to provide a control to laboratories that do not use fibroblasts.

Participants were asked to express enzyme results as a percentage of sample LEFB 01: all participants must enter this data correctly.

LEFB 02 was a patient affected with **Maroteaux Lamy (MPS type VI).** Fifty of the fifty-two participants provided the correct interpretation: proficiency for this enzyme was 96.2%.

Some laboratories correctly mentioned that another sulphatase enzyme should be measured to exclude the possibility that the patient could have the diagnosis of a multiple sulphatase deficiency

LEFB 03 was a patient affected with **Tay Sachs disease (GM2 gangliosidosis- classical Tay Sachs variant).** Fifty-two participants assayed hexosaminidase A activity: proficiency for this enzyme was 98.1%.

LEFB 04 was a patient with mucolipidosis type II (I-cell disease).

Mucolipidosis II/ III (MLII – I-cell disease, MLIII - pseudo-Hurler polydystrophy)

Due to a deficiency or dysfunction of the enzyme N-acetylglucosamine-1 phosphotransferase the mannose residues of the lysosomal hydrolases are not phosphorylated. Hydrolases without mannose-6-phosphate markers are not recognised by the lysosome, and are not transported across the lysosomal membrane. This results in Mucolipidosis types II and III (I-cell disease and pseudo-Hurler polydystrophy). A potential diagnosis is suggested by patient having clinical features resembling mucopolysaccharidoses, but without their biochemical abnormalities.

Findings of grossly elevated levels of lysosomal enzymes in plasma/serum are diagnostic (e.g. hexosaminidases, arylsulphatase A). When assayed in cultured fibroblasts severe deficiencies of the majority of lysosomal enzymes are observed. However, NB: lysosomal enzymes that use alternate pathways are not observed to be deficient (e.g. beta-glucosidase).

This year an extra option was added to the drop-down list: 'more than one enzyme deficiency'. If this observation was made participants were required to choose this option and to use the comments box to add their notes on interpretation and reporting for this sample.

Clinical details provided were: Male, sample collected at 1 month of age. Parents consanguineous, fetal death of previous sibling.

In patients affected with ML II/III we would expect participants to note a deficiency of most lysosomal enzymes in cultured fibroblasts (with normal activity of beta-glucosidase).

Sixty-one of participants selected 'more than one enzyme deficiencies' in the drop-down list.

- Forty-eight participants (48/61) suggested diagnosis of I-cell (ML II/III) and provided good comments regarding confirmatory testing: proficiency 78.7%.
- Six participants suggested the sample could be unsuitable because of multiple enzyme deficiencies observed.
- Three participants correctly selected 'more than one enzyme deficiency' but made no comments on the possible diagnosis.
- One participant suggested a diagnosis of alpha fucosidosis or unsuitable sample.
- One lab ticked alpha galactosidase, but discussed the diagnosis of ML II/III well and at length in comment (box ticked in error).
- Two labs confidently suggested a diagnosis of Fabry disease, despite observing other low enzyme levels in the sample.

LEFB 05 was a patient with a beta-galactosidase deficiency (GM1 gangliosidosis). The proficiency for this enzyme – 98.3%. Most laboratories offer this enzyme test and had no problems achieving the correct diagnosis; many also mentioned MPS IVB (Morquio B).

LEFB 06 was a patient affected with alpha-mannosidosis. The alpha-mannosidase enzyme had not been included in the lysosomal enzymes scheme in previous years.

Of 52 participants, seven made an incorrect interpretation: proficiency for this enzyme was 86.5%.

As the proficiency for sample 6 is <90% (alpha mannosidase deficiency) the ERNDIM Advisory Board agreed no critical errors would be issued for this sample.

10. Preview of the scheme in 2022.

a) There will be two submission deadlines for the 2022 scheme:
   - Samples 01, 02 & 03 to be submitted by 27 May 2022
   - Samples 04, 05 & 06 to be submitted by 26 August 2022

b) Some changes have been made to the enzymes included in the 2022 LEFB scheme: see

c) Table 10 below for comparison. For purposes of laboratory accreditation there is an increasing demand for the inclusion of further & different enzymes in the scheme. In order to address this requirement, it is intended that ERNDIM continue to provide regular rotation of the enzymes included each year. Aspartylglucosaminidase is included in 2022: this has not been included in the scheme previously.

