

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

SCIENTIFIC AND CLINICAL ADVANCES ADVISORY COMMITTEE

Note of teleconference to discuss additional evidence provided for Anecova AneVivo intrauterine device novel process application

COMMITTEE MEMBERS	Sue Price (Chair)	Daniel Brison (External)
	Kate Brian	Sheena Lewis (External)
	Alan Thornhill	Jane Blower (External)
	Robin Lovell-Badge (External)	Yacoub Khalaf (not present at teleconference but expressed views shortly after)

COMMITTEE APOLOGIES	Andy Greenfield	Raj Mathur (External)
	Guðrun Moore (External)	Joyce Harper (External)
	Melanie Davies (External)	

EXECUTIVE



1. Background

- 1.1. In its meeting held on 10th June 2015, the Scientific and Clinical Advances Advisory Committee (SCAAC) discussed the application for authorization of a novel process – the intrauterine culture of gametes/embryos using the Anecova AneVivo device.
- 1.2. The purpose of the Committee in the novel process applications process is to:
 - consider whether the process is novel;
 - provide a view on which licensed activity/activities the process should fall under;
 - consider whether there is evidence to suggest that the process is effective; and
 - consider whether there is any evidence to indicate that the process is unsafe (either to patients or embryos).
- 1.3. The Committee then makes a recommendation to the Statutory Approvals Committee (SAC), who have final say on whether or not to authorize the process.
- 1.4. The conclusions of the Committee's discussion were that the process was novel, that the intrauterine culture of gametes and embryos is a process by which multiple licensable activities can be achieved, including: processing gametes, processing embryos, keeping gametes and keeping embryos, and that application contains sufficient evidence to suggest that the Anecova AneVivo intrauterine device is effective, as it has been used in treatment in three European countries resulting in a number of live births (See Annex A).
- 1.5. However the Committee did not feel they had been provided with sufficient evidence to make an assessment of the safety of the intrauterine culture of gametes and embryos in a device such as the Anecova AneVivo intrauterine device and asked for additional evidence to be provided. In particular the Committee felt that information regarding the effect of all the components of the device on embryos, perhaps in an animal system (e.g. a mouse embryo assay), would be useful to aid

their decision to determine the impact of the device on embryo safety (See Annex A).

- 1.6. Therefore the Executive asked the applying centre for this additional evidence and arranged a teleconference with SCAAC to discuss this.

2. Teleconference

- 2.1. On 28th July SCAAC discussed the additional evidence provided by Anecova, relating to the safety of the AneVivo device (Annex B).
- 2.2. The Committee agreed that the mouse embryo assay and bovine embryo assay both indicated that the device did not negatively impact embryo development to the blastocyst stage indicating the device's safety.
- 2.3. The Committee noted that the number of embryos analysed was reasonable and that bovine embryos are very sensitive to culture conditions. However some questioned the rationale of carrying out a bovine embryo assay as this is usually used to assess the longer developmental impact of culture conditions, the negative impact of which can manifest as 'large offspring syndrome'. Members of the Committee commented that this type of analysis would be very expensive and therefore would not be expected from a small commercial venture.
- 2.4. The Committee felt that the toxicity data provided was good, also supporting the safety of the device.
- 2.5. Members of the Committee noted that while the evidence provided asserted that their testing demonstrated the 'capability of the device to be safely and quantitatively loaded and unloaded', no evidence to support this was provided. The Committee felt that it was important to see data demonstrating that the retrieval rate was sufficiently high before concluding that the device was safe.
- 2.6. The Committee discussed some of the previous data considered by the Committee from the Blockeel et al (2009) paper. Some members commented that the initial rate of retrieval of embryos from the device was low but improved over the course of the trial indicating that the device requires a certain level of training and user experience before it can be used successfully and that this should be highlighted to any centre wishing to use the device and to patients in patient information.
- 2.7. The Committee members also noted that the analysis of aneuploidy was carried out in such a limited way (by fluorescent in situ hybridisation (FISH) with only 5 chromosomes analysed) as to cast doubt on the conclusion that the device improved levels of euploidy.
- 2.8. A number of Committee members noted that clinical data for the device is based on a very small sample and does not demonstrate that the device improves IVF outcomes. As such the Committee feels it is not possible to make firm conclusions about the efficacy of the device.
- 2.9. Given this lack of evidence, some members questioned the purpose of the device especially as it may not provide conditions which are more physiologically normal than culture medium. (In the device embryos will be exposed to uterine fluids, whereas normally they would develop in the fallopian tube, exposed to fallopian fluids, which some culture media are designed to imitate.)

