ZEPHEX®

BATCH VS INDIVIDUAL - CERTIFICATE OF ANALYSIS: VERSION 1

1. Introduction

Customers require a confirmation by Certificate of Analysis (CofA) that the product they have purchased meets the specification ordered and has a traceability to comply with the controls of current Good Manufacturing Practice (cGMP). In this respect there are a number of options available which Koura® customer services and technical team can assist in selecting.

Prior to placing an order with Koura® for a quantity of Zephex® 134a, a customer has a number of decisions to make. The sequence of such decisions could be summarised as below.

1. Quantity of Zephex®134a required to fulfill their needs over a period of time (usually their annual demand).
2. Whether the quantity in '1' is best fulfilled as a bulk supply (ISO tank) or package supply (drum or cylinder).
3. That the bulk or package [1] supply decision aligns with customer's global region, site layout, current/future assets and volume requirements.
4. Selection of either *batch* or *individual* analysis for the CofA, for the material requested
5. Whether the independent acceptance testing service [2] is required for the order being placed. This service is only available where *individual* analysis is chosen.

The next section provides guidance in selecting the analysis options that are available to Koura®'s customers and contains a definition of *batch* and *individual* analysis that can be requested, for the selected package CofA.

2. Analysis Options in Brief

2.1. Overview

Koura® recommends that customers review the level of compliance required for acceptance of incoming goods, for the markets for which their end products are licensed.

Bulk supplies of Zephex® propellants (i.e. ISO tanks) are always accompanied by an *Individual* CofA, reporting the results of a sample taken from that specific vessel.

Smaller packages of Zephex® propellants (i.e. drums or cylinders) can either be provided with an *individual* CofA based on a sample taken from the package, or a *batch* CofA based on a sample taken from the ISO tank from which the package was filled.

Analysis is a costly and time-consuming activity, so packaged product accompanied by an *individual* CofA will always cost significantly more than product certified with a *batch* CofA. The balance a user must strike, is between cost and compliance requirements in their target markets.

The analytical options, *individual* or *batch*, that are viable in practice, are summarised in Table 1.

Vessel or Service	Batch CofA	Individual CofA	Comments
Bulk ISO tank	✗	✓	-
Package Ton Drums / GLI	✓	✓	Customer choice
Package Small Cylinders	✓	✗	Individual CofA is only available in exceptional one-off type circumstances
Independent Acceptance Testing Service	✗	✓	

Table 1

2.2. Definitions

Individual CofA

Is a CofA obtained when a 2kg sample of the specific package (ISO tank, drum or cylinder) contents is taken to the QC lab, and fully analysed using all 11 tests that make up a normal Zephex® CofA. It takes a man-day of effort, to do one such analysis. The CofA will be supplied with the package, to the customer.

Batch CofA

Is a CofA reporting the analysis results of the contents of the ISO tank, from which the package was filled. The package itself is not subject to any additional analysis.

3. Analysis Options in Detail for Packed Zephex® Drums and Cylinders

3.1. Individual CofA

An Individual CofA reports a full 11-test analysis of the Zephex® 134a contained within a package, after the package has been filled from an ISO tank.
The results obtained are reported on a CofA which is supplied to the customer, the 'parent' ISO tank's analysis is not provided to the customer, as the individual CofA analysis supersedes it.

Customers should determine if a CofA generated by individual analysis is an absolute requirement for their final product region.

- Applies to bulk and smaller package forms (Table 1).
- Due to prohibitive cost, individual CofAs are only very rarely produced for small vertical cylinders. This would be for exceptional or special purposes only.
- Higher cost than batch analysis.
- Independent acceptance testing service is available.

For individual CofA generation, the below information describes briefly the manufacturing, re-packaging and analytical operations at the Zephex® 134a plant and laboratory.

For a more detailed description of these operations and batch numbering [3] information, contact the Koura® technical team.

1. Zephex® 134a is manufactured in a masterbatch process were several individual production batches are combined in a single masterbatch of up to 200 tonnes.
2. On release, the masterbatch is assigned a batch number in the format RB/XX/YYY.
3. ISO tanks are then filled from the released masterbatch and assigned a sub-batch number in the format RB/XX/YYY-ZZ.
4. A package is filled for the customer and the sub-batch number is retained from the ISO tank.
5. A further full analysis takes place of the Zephex® 134a contained within the package.
6. Customer is provided with one single CofA for the package, containing the details of the test in '5' above. Appendix 1 is below.

   For individual CofAs, other characteristics include:

   - Container type is documented on the CofA.
   - Package ID number is documented on the CofA.
   - The unique numbers of the tag seals securing the valves are documented on the CofA.