Table 10: Analytes to be measured in 2022

Analyte	2018	2019	2020	2021	2022
Protein	✓	✓	✓	✓	✓
Arylsulphatase A	×	✓	✓	×	✓
Arylsulphatase B	×	×	×	✓	×
Aspartylglucosaminidase	×	×	×	×	✓
Galactose-6-sulphate sulphatase	✓	×	×	×	×
Galactosylceramidase	✓	✓	✓	×	✓
Iduronate-sulphatase	×	✓	×	×	×
Lysosomal acid lipase (LAL/acid/esterase)	×	✓	✓	×	×
Palmitoyl protein thioesterase	×	✓	✓	×	×
Sphingomyelinase	✓	×	×	✓	✓
Tripeptidyl peptidase	×	✓	×	×	×
α -Galactosidase	✓	✓	✓	✓	✓
α -Glucosidase	✓	✓	✓	✓	✓
α -Iduronidase	✓	×	×	×	×
β -Galactosidase	✓	✓	✓	✓	✓
β -Glucosidase	✓	✓	✓	✓	✓
β -glucuronidase	×	×	✓	×	×
β -Hexosaminidase A	✓	×	×	✓	✓
β -Hexosaminidase A+B	✓	×	×	✓	✓
α-fucosidase	×	×	×	✓	×
α-mannosidase	×	×	×	✓	×
α-N-Ac-glucosaminidase	×	×	✓	×	×

11. Questions, Comments and Suggestions

If you have any questions, comments or suggestions in addition to specific user comments please address these to the either the ERNDIM Administration Office (admin@erndim.org), the scientific advisor of the scheme, Ms Marie Jackson, (Marie.Jackson@viapath.co.uk) or the scheme organiser Dr Eline van der Hagen (E.vanderHagen@skbwinterswijk.nl).

12. Confidentiality Statement

This annual report is intended for participants of the ERNDIM Lysosomal Enzymes in fibroblasts scheme. The contents should not be used for any publication without the permission of the Scientific Advisor and Administration Office.

Marie Jackson
Scientific Advisor

APPENDIX 1. Results per laboratory (part 1)

(see page 12 for key)

Anon	Protein/vial		Score				
Lab No.	CV	Score	ASB	α-Galactosidase	β-Galactosidase	α-Glucosidase	β-Glucosidase
1	5	2	1	1	1	1	1
2	21	2	1	1		1	1
3	8	2	1	1	1	1	1
4	20	2	1	1	1	1	1
5	16	2		1	1	1	1
6	10	2	1				1
7	R0	0	(PS)	(PS)	(PS)	(PS)	(PS)
8	61	0	1	1	1		1
9	10	2	1	1	1	1	1
10	947	0	1	1	1	1	1
11	26	2	1	1	1	1	1
12	27	2	1	1	1		
13	48	1	0	1	1	0	1
14	5	2	1	1	1	1	1
15	24	2	1	1	1	1	1
16	17	2	1	1	1	1	1
17	46	1	1	1	1	1	1
18	R0	0		(PS)	(PS)		(PS)
19	21	2	1	1	1	1	1
20	35	1	1	1	1	1	1
21	20	2	1	0	1	1	1
22	31	2				1	1
23	19	2	0	1	1	1	1
24	15	2		1	1		1
25	43	1	1	1	1	1	1
26	10	2	1	1	1	1	1
27	22	2	1	1	1	1	1
28	9	2	1	1	1	1	1
29	21	2	1	1	1	1	1
30	13	2		1	1	1	1
31	1.4	2	1	1	1	1	1
32	8	2	1	1	1	1	1
33	55	1		1	1		
34	6.5	2	1	1	1	1	1
35	45	1		1	1	1	1
36	12	2	1	1	1	1	1
37	44	1	1	1	1	1	1
38	27	2		1		1	
39	20	2	1	1	1	1	1
40	2	2	1	1	1		1
41	R0	0		(PS)	(PS)	(PS)	(PS)
42	20	2	1	1	1	1	1
43	15	2	1		1		1
44	10	2	1	1	1	1	1
45	18	2	1	1	1	1	1
46	25	2		1	1	1	1
47	25	2	1	1	1	1	1
48	R0	0	(PS)	(PS)	(PS)	(PS)	(PS)
49	3	2	1	1	1	1	1
50	11	2	1		1		1
51	21	2	1	1	1	1	1
52	40	1	1	0	1	1	1
53	12	2	1	1	1	1	1
54	19	2	1	1	1	1	1
55	11	2	1	1	1	1	1
56	2	2	1	1	1	1	1
57	7	2		1	0		1
58	7	2		1	1	1	1
59	R0	0	(PS)	(PS)	(PS)	(PS)	(PS)

