

1 **General Considerations for Animal**  
2 **Studies for Medical Devices**

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3 **Draft Guidance for**  
4 **Industry and Food and Drug**  
5 **Administration Staff**

6  
7 ***DRAFT GUIDANCE***  
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10

11 **Document issued on: October 14, 2015.**  
12

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17 rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the  
18 notice of availability that publishes in the *Federal Register*.  
19

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22

23 **When final, this guidance will supersede “Guidance for Industry and FDA**  
24 **Staff: General Considerations for Animal Studies for Cardiovascular**  
25 **Devices” issued July 29, 2010.**  
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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Device Evaluation  
Office of Compliance

## **Preface**

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# General Considerations for Animal Studies for Medical Devices

## Draft Guidance for Industry and Food and Drug Administration Staff

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

### I. Introduction

FDA has developed this guidance document to assist industry in designing evaluation strategies for, and reporting the results of, animal studies for medical devices. The animal studies utilized for the assessment of these devices typically provide initial evidence of device safety, their potential performance when used in a living system, and the biologic response that a living system may mount towards the device. This guidance provides recommendations for members of industry who perform, and FDA staff who review evaluations of, animal studies for medical devices. In this document, the terms “you” and “your” refer to members of industry, also known as “sponsors” or “applicants.” The terms “we,” “us,” “our,” and “Agency” refer to FDA.

The intent of this guidance is to provide a reference of best practices for the approach to and conduct of animal studies, and the presentation of animal study data intended to demonstrate that the device under study is sufficiently safe for early human experience [e.g., to support an investigational device exemption (IDE) application] or to demonstrate device safety in support of a marketing application, while incorporating modern animal care and use strategies. We recommend that you use this guidance to develop and present animal study protocols, methods, and reports that support the safety and performance<sup>1</sup> of medical devices. When considering the number of animals and the amount of data that can support the safety and performance of a medical device, FDA recommends balancing the ethical principles of reduction/replacement/refinement as well as regulatory least burdensome principles, with the goal of using the minimum number of animals necessary to generate valid scientific data to demonstrate reasonable safety and performance.

<sup>1</sup> While the handling/performance of a medical device may be demonstrated in an animal model, additional data in a human model may be necessary to assess outcomes demonstrating device effectiveness.

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135 Although this document is not intended to address the regulations and policies of other agencies,  
136 or other laboratory animal guides, we note that there are other relevant regulations and policies  
137 involving animal care and use that are administered by other agencies, some of which are  
138 referenced in this guidance.<sup>1-4</sup> A summary of relevant federal regulations is provided in  
139 Appendix E, and additional resources on animal care and research are provided in Appendix F.  
140 Of note, FDA maintains a memorandum of understanding (MOU) with the U.S. Department of  
141 Agriculture (USDA) and the National Institutes of Health (NIH) that addresses common areas of  
142 regulatory interest concerning animal care and use.<sup>5</sup>

143  
144 This draft guidance, when finalized, will supersede the July 2010 guidance entitled “Guidance  
145 for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular  
146 Devices.”

147  
148 FDA's guidance documents, including this guidance, do not establish legally enforceable  
149 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
150 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
151 cited. The use of the word *should* in Agency guidances means that something is suggested or  
152 recommended, but not required.

## 153 **II. Scope**

154 This guidance applies to medical devices intended for use in humans, as defined in section  
155 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The recommendations in this  
156 guidance apply to animal studies submitted in support of an IDE application, premarket approval  
157 (PMA) application, premarket notification (510(k)), humanitarian device exemption (HDE)  
158 application, or a request for *de novo* classification.

159  
160 This guidance is intended specifically to apply to *in vivo* nonclinical laboratory studies as defined  
161 in 21 CFR 58.3(d). A list of common acronyms encountered in relation to these studies is  
162 provided in Appendix A.

## 163 **III. Overview**

164 FDA recommends that you consider the following general principles when developing animal  
165 study protocols for medical devices:

- 166
- 167 • For animal studies that are to be submitted to the Agency to support the safety of a  
168 medical device, Good Laboratory Practice (GLP) applies (21 CFR Part 58). If your  
169 animal study was not conducted in compliance with Part 58, your statement provided in  
170 your submission explaining the reasons why the study was not in compliance with GLP  
171 regulations should also describe in detail all deviations from the regulations. The  
172 statement should include information that will help FDA reconstruct the study, explain  
173 any confounding variables, and demonstrate that authentic and complete test data have  
174 been collected and reported.

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- The animal model selected should be generally accepted for the study of the device type.<sup>6-12</sup> There should be a reasonable amount of scientific evidence that the animal model has utility for the study of the device type. In some cases there may not be an established or accepted animal model for a specific device type. We recognize that the utility of animal testing may be limited in these situations, and it may be most appropriate to proceed with limited clinical evaluation in humans, if scientifically justified. In other cases, an alternative animal model may be used and appropriately justified.
  - FDA's primary purpose in recommending an animal study is for the applicant to provide evidence of safety, including performance and handling. Note that in many cases, the performance of a particular device is intricately linked to its safety, such as for products that provide circulatory support.
  - A secondary objective for conducting the animal study can be to evaluate the efficacy of the device or to demonstrate proof of principle.
  - The *in vivo* setting generally provides an initial assessment of how the device interacts with biologic systems and also how the biologic system may affect the device, such as via device corrosion and structural deformities.