3.2. Batch CofA

A batch CofA reports analysis of the Zephex® 134a from the 'parent' ISO tank. No further analysis of the package contents takes place.

The results obtained are reported on a CofA which is supplied to the customer from the 'parent' ISO tank's analysis.

- Can be applied to all smaller package forms (Table 1).

- Lower cost than individual analysis.
- Independent acceptance testing service is not available for batch CofA.

For Batch CofA generation, the below information describes briefly the manufacturing, re-packaging and analytical operations at the Zephex® 134a plant and laboratory.

For a more detailed description of these operations and batch numbering information [3] contact the Koura® technical team.

1. Zephex®134a is manufactured in a masterbatch process where several individual production batches are combined in a single masterbatch of up to 200 tonnes.
2. On release, the masterbatch is assigned a batch number in the format RB/XX/YYY.
3. ISO tanks are then filled from the release batch and assigned a sub-batch number in the format RB/XX/YYY-ZZ.
4. A set of packages for the customer are filled from an ISO tank. The sub-batch number and analytical data from the ISO tank are retained and used to certify the set of packages filled from that ISO tank. No further analysis of the package takes place.
5. Customer is provided with a CofA reporting the above ISO tank analysis as illustrated in Appendix 2.
6. Customer is provided with a batch CofA cover note displaying the following information:

    - Name of product being supplied.
    - Customer address.
    - Order number.
    - Package size.
    - Number of packages
    - Batch number of ISO tank which it was released from (RB/XX/YYY-ZZ) and ISO tank number.
    - Serial Numbers of all packages in the shipment that were filled from this ISO tank, together with the unique numbers on the security seals protecting the valves on the packages.

There are some other slight differences that result from taking this approach, that will now be outlined.

Full or empty packages are always kept under cGMP control. The remaining contents of a package, the remaining gas ‘heel’, will always meet specification. However, when that package is refilled from an ISO tank filled from a different masterbatch of Zephex® 134a, it is possible that impurity levels may change slightly. This is because of the ‘heel’ and the incoming ‘fresh’ material, are being mixed together in the cylinder.

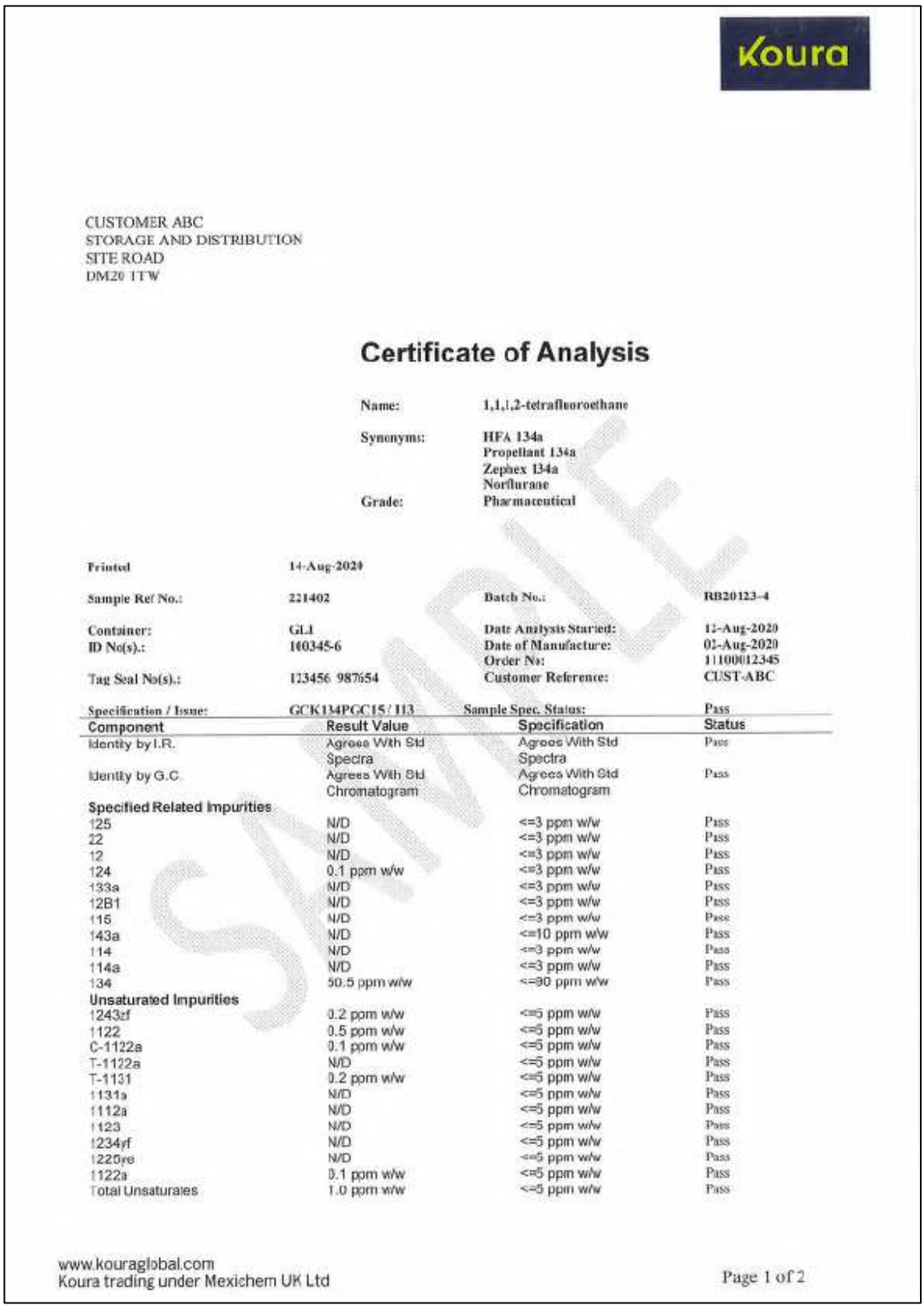
This means that the actual impurities content, whilst always definitely in spec, may vary slightly from the ISO tank analysis that appears on the batch CofA. This also applies to the non-condensable gases result, as this relies on a headspace sample. On a batch CofA, this aspect is therefore a conformance statement rather than a live result.

