Comment Response Document (CRD) to ESF-F25.1443-01 Issue 1 on

"Passenger Breathable Gas Mix Supplemental System "

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SUMMARY OF THE OUTCOME OF THE CONSULTATION

56 Comments has been recorded for this Public Consultation, from which 15 initiated by authorities. Several comments are related to the subparagraph (h) in the MoC to the ESF and below a generic reply to that is presented.

Generic reply describing the modification of the MOC subparagraph (h).

Following the review of received comments about the MOC to ESF paragraph (h) dealing with the consideration of the subject with health conditions, EASA further investigated the possible mean of compliance approaches and came to the following conclusions:

1) **EASA agrees that the extrapolation of the physiological response of a person suffering from COPD (or any other identified health issue) with healthy test subjects would have limitations. EASA will accordingly amend sub-paragraphs (c) and (h) of the MOC to ESF by requiring the testing of subjects with some health conditions.**

2) **COPD can be considered a major issue when those persons are exposed to hypobaric environments and also considering the new gas mix, along with some other disorders either respiratory or cardiovascular, such as Asthma, Congestive Heart Failure, Bronchiectasis, Tuberculosis, Obliterative bronchiolitis, Diffuse Panbronchiolitis, Pneumothorax, Pulmonary Thromboembolism...**

   Consequently, the amended paragraph (h) of MOC to ESF now refers to specific medical conditions (respiratory disorders such as Chronic Obstructive Pulmonary Disease (COPD), but not limited to COPD and cardiovascular disorders) to be considered for human subject testing. It is also clarified that Different degrees and severity of the unhealthy conditions should be tested. Such conditions should allow flight travel without any supplemental medical oxygen,

3) **These patients affected by the above-mentioned medical conditions may have CO2 retention and reduced CO2 ventilatory response. PaCO2 falls when a person hyperventilates. Respiratory drive is very sensitive to level the of PaCO2, such drop in PaCO2 can reduce respiratory drive to a point where the subject will become apneic. Apnea will then cause the PaCO2 level to rise due to continuous metabolic production of CO2. Measurement of PaCO2 is necessary to get objective data of the impact of mixed gases breathing (O2 + CO2) in a subject that might be hypercapnic due to the underlying disease. By providing mix gases (CO2 and O2), CO2 might increase the level of hypercapnia and consequently respiratory acidosis.**
   Evaluation/measurement of PaCO2 has a major clinical value that must be considered in the definition of the testing.
   The PaCO2 levels should be measured in order to ensure the safe range of CO2 that might be associated to the physiological response to altitude exposure and monitor any

potential hyperventilation (to be measured and evaluated in the context of the clinical situation of the patient).
(h) will be amended to require the measurement and monitoring of the subject PaCO2 (Carbon dioxide blood pressure) or equivalent parameter (such as transcutaneous carbon dioxide measurement) all along the test duration.

4) **It shall be ensured that adequate emergency measures are set in place and agreed with the Ethical committee to ensure that the exposure of such subjects with medical conditions to high altitude conditions achieving safe testing. The need for such measure is now captured in the paragraph (h)**

5) **The scale used to monitor the presence and severity of symptoms should be adapted as the scale defined in (g) of the current MOC to ESF is more relevant to heathy population. The modified Medical Research Council (mMRC) dyspnea scale (Grade 0 strenuous exercise till Grade 4 breathless when dressing or undressing) or the validated Multidimensional questionnaires such "as St George´s Respiratory Questionnaire" or the "CAT Assessment" could be used and have been added in the paragraph (h)**

6) **The number of test subjects with medical conditions should be statistically justified. This aspect is now captured in the amended paragraph (h) of the MOC to ESF**

INDIVIDUAL COMMENTS AND RESPONSES

GENERAL COMMENTS

Commenter: LBA, comment #6

LBA has no comments

Response:

NOTED

Commenter: Jürgen Wenzel, comment #7

As a general impression, the paper does not really describe a certification approach but gives general steps to define a system which can subsequently undergo a certification.

Response:

NOT ACCEPTED

– EASA does not agree with the comment.

The objective of this Equivalent Safety Finding (ESF) / Means of Compliance (MoC) consultation paper is not to define a system but to propose a certification approach which would be equivalent to the compliance to CS25.1443(c) by establishing:

- **Compensating/equivalent safety factors when the hypoxia protection performance does not rely on the oxygen tracheal partial pressure assessment, or a breathable gas mix other than O2/Air is used.**
- **Specific means of compliance.**

EASA will not change the text.

Commenter: Nicolas BLOCH, comment #23

1. General impression is that the document posted for review is mostly designed for some novel passenger breathable gas mix supplemental system performance **investigation** purposes
2. ELOS demonstration or ESF both require that a **clearly specified system** be proven to comply with **established minimum requirements** on the basis of **fully defined Pass/Fail criteria**
3. Minimum novel **system description**, including gas mixing and mix dispensing subsystems, is needed to support the proposed evaluation approach clarification
4. Reduced response to the positive carbon dioxide effect is tentatively looked at on the basis of equivalent SpO2 assessment but **adverse response to CO2** inhalation is not substantially researched
5. Test Set Up Section does not cover the **deep desaturation scenario** described in Section 3.c)

Response:

PARTIALLY ACCEPTED.

- **About comment item (1): The commenter is right. This Equivalent Safety Finding (ESF) / Means of Compliance (MoC) consultation paper addresses a novel passenger breathable gas mix supplemental system. Nevertheless, the aim is not for investigation but to support an application for a certification of a new cabin supplemental system.**
- **About comment item (2): EASA agrees. The ESF provides requirements as compensating factors and the MoC proposes verifications means with pass/fail criteria,**
- **About comment item (3): EASA disagrees in the sense that the description of the system is not necessary to address the novelty & certification strategy for a system principle supplying a gas mix of O2 and CO2,**
- **About comment item (4): EASA partially agrees. The evaluation of the adverse effect of prolonged carbon dioxide inhalation is captured in the sub-paragraphs (3)(d)(e) of the ESF and (g)(h) of the MoC. Although the positive effect of carbon dioxide inhalation on healthy subjects exposed to high altitude conditions had been already experimented in the past in laboratory conditions, EASA acknowledges that there is a limited experience feedback on such technology and the population travelling by flight is large with different profiles (physical, physiological, health…), due to that EASA recommend to perform additional tests with health conditions criteria.**
- **About comment item (5): The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems without providing any test set-up guidance.**

EASA will change the text to address comment item (4)

Commenter: Aeronautical Data Systems Inc., comment #30

This document needs to include the following:

There needs to be a distinction made between requirements for Cabin crew members and passengers since the cabin requirements should include some form of work load and an SPO2 level needed to maintain that level of work at altitude.

There is an increase in male passengers and cabin/flight crew to wear facial hair (beards). There should be mention that subjects with beards will be utilized in this testing or a restriction placed on this mask that requires only clean shaven occupants permitted to fly on aircraft with these type maskes installed.

Response:

NOT ACCEPTED

About 1st comment item (cabin / passenger requirement distinction): EASA disagrees with the comment as there is a single requirement applicable to the minimum mass flow supplemental oxygen delivered by fixed system for passengers and cabin crew members: CS25.1443(c). A different requirement would only apply for cabin crew portable oxygen.

About 2nd comment item (users with facial hair/beard): This comment would be valid for any type of mask and is already addressed in the SAE AS8025 (Passenger Oxygen Mask) with the following note in §5.9 Mask Performance.

NOTE: When used by cabin crew members, physically active individuals with critical duties to perform, the performance of this equipment may be compromised when used in conjunction with facial hair that interferes with the seal between the mask and skin.

EASA will not change the text of the ESF and MoC.

Commenter: FOCA (Switzerland), comment #32

Thank you for the opportunity to comment. There are no objections from the FOCA side, the project is expected to bring positive benefits.

Response:

NOTED

Commenter: Swedish Transport Agency, Civil Aviation Department (Transportstyrelsen, Luftfartsavdelningen), comment #33

General

Thank you for the opportunity to comment on 'Passenger Breathable Gas Mix Supplemental System' Issue 01. Please be advised that there are no comments from the Swedish Transport Agency.

Response:

NOTED

Commenter: DGAC FR, comment #34

DGAC France thanks EASA for the consultation.

It is DGAC's understanding that the discussed ESF CRI may have to be complemented with an IM/MoC CRI in order to clarify EASA's expectations with respect to CS 25.1529 compliance demonstration. Indeed, the applicant should define acceptable instructions for operators to determine the amount of gaseous mix to be carried in order to keep the airplane in an airworthy state and meet CAT.IDE.A.235 objectives (operational rules do not refer to gaseous mixes but only to oxygen).

Response:

NOT ACCEPTED.