- 2.10. However others felt that the device had potential and was part of the process of innovation which might lead to improvements in IVF success, particularly if it were to be used as part of a clinical trial.
- 2.11. The Committee felt that it was vital for any clinics using the device to have good patient information in place, explaining the purpose of the device and any risks, setting out the limitations of the data on efficacy and addressing any patient concerns about acting as a living incubator.

3. Conclusions

- 3.1. The Committee still feels that the information provided goes some way to providing assurances that the device is safe but is not sufficient as data on retrieval success rates have not been provided.

Actions:

The Scientific Policy Manager will contact Anecova to obtain data regarding retrieval success rates and circulate this to the Committee.

4. Embryo retrieval success

- 4.1. Anecova have provided the Committee with additional data on retrieval success rates (Annex C).
- 4.2. The Committee has reviewed this data and has agreed that there is no evidence to suggest that the process is not safe.

5. Next steps

- 5.1. The Scientific Policy manager will write a note for the Statutory Approvals Committee setting out SCAAC's view:
 - that the device is not unsafe; and
 - that the clinical data on the device is limited and therefore does not demonstrate its efficacy, although there is not evidence to indicate that the process would not be effective.

ANNEX A – Extract of minutes of the 10th June SCAAC meeting - Novel process application

4. Novel process application

- 4.1 The Scientific Policy Manager presented an application for authorization of a novel process: the intrauterine culture of gametes/embryos, and in particular use of the Anecova AneVivo intrauterine device which is porous titanium chamber which allows fertilisation and the first day of embryo development to occur in the patient's uterus, exposed to tubal and uterine fluids, rather than in an artificial medium, in an incubator. The device is then removed and the embryos are cultured until day 5 at which point an embryologist can select the blastocyst with the best morphology for transfer.
- 4.2 The Committee was asked to:
- consider whether the use of intrauterine culture devices (such as Anecova AneVivo) constitutes a novel process
 - provide a view on which licensed activities ('keeping gametes', 'processing gametes', 'keeping embryos' and/or 'processing embryos') the process of using an intrauterine device should fall under
 - consider whether there is evidence to suggest that the use of an intrauterine culture device is effective
 - consider whether there is any evidence to indicate that the use of an intrauterine culture device is unsafe (either to patients or embryos) and
 - to provide feedback on the current procedure in place for processing applications for novel processes, such as the application forms used, the information submitted to the Committee, and timeframes involved.
- 4.3 The Committee agreed that intrauterine culture devices such as the Anecova AneVivo constitutes a novel process, both because it exposes the embryo to a novel environment (the device itself, which contain a number of components, and the uterine fluids where the embryo would usually develop in the fallopian tube) and because the embryos are placed in the woman and then removed again.
- 4.4 The Committee discussed carriage, distribution and biosecurity elements of the Anecova Avevivo intrauterine device and how this may affect HFEA guidance on consent, import and export of gametes and embryos.
- 4.5 The Committee agreed that use of an intrauterine culture of gametes and embryos addresses multiple categories of licensable activities which include, processing gametes, processing embryos, keeping gametes and keeping embryos.