Anon Lab No.	Protein/vial		Score				
	CV	Score	ASB	α-Galactosidase	β-Galactosidase	α-Glucosidase	β-Glucosidase
60	13	2	1	1	1	1	1
61	9	2		1		1	1
62	11	2		1	1		
63	13	2	1	1	1	1	1
64	31	2	1	1	1	1	1
65	6	2	1	1	1	1	1
66	51	1	1	1	1	1	1
67	2	2	1	1	1		1
68	34	2		1	1		1
69	3	2	1	1	1	1	1

APPENDIX 1. Results per laboratory (part 2)

(see page 12 for key)

Anon Lab No.	Score				
	α-fucosidase	Hexosaminidase	Hexosaminidase A	α-mannosidase	Sphingomyelinase
1	1	1	1	1	1
2		1	1		
3	1	1	1	1	1
4	1	1	1	1	1
5	1	1	1	1	1
6	1			1	
7		(PS)	(PS)		
8	1	1	1	1	
9	1	1	1	1	1
10	1	1	1	1	1
11	1	1	1	1	1
12					
13	1	1	1	0	1
14	1	1	1	1	1
15	1	1	1	1	1
16	1	1	1	1	1
17	1	1	1	1	1
18	(PS)	(PS)	(PS)		
19	1	1	1	1	1
20	1	1	1	1	
21	1	1	1	0	1
22					
23	1	1	0	1	1
24		1	1		
25	1	1	1	0	1
26	1	1	1	1	1
27	1	1	1	1	1
28	1	1	1	1	1
29	1	1	1	1	1
30		1	1		1
31	1	1	1	1	1
32	1	1	1	1	1
33	1	1	1	0	
34	1	1	1	0	1
35	1	1			
36	1	1	1	1	1
37	1	1	1	1	1
38					
39	1	1		1	
40	1	1	1	1	1
41	(PS)	(PS)	(PS)	(PS)	(PS)
42	1	1	1	1	1
43	1	1	1	0	1
44	1			1	
45	1	1	1	1	
46	1	1			1
47	1	1	1	1	1
48	(PS)	(PS)	(PS)	(PS)	(PS)
49	1	1	1	1	1
50	1	1	1	1	
51	1	1	1	1	1
52			1		
53		1			
54	1	1	1	1	1
55	1	1	1	1	
56	1	1	1	1	1
57			1		
58	1	1		1	1

Anon Lab No.	Score				
	α-fucosidase	Hexosaminidase	Hexosaminidase A	α-mannosidase	Sphingomyelinase
59	(PS)	(PS)	(PS)	(PS)	(PS)
60	1	1	1	1	1
61					
62		1	1		
63	1	1	1	1	1
64	1	1	1	0	
65	1	1	1	1	1
66	1	1	1	1	1
67	1	1	1	1	
68	1	1	1	1	1
69	1	1	1	1	1

Key

green cells = correct interpretation

(pale green cells = incorrect but no critical error for α-mannosidase)

red cells = incorrect interpretation

R0 = CV calculation not possible as insufficient data.

PS = partial submitter

APPENDIX 2. Change log (changes since the last version)

Version Number	Published	Amendments
1	10 June 2022	• 2021 annual report published
2	15 August 2022	• Page 4, tables 5 and 6 corrected • Page 5, table 8 – results for lab 30 corrected • Pages 9 & 11, Appendix 1 – results for lab 30 corrected

END OF REPORT