The objective of this Equivalent Safety Finding (ESF) / Means of Compliance (MoC) consultation paper is to address an equivalent compliance to CS25.1443(c) (minimum mass flow of supplemental oxygen).
As the CS25 only specifies the O2 flow requirements to meet the hypoxia protection while the operational regulation (CAT.IDE.A.235) defines the quantity of O2 to be loaded on the airplane in accordance with the operated routes. Consequently, it was not intended to adapt the ESF/MoC to address the operational CO2 quantity aspect.

EASA will not change the text of the ESF and MoC.

Commenter: FAA, comment #45 medicXX

Comment summary:
The FAA agrees that Paragraph 3 (Compensating Factors), sub-paragraphs (a) through (c) are consistent with previously issued equivalent level of safety (ELOS) determinations regarding the use of "optimized" oxygen delivery systems. The FAA also recognizes that sub-paragraphs (d) and (e) are unique to the proposed system since carbon dioxide (CO2) gas will be added to the supplemental oxygen system to create a breathable gas mixture. . The FAA understands that the intent of these proposed Compensating Factors is to try and substantiate the proposed system for healthy passengers and for passengers with existing medical conditions such as chronic obstructive pulmonary disease (COPD). However, there are many medical unknowns related to this proposal. Previous research and testing shows that the human physiological response following a rapid decompression has many variables. Although CO2 plays an important role in regulating blood pH, respiratory drive, and the affinity of hemoglobin for oxygen (which in turn becomes important in the treatment of hypoxia), increased concentrations of CO2 in a gas mixture can have a negative effect. Carbon dioxide concentrations exceeding the 0.5% limit identified in 14 CFR 25.831(b) may cause other negative health effects depending on exposure duration for both healthy and medically impaired passengers. At this time, it is unclear that a test using a healthy research participant can adequately simulate a passenger with even mild COPD. As such, EASA may want to consider convening a medical panel to discuss such testing in detail if the intent is to ensure adequate protection and that there are no negative effects for passengers with COPD or other respiratory medical issues.

A modification of the published text is: Not requested

Response:
NOTED.

ABBREVIATIONS

Commenter: in flight physiological protection, comment #2
Page 2 (abbreviations) : in « SpO2 », « p » means “pulse” (not “peripheral”) , which is a mode of measure of SaO2 (“a” being “arterial”)
Response: **ACCEPTED** **–The text in the paragraph (a) of the MOC part will be changed and it will be clarified that ”p“ in « SpO2 » means “pulse”.**

Commenter: Jürgen Wenzel, comment #8 medicXX
The “p” in SpO2 does not mean “peripheral”, but indicates that this is a measurement of ARTERIAL blood saturation (SaO2), assessed by pulse oximetry. SaO2 is by definition a central parameter, not peripheral; SpO2 reflects the alveolar gas exchange about 10 s in the past, the resulting arterial oxygen saturation in the blood is frozen until the blood arrives at the SpO2 sensor.
Response: **ACCEPTED** **See response to comment #2**

Commenter: Safran Aerosystems, comment #11 medicXX
P.2, ABBREVIATIONS: SpO2 is rather blood oxygen saturation measured by pulse oximetry than “peripheral level”
Response: **ACCEPTED** **See response to comment #2**

Commenter: Nicolas BLOCH, comment #25 medicXX
SpO2: "p" stands for "pulsed" and not "peripheral"
Response: **ACCEPTED** **See response to comment #2**

Commenter: SAFRAN AEROSYSTEMS, comment #35 medicXX

Page 2 (abbreviations) : in « SpO2 », « p » means “pulse” (not “peripheral”) , which is a mode of measure of SaO2 (“a” being “arterial”)

Response:
ACCEPTED
See response to comment #2

Commenter: in flight physiological protection, comment #36 medicXX

Page 2 (abbreviations) : in « SpO2 », « p » means “pulse” (not “peripheral”) , which is a mode of measure of SaO2 (“a” being “arterial”)

Response:
ACCEPTED
See response to comment #2

Commenter: in flight physiological protection comment #37 medicXX

Page 2 (abbreviations) : in « SpO2 », « p » means “pulse” (not “peripheral”) , which is a mode of measure of SaO2 (“a” being “arterial”)

Response:
ACCEPTED
See response to comment #2

IDENTIFICATION OF ISSUE

Commenter: in flight physiological protection, comment #3 medicXX

Page 2: Identification of the issue:
"The system uses a breathable gas mix based on oxygen and carbon dioxide. The carbon dioxide allows to improve the oxygen processing by blood and lungs and increases the cerebral blood flow. These physiological effects help to maintain a high blood oxygen saturation and allow a reduction in the oxygen flow below the values specified in the CS 25.1443(c)."
Please be careful to not mix "cerebral blood flow" and "PO2" in cerebral tissues:
1) The oxygen supply to cells is dependent of PO2.
2) There is an interaction between PO2 and PCO2 on SaO2 (or SpO2).
Human tests in France for the 80's, in altitude chamber, then in mountains (Bolivia), with variations of PO2 and/or PCO2, demonstrated the main factor of variations of carotid blood flow was PO2 (or was close exclusively)

In the reference to JAR 25.831: it's necessary to refer PCO2 physiological effect in terms of partial pressure and not in %. As a reference value, 3 kPa (3% at SL) is OK.

Response:
NOTED
–EASA does not see the need to change the text.

About the comment item related to JAR 25.831: The "not to exceed" CO2 concentration specified by JAR/CS25.831(b) is reminded in the Identification of Issue for the ESF.
Quote
-The CS25.831(b) requires the carbon dioxide concentration during flight in the compartments normally occupied by passengers or crew members, to never exceed harmful/hazardous levels such as 0.5% by volume sea level equivalent.
-The JAR 25.831(b) at Change 15 or before defined in the past a carbon dioxide concentration greater than 3% by volume sea level equivalent as hazardous.
Unquote

Commenter: Jürgen Wenzel, comment #9 medicXX

The remark on cerebral blood flow is in accordance with common textbook knowledge, the influence of CO2 as one of the main factors on Hemoglobin oxygen binding needs a more detailed look. SaO2 is increased with low CO2 in the lungs, which is promoted by hyperventilation during hypoxia exposure. Second, each hPa CO2 less is substituted by O2 (Alveolar Gas Equation). Therefore, CO2 removal in the lungs, together with increase of blood circulation, is the first line of defence under acute hypoxia exposure, allowing improved operation of e.g. motor systems for self rescue or maintenance of life in the extreme. Superior cerebral performance is neither necessary nor important for a seated passenger, whose main intention would be to arrive at his/her destination alive and without permanent damage. Furthermore, if the intended limit in current regulations, altitude exposure to a

maximum of 10 kft during diversion, no hyperventilation effect is present, and no additional CO2 is needed to counteract any negative effect of hypocapnia.

Response:
NOTED.
no change to the text is considered necessary

Commenter: Safran Aerosystems, comment #12

P.2, IDENTIFICATION OF ISSUE, first and third paragraph.: …passenger oxygen system, system proposed…: a system is not described, only described an unspecific breathable gas mix of >0.5 (3) % by volume CO2 and O2 ǂ minimum mass flow acc. to CS 25.1443(c).

P.2, IDENTIFICATION OF ISSUE, fourth paragraph.: …These physiological effects help to maintain a high blood oxygen saturation and allow a reduction in the oxygen flow below the values specified in the CS 25.1443(c)…: If this is the same for a long-term application is not clear, and needs to be demonstrated by testing.

Response:
NOT ACCEPTED.

- **About comment item (1 – system description): EASA disagrees in the sense that the description of the system is not necessary to address the novelty & certification strategy for a system principle based on a supplied gas mix of O2 and CO2.**
- **About comment item (2- long-term usage): The long term and representative usage is already addressed and needs to be demonstrated in accordance with (3)(d) of the ESF consultation paper.**

Commenter: SAFRAN AEROSYSTEMS, comment #14

Attachment #1
Highly Critical: It is proposed to use SPO2 value to assess the performance of the new system. However it is important to know that the measured SPO2 criteria is influenced by the PCO2 impact on barcroft curve. See here joined the chart showing how dissociation curve used by SPO2 measurement systems is influenced by PCO2.
Or in other words: **all SPO2 measurements** made here with the new system artificially increasing PCO2 **will be wrong** if nothing is done about it.

Response:
NOT ACCEPTED.
The Accuracy of the proposed methodology is deemed acceptable. EASA will not change the text.

Commenter: Nicolas BLOCH, comment #26

Attachment #2

Provided elevated CO2 concentration in the lungs shifts the oxyhemoglobin dissociation curve to the right (see attachment), stating that "*The carbon dioxide allows to improve the oxygen processing by blood and lungs*" needs further elaboration

Response:

NOTED

– no change to the text is considered necessary.

Justification. The capability of the carbon dioxide to improve the oxygen processing by blood and lungs has been validated by tests on human subjects in the past and is also documented in the literature.