- 4.6 The Committee commented that sample sizes of people included in each study were small, and also the paper may be misleading when describing the experience of the embryo as more 'natural' in comparison to the lab environment when the device is placed in the uterine cavity. Committee stated that naturally the embryo should be in the fallopian tube at this stage in development.
- 4.7 Due to the limitations of the data provided the Committee felt that they could not make an assessment of the efficacy of the process. However, the Committee noted that Anecova AneVivo intrauterine device as it has been used in for treatment in three European countries resulting in a number of live births, suggesting that it is sufficiently effective to give successful IVF outcomes some of the time.
- 4.8 The Committee agreed that insufficient evidence was provided in the application to determine the whether intrauterine culture of gametes and embryos in a device such as the Anecova AneVivo intrauterine device is safe.
- 4.9 The Committee requested additional data, such as that submitted for CE marking of Conformity on the Anecova AneVivo intrauterine device, be made available to the Committee. In particular the Committee felt that information regarding the effect of all the components of the device on embryos, perhaps in an animal system would be useful to aid their decision to determine the impact of the device on embryos.
- 4.10 Some members of the Committee commented on the lack of information provided in the paper regarding patient experience and patient risks though recognised that this information was beyond the remit of their considerations.
- 4.11 The Committee agreed that a defined framework, in addition to the decision tree, would be useful to determine applications for novel processes.

Actions

- 4.12 The Scientific Policy Manager agreed to contact the PR from the applying clinic to inform them of SCAAC request for additional information and to arrange a teleconference for SCAAC to further consider any information provided.

ANNEX B – Additional information on embryo safety provided by Anecova

Anecova Answers to HFEA request from July 8th 2015

HFEA:

As a side point the Committee highlighted that any centre using the Anecova AneVivo intrauterine device, or similar, should take into account the fact the device allows for transport of gametes/embryos. They also expressed a desire to see any patient information which might be provide and were interested to know whether any studies on patient experience have been conducted, though recognised that this information was beyond the remit of their considerations.

Anecova:

We are currently starting commercialization in a progressive controlled market release in selected Fertility centres in countries where authorisations from Competent authorities have been obtained (Czech Republic, Spain, Denmark). To date, the first healthy pregnancies are being reported in clinical use in Spain.

Other Fertility centres are in the pipeline to start commercialization. The Fertility centres are currently in the process of Product/ Procedure validation by their local Competent Authorities in (UK, Finland, Hungary).

HFEA:

On the day, the Committee did not feel they had been provide with sufficient evidence to make an assessment of the safety of the intrauterine culture of gametes and embryos in a device such as the Anecova AneVivo intrauterine device and asked for additional evidence to be provided. In particular the Committee felt that information regarding the effect of all the components of the device on embryos, perhaps in an animal system (e.g. a mouse embryo assay), would be useful to aid their decision to determine the impact of the device on embryo safety. Subsequently, the Committee has been made aware that that the CE mark that the device has been given is that of a Class IIa device and that this classification of medical device would require conformity assessment by a notified body, which includes the requirement for a clinical evaluation conducted in accordance with Annex X to Directive 93/42/EEC or with Annex 7 to Directive 90/385/EEC. It's a slightly tricky situation. While the purpose of the Committee is to assess the safety and efficacy of the process and not the device (which has already had its safety assessed in the CE marking process), in this case the members feel that the two things are so inextricably linked that they cannot make an assessment of one and not the other. Do you think you would be able to get any information from AneCova on the effect of the device on embryos?

Anecova:

Please find below an extract from the CE mark Tech file for the AneVivo medical device (Class IIa). Please note that the tech File and all other applicable documents are assessed and validated regularly by our Notified Body (DEKRA).

This extract contains:

- **Bovine Embryo Assay:** Bovine Embryo Toxicity Testing on AneVivo device residence from fertilisation to blastocyst stage.
- **ISO 10993-5 and ISO 10993-10 tests of raw materials.**

In addition you will find the results of our **Routine Mouse Embryos Assay / embryo toxicity test** from fertilisation to blastocyst stage.