4. References

Documents below can be supplied by Koura® customer service & technical service teams when required.

1. Engineering Note: TES82 Drum & Cylinder Market Approvals
2. Quality Control Note: Independent Acceptance Testing Service
3. Quality Assurance Note: Batch Numbering System

Appendix 1 - Individual CofA Example



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CUSTOMER ABC
STORAGE AND DISTRIBUTION
SITE ROAD
DM20 1TW

Certificate of Analysis

Name: 1,1,1,2-tetrafluoroethane

Synonyms: HFA 134a
Propellant 134a
Zephex 134a
Norflurane

Grade: Pharmaceutical

Printed 14-Aug-2020

Sample Ref No.: 221402 Batch No.: RB20123-4

Container: GL1 Date Analysis Started: 12-Aug-2020
ID No(s).: 160345-6 Date of Manufacture: 02-Aug-2020
Order No: 11100012345
Tag Seal No(s).: 123456 987654 Customer Reference: CUST-ABC

Specification / Issue: GCK134PGC15 / 113 Sample Spec. Status: Pass

Component	Result Value	Specification	Status
Identity by I.R.	Agrees With Std Spectra	Agrees With Std Spectra	Pass
Identity by G.C.	Agrees With Std Chromatogram	Agrees With Std Chromatogram	Pass
Specified Related Impurities			
125	N/D	<=3 ppm w/w	Pass
22	N/D	<=3 ppm w/w	Pass
12	N/D	<=3 ppm w/w	Pass
124	0.1 ppm w/w	<=3 ppm w/w	Pass
133a	N/D	<=3 ppm w/w	Pass
12B1	N/D	<=3 ppm w/w	Pass
115	N/D	<=3 ppm w/w	Pass
143a	N/D	<=10 ppm w/w	Pass
114	N/D	<=3 ppm w/w	Pass
114a	N/D	<=3 ppm w/w	Pass
134	50.5 ppm w/w	<=90 ppm w/w	Pass
Unsaturated Impurities			
1243zf	0.2 ppm w/w	<=5 ppm w/w	Pass
1122	0.5 ppm w/w	<=5 ppm w/w	Pass
C-1122a	0.1 ppm w/w	<=5 ppm w/w	Pass
T-1122a	N/D	<=5 ppm w/w	Pass
T-1131	0.2 ppm w/w	<=5 ppm w/w	Pass
1131a	N/D	<=5 ppm w/w	Pass
1112a	N/D	<=5 ppm w/w	Pass
1123	N/D	<=5 ppm w/w	Pass
1234yf	N/D	<=5 ppm w/w	Pass
1225ye	N/D	<=5 ppm w/w	Pass
1122a	0.1 ppm w/w	<=5 ppm w/w	Pass
Total Unsaturates	1.0 ppm w/w	<=5 ppm w/w	Pass