See also reply to comment #14

Commenter: in flight physiological protection, comment #37 medicXX

Page 2: Identification of the issue:
"The system uses a breathable gas mix based on oxygen and carbon dioxide. The carbon dioxide allows to improve the oxygen processing by blood and lungs and increases the cerebral blood flow. These physiological effects help to maintain a high blood oxygen saturation and allow a reduction in the oxygen flow below the values specified in the CS 25.1443(c)."
è Please be careful to not mix "cerebral blood flow" and "PO2" in cerebral tissues:
o 1) The oxygen supply to cells is dependent of PO2.
o 2) There is an interaction between PO2 and PCO2 on SaO2 (or SpO2).
Human tests in France for the 80's, in altitude chamber, then in mountains (Bolivia), with variations of PO2 and/or PCO2, demonstrated the main factor of variations of carotid blood flow was PO2 (or was close exclusively)

In the reference to JAR 25.831: it's necessary to refer PCO2 physiological effect in terms of partial pressure and not in %. As a reference value, 3 kPa (3% at SL only) is OK.

Response:

NOTED

– no change to the text is considered necessary.

Commenter: in flight physiological protection, comment #38

3 c :

Additional factor to be mentioned here as a root cause for hypoxia appearance is the delay to flush intra-pulmonary nitrogen, which is present at the beginning of the (quick) depressurization. Which is what is qualified Hyperacute / Suracute hypoxia.
Response: **NOTED** **– no change to the text is considered necessary.** **The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF CRI the same way in the past on previous projects for O2 supplemental systems without providing any additional details.**

INTRODUCTORY NOTE

Commenter: in flight physiological protection, comment #40
page 2, 4th §, 2nd line, 1st word: I propose “modify” instead of “improve”. We only hope the new device will “improve”.
Response: **NOTED** **– no change to the text is considered necessary.**

Commenter: in flight physiological protection, comment #41
Generally: the problem is not in the partial pressure of O2 but in the possibility to extract the needed oxygen mass from the blood, i.e. the product of arterio-venous difference of PO2 multiplied by blood flow.
Response: **NOTED** **– EASA position is that additional explanation is not necessary in the ESF/MOC.**

COMPENSATING FACTORS

Commenter: UK RAF Centre of Aviation Medicine, comment #1

Point 1: validity of peripheral blood oxygen saturation level

We would recommend that extreme caution is applied when attempting to certify an oxygen system using the measurement of peripheral blood oxygen saturation level (SpO2) alone. Especially during hypoxic conditions, SpO2 can lead to falsely reassuring results. For more information on this topic the reader is directed to:

Haddon A, Kanhai J, Nako O, Smith TG, Hodkinson PD, Pollock RD. *Cardiorespiratory responses to voluntary hyperventilation during normobaric hypoxia*. Aerosp Med Hum Perform. 2023; 94(2):59–65.

During aircraft oxygen system certification, a measure of end tidal or arterial gas measurement including blood carbon dioxide levels is usually required to interpret SpO2 values. When passenger oxygen system standards were originally developed, tests were developed to avoid the need for complex human trials, as such trials should only be conducted in centres that have experience of the limitations of the various monitoring techniques required. These measurements are particularly important when considering members of the public with medical conditions (such chronic obstructive pulmonary disease), for whom I note that an unvalidated extrapolation technique has been proposed.

Point 2: subatmospheric decompression sickness

Subatmospheric decompression sickness (DCS) is a potentially serious consequence of prolonged exposure to hypobaric conditions. The threshold for DCS is considered to be 18,000ft pressure altitude for a minimum 5-20 minutes, although usually it is rare below 21,000ft pressure altitude in fit and healthy individuals. We have seen significant decompression sickness following 30 minutes exposure to 18,000ft, and would caution against extended exposure for members of the general public (with a range of medical risk factors) to pressure altitudes above 18,000ft.

Response:
PARTIALLY ACCEPTED.

-About 1st comment item (certify an oxygen system using the measurement of peripheral blood oxygen saturation level (SpO2): The consideration of the SpO2 as a reference has been already successfully used in the past for the certification of passenger oxygen supplemental system with oxygen mass flow lower than those specified in the CS25.1443(c). Nevertheless, it is acknowledged that the novelty on this project relies in the use of CO2 to maintain high SpO2 reference values.
EASA agrees that the extrapolation technique is unvalidated and such technique will be accordingly removed from the paragraph(h). The text of the MOC to ESF will be also amended to require tests to be performed with human with different degrees and severity of health conditions and specific instrumentation in order to confirm the applicability of the new system for general public.

-About 2nd comment item (DCS and Exposure to high cabin altitude): Routes above Himalaya are already operated by airlines. In case of cabin depressurization conditions, aircraft would have to

level-off above the mountainous areas above 10.000 ft and up to 25.000 ft for a certain amount of time and aircraft occupants would be exposed to high cabin altitude while being protected by the supplemental oxygen system (Flight crew in accordance with CS25.1443(a)(b) O2 flow and Cabin crew/passengers in accordance with CS25.1443(c) O2 flow). Irrespective of the introduction of a new technology using CO2, Aircraft and Supplemental oxygen system offering high altitude operation capability (route operation and occupant hypoxia protection) have been already successfully certified in the past.

Commenter: in flight physiological protection, comment #4

Page 4, ESF, Compensating factors
3c:
Additional factor to be mentioned here as a root cause for hypoxia appearance is the delay to flush intra-pulmonary nitrogen, which is present at the beginning of the (quick) depressurization. Which is what is qualified Hyperacute / Suracute hypoxia.

Response:
NOTED
– no change to the text is considered necessary.

The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems without providing any additional details.

Commenter: in flight physiological protection, comment #5 medicXX

MOC Page 6 and "test set up"
(a) first line : delete "peripheral"
(b)
We need to be careful with the extension to 40,000 Ft. for a quick depressurization at high altitude resulting in Hyperacute / Suracute hypoxia, it is known that a very high O2% is needed (today: 100% with current systems) and therefore a very low CO2 %.
-> therefore only a bi-phasic architecture would make sense, which supplies 100% O2 for the first 2-3 minutes. And then a CO2 mixture at targeted holding altitude only.
(c) "in accordance with established industry practices" -> please also add "and in accordance with human experience ethic requirements"

(e) « panicking person » : please also indicate "and very anxious person" (to ensure "panick is understood in a proper way)
(f) Disagreed: the comparison will not respect the O2/CO2 equilibrium that we are studying here.
(g): also need to ensure that the proposed method does not impact DCS management, in the particular case of divers for exemple : would the PNO2 increase influence the DCS risk for them ?

(h)
"It should be demonstrated that the carbon dioxide addition still offers relatively positive benefit compared to healthy passengers." -> partially accepted

VO2 for the elderly : VO2 max decreases, but not their rest VO2 (which corresponds to their minimum physiological need). This is when VO2 max decreases below their rest VO2 that the patient passes away.

Page 8 : Second step:
Long term testing at 24,000 Ft would lead to potential DCS risk.
Instead, an equivalence can be expected by decrease of the O2 percentage of the mixture at 21 kft
Second step:
Long term testing at 24,000 Ft would lead to potential DCS risk.
Instead, an equivalence can be expected by decrease of the O2 percentage of the mixture at 21 kft

Response:

PARTIALLY ACCEPTED.

(a) Peripheral will be replaced with pulse

(b) Comment is noted but the aim of the CRI is to propose guidance material with pass /fail criteria and not to define a system architecture nor an operating principle.

(c) *"and in accordance with human experience ethic requirements"* will be added

(e)The "panicking person" is the worst-case situation, and this term was already used on a similar CRI applied on a former project (Oxygen supplemental system). The addition of "and very anxious" would not also change the intent of the test. It is proposed to use the same wording for consistency.

(f) The use of a chamber with hypoxic gas mixtures simulating high altitude has been removed from the CRI

(g) The objective of the test is to be as representative as possible of the real operational condition.

Any high-altitude sickness symptom will be recorded and evaluated to decide on the need to interrupt the test and conclude whether the system supports a safe continuation in depressurized condition and safe landing. Irrespective of the supplemental system technology type, when performing high altitude hypobaric testing:

- **a 100% O2 pre-breathing phase of the test subject prior to altitude ascent is usually considered to prevent decompression sickness symptoms.**
- **Also in accordance with AS8025 (§6.1.8) , ascent to 30.000 ft during hypobaric test is performed while wearing a pressure demand type mask and breathing 100% O2.**

(h) : Refer to the generic reply describing the modification of the MOC CRI subparagraph (h).
About (h) page 8 comment dealing with long term testing at 24.000 ft : The approach consisting in replicating by test the physiological response of a person suffering from COPD (or any other identified health issue) with healthy test subjects has been removed from the MOC to ESF. Consequently the altitude shift of +3000 ft above the targeted long exposure diversion altitude (21.000 ft) is not applicable anymore.