Bovine Embryo Assay:

Early bovine embryo development and bovine oocyte fertilization were chosen for the compatibility trials. The bovine model was chosen for the high sensitivity of bovine zygotes. Experiments on Bovine model with the **AneVivo** device were performed at the following institutions:

Mariensee (FAL – Institut für Tierzucht – Germany); monitored by Dr. C. Wrenzycki.
Jouy-en-Josas (INRA – France); monitored by Dr. Y. Heyman.

The bovine model was chosen for the high sensitivity of bovine zygotes to the culture environment.

For the early embryo development, 315 zygotes (5 distinct experiments) were divided in 3 groups.

Group 1, the control group, (n=125 zygotes) zygotes were cultivated in 400 µl of SOF culture medium for 7 days, 5 zygotes per dish. The embryos were analyzed at the seventh day.

Group 2 (n=99 zygotes), the same protocol was applied with the addition in each dish of one **AneVivo** device.

Group 3 (n=91 zygotes) zygotes were loaded inside the **AneVivo** device (5 oocytes per capsule) and then cultivated with the same culture conditions.

The seventh day the embryos were flushed out of the device and were analyzed.

For the fertilization, n=99 partially denuded oocytes (3 distinct experiments) were divided in 2 groups. For both groups, the oocytes were placed in fertilization medium

(Fert-Talp plus HHE) with the addition of capacitated spermatozoids (5 oocytes and 10000 spermatozoids per dish). Fertilization was assessed after 24 hours. In the group two 2, an **AneVivo** device was added in each dish.

Early development results.

After seven days in culture, the number of healthy embryos was similar for the 3 groups (Table 1). The ratios of healthy embryos as well as the speed of development were not affected by the presence of the **AneVivo** device in the culture dish. The same observation was made for the embryos loaded in the **AneVivo** device.

Fertilization results.

No fertilization rate differences were observed between the control group and the group including the **AneVivo** device in the dish (Table 2).

Interpretation.

These results demonstrated not only the non-toxicity of the material composing the **AneVivo** device, but also the device biological neutrality towards the embryos and the oocyte fertilization.

Table 1, Embryo development results

	Average [%]	SD
Blastocyst & morula at day 7		
Inside AneVivo device	26	7
AneVivo device in the medium	27	15
Control	31	15

Table 2, Oocyte fertilization results

	% of fertilization	SD
AneVivo device in the medium	42	22
Control	57	21

This test provided evidence that components and materials used in the device are not toxic for bovine embryos.

This test also provided evidence that capsulated bovine embryos can be fed by culture medium through capsule wall porosity.

This test also provided evidence on the capability of the device to be safely and quantitatively loaded and unloaded with bovine embryos that have an equivalent size to human embryos at the same development stage.

ISO 10993-5 and ISO 10993-10 tests of raw materials

Raw materials and materials tested:

Connector retrieval string, capsule B (protective silicone), inner polycarbonate micro-porous membrane, distal cap (Ti), insertion kit (PEHD)

Conclusion

Cytotoxicity test, Intracutaneous injection tests and Kligman maximisation test meet the requirement of ISO guidelines.

Implanted material summary

<u>Inserted part (from 1 to 5 days):</u>	
<ul style="list-style-type: none"> • Titanium grad 2 • Stainless steel • Human grad silicone • Polycarbonate vessel 	
<u>Insertion material (from 1 to 10 minutes):</u>	
<ul style="list-style-type: none"> • Polyethylene high density 	
Silicone Human Grad 6	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	USP class 6 certified