SAMPLE

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Sample Ref No.:	221402	Batch No.:	BR20123-4
Container:	GLI	Date Analysis Started:	12-Aug-2020
ID No(s).:	100345-6	Date of Manufacture:	02-Aug-2020
		Order No:	1110012345
Tag Seal No(s).:	123456 987654	Customer Reference:	CUST-ABC
Specification / Issue:	GCK134PGC15 / 113	Sample Spec. Status:	Pass

Component	Result Value	Specification	Status
Any Other Saturated Impurities			
218	N/D	<=3 ppm w/w	Pass
32	N/D	<=3 ppm w/w	Pass
C-318	N/D	<=3 ppm w/w	Pass
152a	0.3 ppm w/w	<=3 ppm w/w	Pass
263fb	N/D	<=3 ppm w/w	Pass
40	N/D	<=3 ppm w/w	Pass
iso-butane	N/D	<=3 ppm w/w	Pass
31	N/D	<=3 ppm w/w	Pass
123	N/D	<=3 ppm w/w	Pass
123a	N/D	<=3 ppm w/w	Pass
11	N/D	<=3 ppm w/w	Pass
132b	N/D	<=3 ppm w/w	Pass
245cb	N/D	<=3 ppm w/w	Pass
227ea	N/D	<=3 ppm w/w	Pass
Total Other Saturated Impurities	0.3 ppm w/w	<=10 ppm w/w	Pass
Total Unknowns	N/D	<=3 ppm w/w	Pass
Total Organics	55.6 ppm w/w	<=100 ppm w/w	Pass
134a Purity	99.99481 % w/w	>=99.99 %wt	Pass
Other Tests			
Water	3 ppm w/w	<=10 ppm w/w	Pass
Appearance	Clear & Colourless	Clear & Colourless	Pass
High Boiling Impurities	<0.01 % v/v	<=0.01 % v/v	Pass
Malodour	No Malodour Present	No Malodour Present	Pass
Halides	Test Pass	Test Pass	Pass
Acidity as HCl	<0.1 ppm w/w	<=0.1 ppm w/w	Pass
Involatile Residue	<1 ppm w/w	<=5 ppm w/w	Pass
Non-absorbable gases	0.3% v/v	<=1.5% v/v	Pass

We certify that this material has been analysed and conforms to the Zephex 134a Specification.
The product was analysed at the Medical Propellants Laboratory, Rocksavage Site, Runcorn, Cheshire using European Pharmacopeia equivalent methods and if tested would comply with the Norflurane specification.

The product was manufactured at the Zephex 134a Plant, Rocksavage Site, Runcorn, Cheshire.
QAD Tel.: +44 (0)1928 514824 or 4689.

Expiry date of this batch is August 2025

Issued By **Name:**..... **Signature:**..... **Date:**.....
Laboratory Analyst

Approved By : **Name:**..... **Signature:**..... **Date:**.....

Position: .....

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Appendix 2 - Batch CofA & Cover Sheet Example

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Certificate of Analysis

Name: 1,1,1,2-tetrafluoroethane

Synonyms: HFA 134a
Propellant 134a
Zephex 134a
Norflurane

Grade: Pharmaceutical

Printed	**14-Oct-2020**		
Sample Ref No.:	**223159**	**Batch No.:**	**RB20607-3**
Container:	**935kg Drum x 4**	**Date Analysis Started:**	**07-Oct-2020**
ID No(s).:	**See Cover Note**	**Date of Manufacture:**	**26-Sep-2020**
		Order No:	**1110016930**
Tag Seal No(s).:	**See Cover Note**	**Customer Reference:**	**70700**
Specification / Issue:	**GCK134PGC15 / I13**	**Sample Spec. Status:**	**Pass**