Commenter: Jürgen Wenzel, comment #10 medicXX

Paras a + b are common practice in all classical certifications, and also have been used in recent ESF procedures, making use of the corresponding SaO2 levels of 90 and 84%, resulting from air exposure to 10/14 kft (as derived from SAE AIR 822 as average values for a normal population).
However, it is quite clear that the 14 kft air equivalent is not suitable for any delayed emergency descent above 18.5 kft, which has been discussed with EASA representatives during the SAPOX study, and which has been clearly stated in the final report. It has been shown, that a 90% saturation can be maintained up to 33 kft, and at the same time still saving oxygen with conserving systems.

Para c: Clear pass/fail criteria have to be defined; "medical significance" is too unspecific.

Para d: To assess the validity of this statement, the amount of added CO2, "long", and the altitude level of diversion have to be specified.
Para e: "Adequate identification" is not outlined in this paper and will be an important issue for the validity of a planned certification.

Test Set Up, a) 1 + 2: Does this mean that two chamber runs will be performed? Common practice is to use a single chamber run and start with the highest altitude and then descend stepwise, assessing equilibrium saturation at each level. It is recommended to follow SAPOX conclusions and not use each individual's baselines to titrate oxygen, but take the above mentioned AIR 822 approach with special attention to interrupted emergency descents as outlined.
b): See my comments under "general"; any gas mix/performance parameters have to be specified before a certification can start.
c) + d): See my comments on a + b above; these are not "established industry practices".
e): It has to be shown, that high breathing minute volumes performed by machine do no change the gas composition of the resulting mix with ambient air.
f) Not acceptable; normobaric hypoxia is useful for the study of hypoxia effects, but not for the assessment of oxygen (+ CO2?) supplementation at altitude.
g) "Targeted operational use" and "longest exposure time" are not defined. As the LL questionnaire is used for AMS, which takes several hours to develop, this hints to an excessive expansion of diversion exposure which is not supported by established aviation medicine. Without details, this cannot be commented. Additionally, it may be doubted that LL and Borg as pure subjective data are really useful for the intention of this ESF; hard physiological data are preferable.
h) COPD is repeatedly mentioned as a critical factor in the population to be exposed to elevated CO2 levels. However, in the following outline to assess the interaction of COPD and a mix of O2/CO2, COPD is reduced to a simulation of oxygenation deficiency, without any approach to the main factor of the disease, i.e. hypercapnia. To even increase this already elevated adverse parameter, appropriate instruments must be defined to assure an adequate protection for this special fraction of the flying population. I do not depict from this para, how CO2 supplementation can be "justified" in these passengers.
Additionally, if really a diversion altitude of 21 to 24 kft is envisaged, there has to be a clear assessment of the corresponding factors. When talking about "long", the Decompression Sickness Risk is one of the important entities limiting such exposures

Response:
PARTIALLY ACCEPTED

(a) Noted. The test set up means of compliance is defined the same way on ESF/MOC CRI applied on previous project for O2 supplemental systems,
(b) Not accepted. The ESF CRI is written in a generic manner and does not specify any gas mix threshold.
(c) Noted. The wording is similar to existing ESF/MOC CRI applied on previous project for O2 supplemental systems.
(d) Noted. The wording is similar to existing ESF/MOC CRI applied on previous project for O2 supplemental systems.
(e) Noted
(f) The use of a chamber with hypoxic gas mixtures simulating high altitude has been removed from the CRI
(g) Partially accepted. The maximum exposure time allowance is addressed in d) of ESF & g) of MOC CRI. LL / BORG scale will be used to record the severity of symptoms (if any) and the physiological data of the test subjects are also measured during the test. PaCO2 (or equivalent transcutaneous carbon dioxide measurement) has been requested to be added in the list of test instrumentation in accordance with the amended (h).
(h) Extrapolation principle based on healthy subject is abandoned and h) has been updated to request test with subjects having specific medical condition.
Refer also to the generic reply describing the modification of the MOC CRI subparagraph (h).

Commenter: Safran Aerosystems, comment #13 medicXX

P.4, para. 3 c): …As an alternative, comparative data should be provided… compared to the use of systems where the minimum flow rate was determined assuming that a homogeneous gas mixture is delivered to the user…, should be changed to: … compared to the use of oxygen systems where the minimum oxygen flow rate was determined assuming that a homogeneous gas mixture is delivered to the user.

P.6, first paragraph: … Based on the novelty of the proposed design…: the system, design, equipment or concept should be described. All this wording is used throughout the text without any description.

P.6, para. (a) (1) and (2): the test chamber runs should always start from the highest altitude down to the lowest. This is in accordance with a real decompression scenario and also comply with industrial common praxis (e.g., AS8025).

P.6, para. (b): the order must be reversed, i.e., the means of compliance should be specified first and demonstrated during the ESF test, this appears to be an engineering test rather than a performance demonstration.

P.6, para. (c): …If new and novel test methods are used, statistical means should be provided to justify the quantity of test subjects… The right/left shift of the haemoglobin saturation curve (Bohr Effect) due

to PpCO2 variation shows the negative SaO2 sensitivity related to CO2. Testing should demonstrate acceptable SaO2 related PpCO2 tolerances for the individual human test subjects and which PpCO2 tolerances could be considered statistically insignificant for the flying population.

P.6, para. (e): Measuring PpO2 and PpCO2 in a mask during a breathing machine test is expected to show significant amplitude fluctuations depending on the mask system design. Due to the higher CO2 sensitivity of the human metabolism, it must be demonstrated that these CO2 fluctuations do not have a negative impact on the acceptable SaO2 saturation.

P.7, para. (f): the procedures acc. to para. (a) to (g) cannot be done by using hypoxic gas mixtures at the same time in order to simulate the altitude test chambers. Breathing under normobaric conditions and using particular hypoxic oxygen mixtures is in contradiction to simultaneously demonstrate other particular O2 + CO2 breathing gas mixtures to fulfil the baseline SpO2.

P.7, para. (h): e.g., asthma and COPD patients/passenger with typical reduced exhalation capability have increased CO2 levels in their lungs. Inhalation of additional CO2 appears not to be an appropriate procedure.

P8., para. (h), second step: the evidence of compliance for unhealthy passengers should also be demonstrated between 10,000 ft and 40,000 ft. in accordance with para. 3(a) – 3(d), not only for 21,000 ft. However, human subject tests at higher altitudes are always safety and ethically critical.

P8., para. (h), second step: the “unhealthy passenger” simulation approach is only considering the SpO2 aspect, not the more relevant aspect of a reduced breathing ventilation capability and an especially reduced exhalation capability.

P8., para. (h), second step, first bullet: mask system concept should be described, is this different from the mix gas system?

P8., para. (h), second step, first bullet: a COPD patient with a remaining ventilatory response might be partially simulated by the “unhealthy passenger” approach, still depending on the individual grade of e.g., COPD or asthma. But it is not clear and self-evident in how far a SpO2 simulation could simulate an interaction with hypercapnia. So, the made conclusion is ambiguous.

P8., para. (h), second step, second bullet: if the baseline of the unhealthy human subject is met, the comparison of the inhaled oxygen concentration within the mask (of the considered system, which is not described…) could give an indication that the CO2 + O2 mix gas concept and hypercapnic breathing might have an oxygen saving effect but only in case less oxygen is consumed in comparison with Curve B/Figure 1 of AS8025. But this is also depending on the mask type design (…which is not described).
It is very doubtful that it can be justified that a COPD patient with a severely reduced ventilatory response to hypercapnia would still benefit from a large oxygen concentration in order to ensure hypoxia protection, unless indirectly compared with already certified oxygen systems, e.g., in accordance with Curve B/Figure 1 of AS8025. But then, if the oxygen concentration was the same as required by Curve B/Figure 1 of AS8025, there is no oxygen saving existing, and still it cannot be assured that a COPD patient with a severely reduced ventilatory response to
hypercapnia would be able to exhale and ventilate a large oxygen concentration to ensure hypoxia protection. So, the made conclusion is ambiguous.

P8., para. (h), last paragraph: It is very suspect how and by which test procedure and by which means it should be justified that a subject with chronic obstructive pulmonary disease (COPD) could not suffer from any significant adverse effect resulting from prolonged carbon dioxide inhalation. This must be described in detail, because beside less mass flow of oxygen the mix with CO2 is the main deviation and cannot be justified indirectly by SpO2 consideration only. A definition for short term and long term should be given, and the related human subject test procedures and demonstration should be defined in detail.