Whether characteristics relevant to safety are known	The materials of the device were extensively experimented in embryo culture on bovine and mouse models and were found safe.
Polycarbonate (vessel)	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	USP class 6 certified
Whether characteristics relevant to safety are known	The materials of the device were extensively experimented in embryo culture on mouse models and were found safe.
Stainless steel	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	316 LVM – Class 6 - Certified
Whether characteristics relevant to safety are known	The materials of the device were extensively experimented in embryo culture on bovine and mouse models and were found safe.
Titanium Grad 2	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	USP – Class 6 - Certified
Whether characteristics relevant to safety are known	The materials of the device were extensively experimented in embryo culture on bovine and mouse models and were found safe.
Polyethylene High density	
Compatibility with relevant substances	N/A

Compatibility with tissues or body fluids	USP – Class 6 - Certified
Whether characteristics relevant to safety are known	The materials of the device were extensively experimented in embryo culture on mouse models and were found safe.
Silicone Adhesive	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	USP – Class 6 - Certified
Whether characteristics relevant to safety are known	Cytotoxicity testing
Retrieval String: Polyamide monofilament	
Compatibility with relevant substances	N/A
Compatibility with tissues or body fluids	CE mark
Whether characteristics relevant to safety are known	USP an EU conform

A routine Mouse Embryo Assay is performed on every batch, before releasing polycarbonate vessel and silicone.

Routine Mouse Embryo Assay / embryo toxicity test

Although all materials used for the manufacture of our device are human grade or USP class 6 certified, it is essential to ensure their non-toxicity and their biological neutrality vis-à-vis embryos viability and development.

Every new material, new raw material lot and sample from produced device batch is tested using *in vitro* mouse embryo assays.

Anecova routine procedure for mouse embryo toxicity assays:

Tested groups

- Control well: *in vitro* culture of mouse zygotes in 400µl of medium
- Control droplet: *in vitro* culture of mouse zygotes in droplet under oil

- Testing group: *in vitro* culture of mouse zygote in 400µl of medium with the presence of the tested material or loaded in device for production batch testing

Measures (when embryo are assessable on a daily basis: not loaded in a device)

- Proportion of fertilized oocytes on day 1
- Proportion of degenerated embryos reported every day until day 5
- Number of cells per embryo reported every day until morula stage
- Proportion of morula reported every day since day 4
- Proportion of blastocysts reported every day since day 5

Measures (when embryo are not assessable on a daily basis: loaded in a device)

- Proportion of blastocysts reaching day 5 (**normal**)
- Proportion of **delayed** development or arrested embryos (morula, cleavage stage embryo) at day 5
- Proportion of **dead** embryos at day 5