Component	Result Value	Specification	Status
Identity by I.R.	Agrees With Std Spectra	Agrees With Std Spectra	Pass
Identity by G.C.	Agrees With Std Chromatogram	Agrees With Std Chromatogram	Pass
Specified Related Impurities			
125	N/D	<=3 ppm w/w	Pass
22	N/D	<=3 ppm w/w	Pass
12	N/D	<=3 ppm w/w	Pass
124	N/D	<=3 ppm w/w	Pass
133a	N/D	<=3 ppm w/w	Pass
12B1	N/D	<=3 ppm w/w	Pass
115	N/D	<=3 ppm w/w	Pass
143a	N/D	<=10 ppm w/w	Pass
114	N/D	<=3 ppm w/w	Pass
114a	N/D	<=3 ppm w/w	Pass
134	27.8 ppm w/w	<=90 ppm w/w	Pass
Unsaturated Impurities			
1243zf	0.2 ppm w/w	<=5 ppm w/w	Pass
1122	0.6 ppm w/w	<=5 ppm w/w	Pass
C-1122a	0.2 ppm w/w	<=5 ppm w/w	Pass
T-1122a	N/D	<=5 ppm w/w	Pass
T-1131	0.4 ppm w/w	<=5 ppm w/w	Pass
1131a	N/D	<=5 ppm w/w	Pass
1112a	N/D	<=5 ppm w/w	Pass
1123	N/D	<=5 ppm w/w	Pass
1234yf	N/D	<=5 ppm w/w	Pass
1225ye	N/D	<=5 ppm w/w	Pass
1122a	0.2 ppm w/w	<=5 ppm w/w	Pass
Total Unsaturates	1.4 ppm w/w	<=5 ppm w/w	Pass

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Sample Ref No.:	**223159**	**Batch No.:**	**RB20607-3**
Container:	**935kg Drum x 4**	**Date Analysis Started:**	**07-Oct-2020**
ID No(s).:	**See Cover Note**	**Date of Manufacture:**	**26-Sep-2020**
		Order No:	**1110016930**
Tag Seal No(s).:	**See Cover Note**	**Customer Reference:**	**70700**
Specification / Issue:	**GCK134PGC15 / I13**	**Sample Spec. Status:**	**Pass**

Component	Result Value	Specification	Status
Any Other Saturated Impurities			
218	N/D	<=3 ppm w/w	Pass
32	N/D	<=3 ppm w/w	Pass
C-318	N/D	<=3 ppm w/w	Pass
152a	0.3 ppm w/w	<=3 ppm w/w	Pass
263fb	N/D	<=3 ppm w/w	Pass
40	N/D	<=3 ppm w/w	Pass
iso-butane	N/D	<=3 ppm w/w	Pass
31	N/D	<=3 ppm w/w	Pass
123	N/D	<=3 ppm w/w	Pass
123a	N/D	<=3 ppm w/w	Pass
11	N/D	<=3 ppm w/w	Pass
132b	N/D	<=3 ppm w/w	Pass
245cb	N/D	<=3 ppm w/w	Pass
227ea	N/D	<=3 ppm w/w	Pass
Total Other Saturated Impurities	0.3 ppm w/w	<=10 ppm w/w	Pass
Total Unknowns	N/D	<=3 ppm w/w	Pass
Total Organics	29.5 ppm w/w	<=100 ppm w/w	Pass
134a Purity	99.99705 % w/w	>=99.99 %wt	Pass
Other Tests			
Water	2 ppm w/w	<=10 ppm w/w	Pass
Appearance	Clear & Colourless	Clear & Colourless	Pass
High Boiling Impurities	<0.01 % v/v	<=0.01 % v/v	Pass
Malodour	No Malodour Present	No Malodour Present	Pass
Halides	Test Pass	Test Pass	Pass
Acidity as HCl	<0.1 ppm w/w	<=0.1 ppm w/w	Pass
Involatile Residue	<1 ppm w/w	<=5 ppm w/w	Pass
Non-absorbable gases*	<=1.5% v/v	<=1.5% v/v	Pass

The drums that this certificate covers were filled from ISO tank 104477-1. The data for this certificate has been transcribed from the analysis of the ISO tank.

The product was analysed at the Medical Propellants Laboratory, Rocksavage Site, Runcorn, Cheshire using European Pharmacopeia equivalent methods and if tested would comply with the Norflurane specification.

*A property of the vapour phase of a container. The host tank contained <=1.5% v/v; any containers filled from this will also contain <=1.5% v/v non-absorbable gases.

The product was manufactured at the Zephex 134a Plant, Rocksavage Site, Runcorn, Cheshire.
QAD Tel.: +44 (0)1928 514824 or 4689.

Expiry date of this batch is September 2025

Issued By
Laboratory Analyst **Name:**..... **Signature:**..... **Date:**.....

Approved By : **Name:**..... **Signature:**..... **Date:**.....

Position: .....

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Re : Order Number : 1110016930
Product : Zephex 134a
Quantity : 935 kg Drums x 4

The Certificate of Analysis attached gives the analysis results for the ISO tank from which the following drums were filled.

We certify that the drums listed below were filled from ISO tank 104477-1 (RB20607-3).

Drum No.	Tag Seal No.
19877	157565 157566
18912	157563 157564
20371	157561 157562
19338	157558 157555

Name..... Signature.....

Position..... Date.....

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Amendments from previous issue:

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