Response:
PARTIALLY ACCEPTED

- **About comment 1 (P 4, para. 3 c): agreed. The text will be changed to *"As an alternative, comparative data should be provided to demonstrate that the time to return from lowered SpO2 levels to baseline or greater values using a breathable gas mix flow is either unchanged or medically insignificant compared to the use of oxygen systems where the minimum oxygen flow rate was determined assuming that a homogeneous gas mixture is delivered to the user)"***

- **About comment 2 (P.6, first paragraph): not accepted. EASA disagrees in the sense that the description of the system is not necessary to address the novelty & certification strategy for a system principle supplying a gas mix of O2 and CO2,**

- **About comment 3 (P.6, para. (a) (1) and (2)) and 4 (P.6, para. (b)): Not accepted. The text is unchanged compared to previous ESF and does not prescribe any test sequence order.**

- **About comment 5 (P.6, para. (c)): Partially accepted. This aspect is now captured in h) (1) with statistical justification of the number of test subjects with a medical condition.**

- **About comment 6 (P.6, para. (e)): noted. The text will not be changed.**
- **About comment 7 (P.7 para(f)): Accepted. The possibility of using an hypoxic gas to simulate high altitude conditions will be removed from the MOC.**
- **About comment 8 (P.7 & 8 para. (h)): Partially accepted. Refer to the generic reply describing the modification of the MOC CRI subparagraph (h).**

Commenter: SAFRAN AEROSYSTEMS, comment #15 medicXX

3 c)
As an alternative, comparative data should be provided to demonstrate that the time to return from lowered SpO2 levels to baseline or greater values using a breathable gas mix flow is either unchanged or medically insignificant compared to the use of systems where the minimum flow rate was determined assuming that a homogeneous gas mixture is delivered to the user.
Need to define "medically insignificant". For exemple: statistics shall shows equivalent gauss curves ? pass / failed criteria shall be defined before testing.

Response:

NOT ACCEPTED.

The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems. The previous ESF did not prescribe any criteria for the "medically insignificant" interpretation. In order to be consistent with the former ESF, the text will remain unchanged.

Commenter: SAFRAN AEROSYSTEMS, comment #16

d) The addition of carbon dioxide into the breathable gas mixture shall be assessed in terms of physiological effects to passengers for the maximum time of use during long depressurized diversion.
è Yes. This aspect need to be fully defined. Long term exposure: need to test and compare both baseline and new system on long duration. Current section g) page 7 could be more precise on acceptance / rejection criteria…
è Also, another time dependent aspect should be addressed: Safety during dynamic changes and resulting effects. And specified with a time parameter target (similar to the work done on SAPOX):
è Exemple from SaPOX study, section 13.2. : (https://www.easa.europa.eu/en/downloads/1229/en)
o For passengers and cabin crew members at rest, the minimum mass flow of supplemental oxygen required for each person at various cabin pressure altitudes may not be less than the flow required to maintain, while using the oxygen equipment (including masks) provided, the **following oxygen blood saturation levels for 95% of the population: (1) for short duration exposure (maximum 1 min), a minimum oxygen blood saturation level of 84%.**
o **(2) for long term duration3 exposure (above 1 min), a minimum oxygen blood saturation level of 90%.**

Response:
NOT ACCEPTED.

g) of the MOC indicates that the system must be tested and the human tested subjects exposed to the longest exposure time of the targeted operational use.

Physiological symptoms (if any) and physiological parameters will be monitored all along the test performance . In accordance with a)b) of MOC it will be also demonstrated that a minimum oxygen blood saturation above SPO2 baseline will be maintained during the time of diversion until 10,000 ft cabin altitude is reached. The retained SpO2 baseline at 10.000/14.000 ft breathing ambient air is in accordance with former certification practices and projects having used similar ESF/MOC CRI.

It should be noted that h) has been updated with the need to test subjects with specific medical conditions. The consideration of PaCO2 instrumentation (or equivalent transcutaneous carbon dioxide measurement) has been also added as a relevant physiological parameter to monitor.

Commenter: SAFRAN AEROSYSTEMS, comment #17

Critical: What is the baseline system to which the new system will be compared? any TSO C64 mask ? How to ensure baseline system is well set to establish the baseline SPO2 ? (as the new applicant is maybe not familiar with the conventional system and its potential specificities,n we need to ensure he will correctly determine the reference to which he will compare his system?)
At least, the resulting baseline SPO2 established here shall be compared to those established during former certification test campaigns: **data established here shall be in accordance with those established for 787 pulse and SaPOX** (https://www.easa.europa.eu/en/downloads/1229/en)**, not less.**

Response:
NOT ACCEPTED.

The baseline will be established in accordance with the paragraph (a) of the MOC by measuring the SpO2 of subjects breathing (without mask) standard ambient air at 10.000 and 14.000 ft.

Commenter: SAFRAN AEROSYSTEMS, comment #18 medicXX

3)
"The range of the population with a possible reduced response to the positive carbon dioxide effect and allowed to travel by flight without any additional medical oxygen equipment, shall be adequately identified, and it shall be demonstrated that this population is still adequately protected by the new system."
By nature of its concept, the new system will accelerate the user's metabolism. More specifically, it will increase ventilation rate and simultaneously heart rate. Just for heart rate example, it seems difficult to anticipate exactly which part of the population, which would survive the usual treatment, will here pass beyond the limit and encounter a heart attack?:
The increase in older passengers means also an increase in unhealthy persons flying**. In the U.S. 11.5% of the population has some type of heart disease, with over 27% of those 65-74 and over 37% of those 75 or older having some type of heart disease** … …In several observation studies, cardiac events caused 10%-20% of all in-flight incidents (Possick and Barry, 2004) and accounted for 12 of 15 in-flight deaths on the five major US air carriers over a one-year period ").
Source : https://www.faa.gov/data_research/research/med_humanfacs/cer/media/HealthEffectsVulnerablePassengers.pdf
-> -> Those people are not impacted by the current certified system which does not modify their heart rate. The new concept will impose their heart rate to accelerate. How many people amongst them will not pass this extra effort ???

Response:
NOTED.
The amended paragraph (h) of MOC to ESF now refers to specific medical conditions (respiratory disorders such as Chronic Obstructive Pulmonary Disease (COPD), but not limited to COPD and cardiovascular disorders) to be considered for human subject testing. It is also clarified that different degrees and severity of the unhealthy conditions should be tested. Such conditions should allow flight travel without any supplemental medical oxygen,

Refer also to the generic reply describing the modification of the MOC CRI subparagraph (h).

Commenter: SAFRAN AEROSYSTEM, comment #19

Test set up

In MOC test set up protocol, steps a.1) and a.2): it proposes to adjust the breathing mixture such that the test subject will show same SPO2 as in baseline.
Then in step b) it says the mixture concentration is recorded into the mask to later on determine and specify the system performances.
This creates 2 issues:
Recording of the concentration will not show how critical the new system is in terms of accuracy on the flow parameter: CO2 flow would need to be piloted by the ventilation flow rate, not only by the altitude (which is different from standard O2 protection today**!). It is totally user's dependent**, whereas current system is not.
The proposed protocol does not allow to establish the acceptable tolerance on the concentrations in this breathing mixture : this is a key parameter here:
ThThe current hypoxia protection made by supplemental oxygen only is based on a minimum and envelop approach -> one minimum flow fit all (and then there is no need for a maximum, it can be oversupplied with no drawback).
C
CRITICAL: With a CO2 administration it is different: each individual will need a specific / individualized flow. Not less (under-protection) , not more (hyperventilation / unstainable) -> for me the **current proposed CRI text does not allow to determine such a "one flow fit all" target flow, + with its acceptable tolerances.**

Response:
NOT ACCEPTED.

EASA disagrees with the comment (One flow fit all by using mix gases). The aim of CRI ESF/MOC is not to specify any system design by imposing a strict breathable gas mix flow but to ensure that the system will meet the certification requirement in an equivalent safe manner and adequate means of compliance will be used.

Refer also to the generic reply describing the modification of the MOC CRI subparagraph (h).

Commenter: SAFRAN AEROSYSTEMS, comment #20

Paragraph e): "To address the increased breathing rate of a panicking person, the equipment should deliver in the above mentioned paragraph (a)(1) and (a)(2) the specified breathable gas mix flow rate under the CS 25.1443(c) specified tidal volume and breathing rate, which may be demonstrated by tests using a breathing machine…"
Not understood. Does it mean that the test shall show that the system will deliver the flow determined in setp a.1) and a.2) and not being sensitive to a user's breathing rate increase due to a panic ? that's seems incompatible with a CO2 mixture concept which needs to maintain an accurate concentration rate whatever is the breathing rate.

Response:
NOT ACCEPTED

The test sequence & use of model in accordance with e) is to ensure that the system to be certified is able to maintain its performance & control the adequate gas mix and flow when exposed to an increased breathing rate of a panicking person.

Commenter: SAFRAN AEROSYSTEMS, comment #21

Step f) "For a subset of the test runs, the altitude chamber may be simulated on ground by using hypoxic gas mixtures. »
Due to the nature of the system, which will be based on a more complex breathing mixture, I'm not sure this is possible. In particular because of the impact on the dissociation curve which will influence the measurement tool with SPO2. And in the end it will for sure impair the measurement of concentration as proposed in step b). Only altitude testing would ensure propoer and reliable results.

Response: **Noted**
The possibility of using a hypoxic gas to simulate high altitude conditions was anyway removed from the MOC.