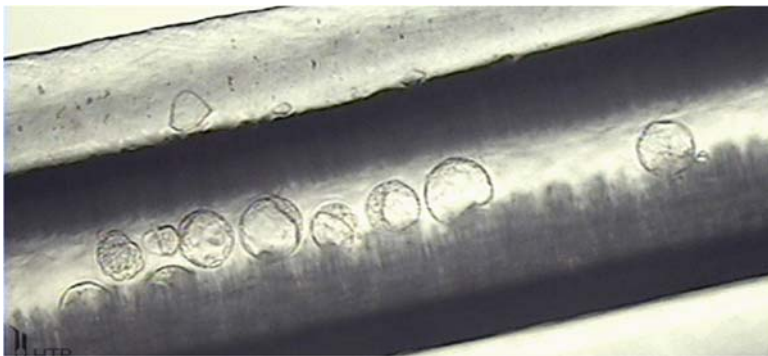
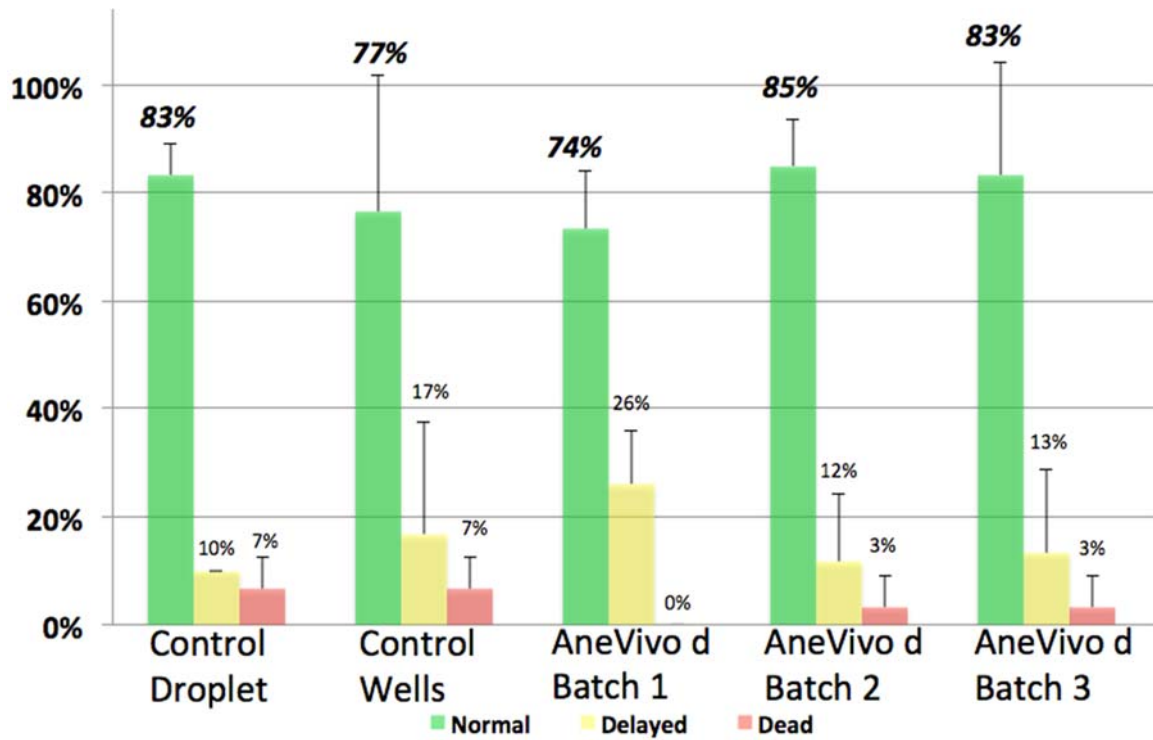
Number of embryos

- At least 3 test replicates per group
- At least 10 zygotes for the control group
- At least 10 zygotes for the testing group

Example of mouse embryo assay performed on 3 different batch of AneVivo device (random assay picked from our routine analysis).

A grand total of 150 mouse embryos were tested (in triplicate) for a 5-day culture with the Anecova routine embryo toxicity conditions (10 oocytes per conditions):

- Control well: *in vitro* culture of mouse zygotes in 400µl of medium
- Control droplet: *in vitro* culture of mouse zygotes in droplet under oil
- Testing group: *in vitro* culture of mouse zygote loaded in device for production batch testing in 400µl of medium for each production batch (**AneVivo device** batch 1, **AneVivo device** batch 2 and **AneVivo device** batch 3).



Picture from one of the triplicate **AneVivo** device batch 1 at day 5



Picture from one of the triplicate **AneVivo** device batch 3 at day 5

Conclusion

For this test no significant differences have been found for embryos developed in the **AneVivo** device (batch 1, batch 2, and batch 3) when compared to control groups. It has been concluded that no negative impact on the development of mouse embryos have been observed from these samplings representing 3 different **AneVivo** device batch.

ANNEX C – Evidence on embryo retrieval rates

Embryos recovered after in vivo residence	Embryos not found after in vivo residence or lost after mismanipulation during procedure execution	1 PN	2 PN	≥ 3 PN	Unfertilized	Degenerated
99.15%	0.85%	0%	72.50%	10%	15%	2.50%
percentage calculated with 118 embryos from all procedures		percentage calculated with 45 embryos from short in vivo residence procedures (18 hours)				
<small>Anecova - Strictly confidential</small>						