Commenter: SAFRAN AEROSYSTEMS, comment #22 medicXX

(g) the proposed method (BORG scale1 and the Lake Louise) are usually used for very long term exposure. They should not be able to capture any relevant symptoms here if we talk of test duration about a couple of hours. Alternate evaluation method will need to be identified.

Response:
NOT ACCEPTED

**It could be adequate to use such scales, "Borg Scale 1-10" and the "Perceived exertion and Lake Louise mountain sickness self questionnaire", but they are much more oriented to healthy personnel. The most recent Global Initiative for Chronic Obstructive Lung Disease (*GOLD Guidelines 2023*), includes the modified Medical Research Council (mMRC) dyspnea scale (Grade 0 strenuous exercise till Grade 4 breathless when dressing or undressing). Also Multidimensional questionnaires are validated such "St George´s Respiratory Questionnaire" or the "CAT Assessment". (*Mahler DA. Comparison of clinical dyspnea ratings and psychological measurements of respiratory sensation in obstructive airway disease. Am Rev respir Dis. 1987; 135: 1229-1233*), (*JM Ruiz et al. Comparison of several scales for assessing dyspnea daily activities in patients with chronic obstructive pulmonary disease. Archivos de bronconeumologia.2000; 36:25-28. DOI:10.1016/S0300-2896/15)30229-5*), (*Nisha Gupta et al. The COPD assessment test: a systematic review. ERJ 2014; 44:873-884. DOI 10.1183/09031936.00025214).*
Borg Scale 1-10 will be appropriate for testing "healthy passengers", but for "unhealthy passengers " it will be much more adequate mMRC dyspnea scale.**

The amended paragraph (h) of MOC to ESF now refers to specific medical conditions to be considered for human subject testing and the consideration of mMRC dyspnea scale has been added.
Refer also to the generic reply describing the modification of the MOC CRI subparagraph (h).

Commenter: Raphaelle AUJARD, comment #24 medicXX

f) It seems important to define which "subset of tests" can be used on ground hypoxic mixtures. The study of the Bohr effect does not seem compatible with hypoxic tests.

g) Use of the Borg scales and the Lake Louise self questionnaire does not seem relevant to me.

- The Borg Scale is a study of the heart rate. Hypoxia induction will increase the heart rate thus distorting the scale when evaluating it. When used in its questionnaire form, the risks of confusion secondary to hypercapnia could lead to false answers. This scale does not allow the effects of hypercapnia to be studied.
- Lake Louise is a questionnaire recommended for use only for higher exposures of 6 hours. It is therefore not an adapted scale in this context.

h) Given that the system uses the Bohr effect, it seems important to ask the question whether people suffering from pathologies modifying the structure of hemoglobin (such as sickle cell disease for example) will react in the same way as others to hypercapnia.

It would be interesting to study these same effects in people taking certain medications. One example is morphine analgesics or morphine derivatives which dose-dependently reduce the response of the respiratory centers to hypoxemic and hypercapnic stimuli and the respiratory rate.
There is also the question of side effects when taking vasodilator drugs such as nitrates or Sildenafil. By inducing vasodilation secondary to hypercapnia isn't there a risk?

A patient with COPD has impaired chemoreceptors.
It's recognized that the COPD patient suffers from an aggravation of his hypercapnia with the introduction of oxygen therapy. This principle depends on three mechanisms:
- Hypoxic stimulation cancellation
- Hypoxic vasoconstriction
- Haldan effect
There is interindividual variability and the proportion of these effects is unknown in medicine. Would it not be interesting to measure PCO2 with blood gases as well as SpO2?

In this study, we propose to reproduce the state of a sick passenger by inducing hypoxemia. In a healthy person, this hypoxemia will lead to compensatory hyperventilation and therefore hypocapnia. It seems to me unwise to want to study the consequences of hypercapnia in an already hypercapnic patient by first inducing a hypocapnia. The result will be false and lead to a significant bias.

Response:
PARTIALLY ACCEPTED

-The amended paragraph (h) of MOC to ESF now refers to specific medical conditions (respiratory disorders such as Chronic Obstructive Pulmonary Disease (COPD), but not limited to COPD and cardiovascular disorders) to be considered for human subject testing. It is also clarified that different degrees and severity of the unhealthy conditions should be tested. Such conditions should allow flight travel without any supplemental medical oxygen,
Refer also to the generic reply describing the modification of the MOC subparagraph (h).
-Less frequent situations associated to medication side effects in potential passengers are difficult to test. Medication is not considered in the ESF/MOC.

Commenter: Nicolas BLOCH, comment #27

- 3.c): *As an alternative, comparative data should be provided to demonstrate that the time to return from lowered SpO2 levels to baseline or greater values using a breathable gas mix flow is either unchanged or* ***medically insignificant*** *compared to the use of systems where the minimum flow rate was determined assuming that a homogeneous gas mixture is delivered to the user*: term "medically insignificant" sounds vague, clarification is needed, supported by fully characterized Pass/Fail criteria.

- 3.d): Respiratory and cardio-vascular physiological effects to passengers should indeed be assessed. Care should be taken to prove that breathing additional CO2 does not create any safety hazard to the flying population

3.e): *The range of the population with a possible* ***reduced response*** *to the positive carbon dioxide effect and allowed to travel by flight without any additional medical oxygen equipment, shall be adequately identified, and it shall be demonstrated that this population is still adequately protected by the new system*: same applies for the range of the population with a possible **negative response** to the positive carbon dioxide effect

- TEST SET UP (a): *The blood oxygenation level in human bodies is characterised by the stabilised* ***peripheral*** *blood oxygen saturation level (SpO2)*: **pulsed**

- TEST SET UP (1): Standard Human Testing Practice requires that subjects be exposed to the maximum altitude first

- TEST SET UP (2): Standard Human Testing Practice requires that subjects be exposed to the maximum altitude first

- TEST SET UP (b), see General Comments Section; ELOS demonstration or ESF both require that a **clearly specified system** be proven to comply with **established minimum requirements** on the basis of **fully defined Pass/Fail criteria:** novel system specification and qualification should be anticipated prior to ELOS/ESF initiation

- TEST SET UP (e), see General Comments Section; Minimum novel system description, including gas mixing and mix dispensing subsystems, is needed to support the proposed evaluation approach clarification: novel system lack of description prevents a sound breathing machine test validity assessment

- TEST SET UP (f): based on experience, hypoxic gas mixture challenge is different from altitude exposure challenge both in terms of physical and physiological effects

- TEST SET UP (g): what is the longest exposure time claimed for the new system ? Attention should be paid to mitigate DCS-related risks. It is suggested to monitor both breathing and heart rates during the whole exposure duration

TEST SET UP (h), see General Comments Section; Reduced response to the positive carbon dioxide effect is tentatively looked at on the basis of equivalent SpO2 assessment but adverse response to CO2 inhalation is not substantially researched: the proposed simulation scenario only covers passengers showing reduced response to the carbon dioxide effect. Nothing is proposed to simulate passengers showing

- adverse response to CO2 inhalation (COPD and asthma for instance)

- TEST SET UP (h): it is unclear whether the Bohr effect was taken into account when compiling exposure scenarios based on the PaO2 /SpO2 oxygen-haemoglobin dissociation curve

- TEST SET UP (h):*The inhaled oxygen concentration within the mask should be measured or derived with a reasonable accuracy from other measured parameters to be presented and agreed with EASA and should be compared with the oxygen concentration of the Curve B/Figure 1 of AS8025 at the target diversion altitude (21,000 ft). This allows to ultimately justify that a COPD patient with a severely reduced ventilatory response to hypercapnia would still benefit from a large oxygen concentration to ensure hypoxia protection without taking credit of the carbon dioxide effect*: seems **to negate the Oxygen savings claimed**

- TEST SET UP (h): *It should also be justified that a subject with chronic obstructive pulmonary disease (COPD) could not suffer from any significant adverse effect resulting from prolonged carbon dioxide*: see above, nothing is proposed to simulate passengers showing adverse response to CO2 inhalation

Response:
PARTIALLY ACCEPTED

Item 3c): Not accepted. The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems. The previous ESF did not prescribe any criteria for the "medically insignificant" interpretation. In order to be consistent with the former ESF, the text will remain unchanged.

Item 3d): Accepted. the amended paragraph (h) of MOC to ESF now refers to specific medical conditions (respiratory disorders such as Chronic Obstructive Pulmonary Disease (COPD), but not limited to COPD and cardiovascular disorders) to be considered for human subject testing. It is also clarified that Different degrees and severity of the unhealthy conditions should be tested. Such conditions should allow flight travel without any supplemental medical oxygen,

Item 3e): Accepted. 3e text will be amended: The range of the population with a possible reduced or adverse response to the positive carbon dioxide effect and allowed to travel by flight without any additional medical oxygen equipment, shall be adequately identified, and it shall be demonstrated that this population is still adequately protected by the new system.

Item test set-up (a): Accepted

Item test set-up (a)(1) and (a)(2): Noted with no text change.

Item test set-up (b). Noted – Noted with no text change.

Item test set-up (e) Not accepted - The description of the system in the CRI should not be necessary to address the novelty & certification strategy for a system principle supplying a gas mix of O2 and CO2.

Item test set-up (f) Agreed – the possibility to use an hypoxic gas to simulate high altitude conditions will be removed from the MOC. Paragraph f) will be deleted.

Item test set-up (g) NOTED: No changes to the text necessary.

Item test set-up (h): Accepted - Refer also to the generic reply describing the modification of the MOC subparagraph (h).

Commenter: Aeronautical Data Systems Inc., comment #29

In 3c state the baseline SPO2 levels you are looking to achieve.

In the test setup under G it is suggested to validate the affects of raised CO2 by asking the subjects in a self questionaire. Physiologically speaking would this be observed in the SPO2 which should be monitored at all times during this test?? Using SPO2 will be more accurate w/o doubt.

The second step mentioned on page 8 references a "flow normally required" there needs to be an SPO2 level to accompany this flow since that is the purpose of this document. In most documents this flow

would be all oxygen, in this case it could be a combination of CO2 and O2 which is meaningless unless there is a resultant SPO2 to conicide with this condition.

There should be some reference to a failed test based on the SPO2 of an applicant to maintain consciousness plus a minimum SPO2 that will invalidate the type mask used. For example "*All tests results must be used or can be discarded by a qualified review board*."

Response:
NOT ACCEPTED:

-About 3c) of ESF: Not accepted. The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems without providing any further requirement/guidance. The text will not be changed to keep consistency.

-About test set up of MOC: noted. SpO2 is expected to be monitored all along the exposure to depressurized conditions.

- About second step page 8 of MOC: Noted. the extrapolation approach of the physiological response of a person suffering from COPD (or any other identified health issue) with healthy test subjects is not pursued anymore.

Commenter: in flight physiological protection, comment #39

Page 6 (a) first line : delete "peripheral"
(b) We need to be careful with the extension to 40,000 Ft. for a quick depressurization at high altitude resulting in Hyperacute / Suracute hypoxia, it is known that a very high O2% is needed (today: 100% with current systems) and therefore a very low CO2 %.
-> therefore only a bi-phasic architecture would make sense, which supplies 100% O2 for the first 2-3 minutes. And then a CO2 mixture at targeted holding altitude only.

(c) "in accordance with established industry practices" -> please also add "and in accordance with human experience ment ethic requirements"
è concentration rate whatever is the breathing rate.

(e) « panicking person » : please also indicate "and very anxious person" (to ensure "panick is understood in a proper way)

(f) Disagree : the comparison will not respect the O2/CO2 equilibrium that we are studying here.

(g): also need to ensure that the proposed method does not impact DCS management, in the particular case of divers for exemple : would the PNO2 increase influence the DCS risk for them ?

(h)

"It should be demonstrated that the carbon dioxide addition still offers relatively positive benefit compared to healthy passengers." -> disagree.

VO2 for the elderly : VO2 max decreases, but not their standard / needed VO2. This is when VO2 max decreases below their needed VO2 that the patient passes away.

Second step:
Long term testing at 24,000 Ft would lead to potential DCS risk.
Instead, an equivalence can be expected by decrease of the O2 percentage of the mixture at 21 kft

Response:
PARTIALLY ACCEPTED

See response to Comment #5 (from *in flight physiological protection*)

Commenter: in flight physiological protection, comment #42 medicXX

Page 5, 1st line: "medically insignificant": "a statistical analysis of the tests have to demonstrate there is no significant difference between the 2 experiments: with the BL equipment versus the new one. The organization of the tests must provide the better mean to optimize the discrimination between the tests".

Response:
NOTED

The deep desaturation scenario (3)(c). This is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems without providing any further test guidance. The text will not be changed to keep consistency.
It should be also noted that the MOC (sub para (h)) will be updated to incorporate tests with subject having a medical conditions and the number of subject should be statically justified.

Commenter: in flight physiological protection, comment #43

Pages 4 and 5: "homogenous gas mixture". With the current passenger masks, the O2 is supply at the beginning of the inhalation; the inhaled gas is not homogenous.

Response:
NOT ACCEPTED

The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for O2 supplemental systems with the reference to "homogeneous gas mixture". The text will not be changed for consistency.

Commenter: in flight physiological protection, comment #4 medicXX

Page 6 (a): the hypothesis is made that the demonstration of the efficiency of the new device is afforded only with the measure of SpO2. Perhaps we can have other physiologically or psychophysiologically means of estimation (heart rate, scale of comfort, …).

Response:
NOTED

Heart rate/scale of comfort / blood pressure are considered as basic measurements and standard practices for hypobaric/high altitude testing. The text does not need to be changed.

SCOPE

Commenter: Aeronautical Data Systems Inc., comment #28

Add to the scope: It is the intent of this ELOS to replace the tradional prescriptive pressures and flows found in CS 25.1443(c) with performance based metrics i.e. SPO2 levels to determine safe minimum oxygen requirements for passengers during a decompression event.

Response:

NOTED

This information is already provided in the paragraph "identification of issue" of the ESF: *"CS 25.1443(c) specifies minimum mass flow requirements for passenger and cabin crew supplemental oxygen systems in terms of mean tracheal partial pressure, breathing rate, and tidal volume per breath. The system proposed is not designed to deliver oxygen per the minimum mass flow performance parameters specified in CS 25.1443(c)".*

The use of performance-based metrics such as SpO2 is detailed in the paragraph 3) Compensating Factors.

ESF-F25.1443-01

Commenter: Airbus-Regulations-SRg, comment #31

PAGE / PARAGRAPH / SECTION this comment is related to:
***Medical* compliance demonstration.**

Comment:

AIRBUS Commercial Aircraft has ***no comment*** to the proposed ESF-F25.1443-01.

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NOTE:
Airbus Document Classification: AMBER
Export Control: Not technical.

Response:
NOTED

Commenter: FAA, comment #46

Section 2, Scope, page 4
Comment summary:
The Scope should remove reference to TSO-C64a and SAE AS8025. Although these minimum performance standards are commonly used as a means of compliance for regulations such as 14 CFR 25.1443(c), the TSO and SAE documents are not themselves regulatory documents (i.e., requirements). As such, an ELOS to the TSO or corresponding SAE document is not needed. For clarity, discussion related to the TSO and corresponding SAE document should be kept to the Means of Compliance (MOC) section or used as background information, since these documents describe the traditional means of compliance to 14 CFR 25.1443(c).

Suggested resolution:
The Scope should remove reference to TSO-C64a and SAE AS8025, or add additional clarification that the ELOS determination only pertains to CS 25.1443(c). Modifications to previously used MOC's, such as TSO –C64 and AS8025 are described in the MOC section.

A modification of the published text is: Recommended

Response:
NOTED.
Nevertheless, the text will not be changed to maintain the consistency with the similar ESF dealing with minimum mass flow of passenger supplemental oxygen and used on previously certified optimized O2 system.

Commenter: FAA, comment #47

Section 3, Compensating Factors, sub-paragraph (c), page 4
Comment summary:
For clarification, the first sentence should refer to oxygen masks in general, not specifically to the "new supplemental system masks". The rapid drop in SaO2 following sudden exposure to a decompression is not specific to a mask, but rather a physiological response.

A modification of the published text is: Recommended

Response:
NOT ACCEPTED

The deep desaturation scenario (3)(c) is not specific to the novel technology and had been specified in an ESF the same way in the past on previous projects for optimized O2 supplemental systems. In order to be consistent with the former ESF, it is proposed to keep the text unchanged.

Commenter: FAA, comment #48

Section 3, Compensating Factors, sub-paragraph (c), page 4
Comment summary:
There is a sentence (lines 7 – 8) referring to "…ensuring a high flow rate of oxygen is available when the new system mask is first donned". Since the supplemental source is not considered "oxygen", this section should consistently use the term "breathable gas mix".

The FAA assumes that EASA did not intend to require two separate gas supply sources, one with oxygen for initial use, then a second mixed gas source of of oxygen and CO2 for use after some period of time.

Suggested resolution:
Sentence could be clarified by modifying as follows:

This could be accomplished by ensuring that a high flow rate of oxygen breathable gas mix is available when the new system mask is first donned such that the users SpO2 levels would fully recover to baseline values before using a lower flow of oxygen intended to sustain the user at the baseline value.

A modification of the published text is: Recommended

Response:
NOTED.

The ESF & MOC does not prescribe any system architecture (single / multiple gas source(s)) and consequently, it is preferred to keep the wording unchanged.

Commenter: FAA, comment #49

Section 3, Compensating Factors, sub-paragraph (d), page 5
Recommend this section be re-phrased to specify the criteria that must be met. For example, would just an assessment be acceptable regardless of the outcome?

In addition, the physiological effects should also consider potential cabin attendant use since most aircraft have oxygen masks located throughout the passenger cabin for use by cabin attendants, in addition to the oxygen masks located above cabin attendant seats.

Suggest that sub-paragraph (d) be changed to the following:
It shall be shown that the addition of carbon dioxide to the breathable gas mixture does not have any adverse physiological effects to passenger cabin occupants for the maximum time of use.

A modification of the published text is: Requested

Response:
Accepted.
The text of the final ESF has been updated accordingly.

Commenter: FAA, comment #50

Section 3, Compensating Factors, sub-paragraph (e), page 5
Comment summary:
The FAA understands that the intent of this section is to expand on the requirement specified in sub-paragraph (d), to ensure that passengers allowed to travel without the use of medical oxygen equipment are considered when performance of the proposed system is substantiated. As proposed, the paragraph makes the assumption that adding carbon dioxide to the supplemental oxygen system, which is typically nearly pure oxygen, has a positive physiological effect. The assumption may not be true and should be removed.

For clarification, we propose wording section (e) as follows:
The range of the population allowed to travel by flight without any additional medical oxygen equipment and who may have a reduced response to the addition of carbon dioxide to the supplemental mixed gas system, shall be adequately identified, and it shall be demonstrated that this population is still adequately protected by the new system.

A modification of the published text is: Recommended

Response:

ACCEPTED.

EASA will change the text clarifying that the range of the population allowed to travel by flight without any additional medical oxygen equipment and who may have a possible reduced or adverse

response to the positive carbon dioxide effect and shall be adequately identified, and it shall be demonstrated that this population is still adequately protected by the new system.

MoC to ESF-F25.1443-01

Commenter: FAA, comment #51

Test Setup, General comment, page 6
Comment summary:
The FAA understands that it is implicit in the proposed test set up that additional basic physiological measurements such as blood pressure, heart rate, respiration rate, etc. will be measured throughout the testing.

Suggested resolution:
Additional details should be added to the test protocol if the intent is for the test protocol to be all inclusive.

A modification of the published text is: Not requested

Response:
NOTED

Heart rate/scale of comfort / blood pressure are considered as basic measurements and standard practices for hypobaric/high altitude testing. The text does not need to be changed. The adequate list of measurement means shall be anyway agreed with the authority in the frame of the review of the applicant test protocol and prior to the human test campaign.

Commenter: FAA, comment #52 medicXX

Means of Compliance (MOC), Test Set Up, page 6
Comment summary:
There is no indication as to the minimum number of test subjects required.
In addition, sub-paragraph (f) does not identify either a percentage or other means of describing how large a subset of test runs (and thus the number of test subjects) can use ground test facilities with a hypoxic gas mixture in lieu of the altitude chamber.

Suggested resolution:
The minimum number of test subjects should be determined statistically, but will depend on the variability of the selected dependent variables and the inherent (i.e, normal) physiological variability between test subjects. proposed mixed gas system
The MOC should describe some criteria that may be used to determine the minimum number of test subjects that will be required, with additional testing to be performed if the results are inconsistent (i.e., too much variability). For example, additional test subjects may be with results from previously certified oxygen systems.

A modification of the published text is: Recommended

Response:
PARTIALLY ACCEPTED

The number of test subjects will have to be agreed with the authority prior to the start of the human test campaign in accordance with MOC to ESF sub-paragraph (c)and (h). If justified, industry practice could be considered for the validation of the total number of subjects to be tested but the number of subjects with health conditions should be statistically justified and agreed in accordance with (h).

Commenter: FAA, comment #53 medicXX

MOC, sub-paragraph (g), page 7
Comment summary:
The Modified Borg Scale quantifies dyspnea.

If elevated CO2 increases the rate of ventilation, it could invalidate this metric as a measure of the effectiveness of a supplemental O2/CO2 gas mixture.

At this time it's unclear if anyone has validated the use of the Modified Borg Scale in COPD or other respiratory conditions in evaluating the effects of altered atmospheres.

Suggested resolution:
Additional consideration may be necessary to determine a suitable evaluation method.

A modification of the published text is: Recommended

Response:
ACCEPTED.

It could be adequate to use such scales, "Borg Scale 1-10" and the "Perceived exertion and Lake Louise mountain sickness self questionnaire", but they are much more oriented to healthy personnel. The most recent Global Initiative for Chronic Obstructive Lung Disease (*GOLD Guidelines 2023*) includes the modified Medical Research Council (mMRC) dyspnea scale (Grade 0 strenuous exercise till Grade 4 breathless when dressing or undressing). Also Multidimensional questionnaires are validated such "St George´s Respiratory Questionnaire" or the "CAT Assessment". (*Mahler DA. Comparison of clinical dyspnea ratings and psychological measurements of respiratory sensation in obstructive airway disease. Am Rev respir Dis. 1987; 135: 1229-1233*), (*JM Ruiz et al. Comparison of several scales for assessing dyspnea daily activities in patients with chronic obstructive pulmonary disease. Archivos de bronconeumologia.2000; 36:25-28. DOI:10.1016/S0300-2896/15)30229-5*), (*Nisha Gupta et al. The COPD assessment test: a systematic review. ERJ 2014; 44:873-884. DOI 10.1183/09031936.00025214).*
For candidates with health conditions appropriate and approved scales should be used.
The consideration of such scale has been added to MOC paragraph h).

Commenter: FAA, comment #54 medicXX

MOC, sub-paragraph (g), page 7
Comment summary:

The Lake Louise mountain sickness self-questionnaire measures symptoms that are the result of both acute and sub-acute altitude exposure.

At this time it's unclear how this may be relevant to acute exposure to altitude in an airplane by somebody with COPD. Besides, CO2 can cause headaches, changes in mental status, and other symptoms, which may invalidate use of this scale.

Suggested resolution:
Additional consideration may be necessary to determine a suitable evaluation method.

A modification of the published text is: Recommended

Response:
ACCEPTED

See response to comment #53.

Commenter: FAA, comment #55 medicXX

MOC, sub-paragraph (h), pages 7-9
Comment summary:
The FAA agrees that COPD is probably the most severe, as well as the most common, resipiratory disease to been seen in the flying public, so if the mixed gas system works well/has an ELOS for passengers with COPD, it will likely be effective for passengers with other types of respiratory diseases.

However, after consulting several research physicians on the subject, at this time the FAA contends that using healthy test subjects in an attempt to replicate the physiological response of a person suffering from COPD is a flawed premise.

There are anatomical/structural, ventilatory, and blood perfusion changes in the lungs associated with COPD (even mild COPD) that are difficult, if not impossible, to simulate using healthy test subjects. As such, it would not be an accurate comparison.

In addition, COPD causes air trapping, which leads to hyperinflation of the lungs. During mechanical ventilation, it is very important to control ventilation with techniques such as reducing respiratory rate with a longer expiration time to reduce air trapping. The FAA is aware of some medical concern with COPD patients in that during an emergency, they will be breathing hard and fast, increasing their risk for air trapping and hypercapnia. Adding CO2 to the inspired gas mixture could worsen the hypercapnia, leading to significant respiratory acidosis.

Suggested resolution:
If EASA intends the applicant to ensure that the mixed gas system does not have a negative affect on passengers with medical conditions such as COPD, additional consideration may be necessary to determine a suitable evaluation method that can be used as a MOC Since there are no existing test procedures used in the medical community to simulate COPD in a healthy test subject, it may be necessary to include some testing with individuals that have COPD.

A modification of the published text is: Recommended

Response:
ACCEPTED.

EASA agree that additional testing should be performed with passengers having some specific health conditions (paragraph (h) of the MOC).
Refer also to the generic reply describing the modification of the MOC subparagraph (h).

Commenter: FAA, comment #56 medicXX

MOC, sub-paragraph (h), pages 7-9
Comment summary:
Measuring blood saturation level (SpO2) as the sole dependent variable is a very one dimensional measurement in an ELOS assessment of a supplemental mixed gas system that uses CO2.

PaCO2 levels should also be measured to ensure that the increased levels of CO2 in the mixed gas system do not have a detrimental physiological effect.

Note: There are many ways to measure PaCO2 (arterial blood line, arterial blood gas draws, continuous capnography/end tidal CO2 measured from respiratory gases/exhalation, finger CO2 monitors very similar to a pulse oximeter, etc.).

Suggested resolution:
Recommend measuring test subject PaCO2 levels to ensure that the increased levels of CO2 in the mixed gas system do not have a detrimental physiological effect. As noted in the Test Setup section (d), the test subjects should be exposed to the full range of altitudes for which the system will be certified. A series of exposures at maximum increments of 7,500 feet pressure altitude is acceptable for compliance demonstration.

A modification of the published text is: Recommended

Response:
ACCEPTED.

Paragraph (h) will be amended to require the measurement and monitoring of the subject PaCO2 (Carbon dioxide blood pressure) or equivalent parameter (transcutaneous carbon dioxide measurement) all along the test duration.

APPENDIX A

APPENDIX B