196 FDA is available to review your rationale for and design of an animal study as part of a Pre-  
197 Submission.<sup>13</sup> Additionally, it is important to consider the following points when designing your  
198 study: adequacy of controls, timing and route of intervention, and methods to minimize bias (e.g.  
199 blinding, randomization, use of controls, sample size based on expected magnitude of the  
200 biological response, reporting missing data, and clearly stated statistical considerations). If you  
201 are uncertain regarding elements of the animal study that are important to the Agency, please  
202 initiate contact with your respective review division for clarification.  
203

204 You should observe the best practices of refinement, reduction, replacement, and current  
205 standards of humane veterinary care and use. This may also involve consideration of available  
206 validated alternatives.<sup>14- 20</sup>  
207

208 Recommendations regarding specific elements of animal studies and other considerations are  
209 provided in the following sections.

## 210 **IV. Study Planning and Protocol**

211 FDA believes that an animal study that is carefully planned and executed is more likely to  
212 provide useful data in support of a device premarket submission. In this regard, the study should  
213 be planned by individual(s) with appropriate credentials and experience, and must be directed by  
214 a designated study director with appropriate credentials and experience in accordance with 21  
215 CFR 58.33. The study director should be located in close proximity to the actual study location  
216 so that s/he can provide oversight for the technical conduct of the study. The study director is  
217 also responsible for the interpretation, analysis, documentation and reporting of the study results

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218 (21 CFR 58.33). In some cases, additional investigators or contributing scientists may need to be  
219 designated for different aspects of the study, e.g., in-life portion and *ex vivo* imaging.

220  
221 Because the primary purpose of the study is to evaluate safety and performance, we recommend  
222 you consider your risk analysis (i.e., the identified risks associated with your device through  
223 bench testing, and other information, such as scientific presentations, literature review, etc.) and  
224 design the study objectives to enable study of all identified risks of your device as well as any  
225 known risks of the device type.

226  
227 The study must be guided by an *a priori* study protocol that is approved by the sponsor and  
228 signed and dated by the study director (21 CFR 58.120). The protocol must contain the elements  
229 outlined in 21 CFR 58.120 and should contain study instructions as dictated by the particular  
230 circumstances. Any changes or revisions to the final approved protocol, and the reason for the  
231 change, must be documented, dated and signed by the study director (21 CFR 58.120). The  
232 protocol and any revisions must be available for Agency review and are subject to inspection (21  
233 CFR 58.15).

234  
235 FDA recommends that an Institutional Animal Care and Use Committee (IACUC) review and  
236 approve all elements of the *a priori* protocol that address animal care and use prior to the  
237 initiation of the study and any major protocol amendment that affects animal care or use before  
238 the change is implemented (such review and approval may be required for some studies<sup>1</sup>). The  
239 IACUC will provide guidance as to the process and format for providing that information to the  
240 Committee.

241  
242 The number of animals and experimental groupings should be designed after pilot and bench  
243 testing provide some idea of reliability and outcome. A thoughtful attempt at utilizing the least  
244 number of animals that will provide meaningful interpretation is paramount and includes such  
245 measures as attention to the appropriate experimental control, consideration of potential  
246 experimental confounders, and an idea of best observation intervals (See Appendix C).

## 247 **V. Elements of the Animal Study**

248 We recommend that your regulatory submissions include a discussion of each of the following  
249 key animal study features, in addition to the requirements outlined in 21 CFR 58.185:

- 250
- 251 • introduction, including a rationale for the selection of the particular animal model;
  - 252
  - 253 • the study assurances (e.g., USDA registration, AAALACi accreditation, NIH Office of  
254 Laboratory Animal Welfare [OLAW] Assurance Statement number);
  - 255
  - 256 • the purpose of each test protocol;
  - 257
  - 258 • the study schedule;
  - 259
  - 260 • any *ex vivo* tissue characterization; and



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- any limitations imparted by the choice of the animal model and any amendments and deviations from the original test protocol.

Specific recommendations for how to optimize the development and reporting of some of these elements, as well as some of the elements required under 21 CFR 58.185, are provided below.

267 **A. Rationale for Selecting Animal Models**

268 FDA recommends that you provide your rationale for the selection of particular animal  
269 models for your animal study. A sample decision analysis flowchart for this  
270 determination is provided in Appendix B. The animal and its related environmental and  
271 physiologic attributes should provide a test system that offers a best attempt at simulating  
272 the clinical setting. The rationale for the conduct of an animal study should clearly state  
273 which of the elements of your risk analysis will be addressed and why the particular  
274 animal model was selected. If there are limitations to the animal model such that certain  
275 risks of the device are best addressed by bench or cadaver testing, these relationships  
276 should be described. Your rationale should also describe inherent challenges to the test  
277 system, such as:

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- the similarities and differences between the test system and humans in the metabolism of drugs or the use of ancillary devices that represent the standard of care for the procedures utilized in device implantation;
- the dimensions of the device and delivery systems, as compared to the same characteristics of the device version intended for human use;
- the location of device insertion and the tracking pathway or, if surgically placed, the anatomic point of surgical entry and the surgical technique utilized in the animal versus the human; and
- size limitations that exist as barriers (exclusive of cost) to use of the most size-appropriate and anatomically appropriate model.

292 **B. Study Assurances**

293 Animal studies that are intended to support the safety of a medical device must comply  
294 with the GLP requirements detailed in 21 CFR Part 58. As part of these requirements,  
295 under 21 CFR 58.35, the Quality Assurance Unit (QAU) must be separate from and  
296 independent of the personnel engaged in the direction and conduct of the study. The final  
297 study report must contain the signed Quality Assurance Statement (QAS) (21 CFR 58.35  
298 and 58.185), which should also be dated. The statement must also include dates of each  
299 inspection (21 CFR 58.35).

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FDA recognizes that, for various reasons, use of a GLP facility may not be possible, such as when a highly specialized skill set of investigators is only available at a particular non-

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303 GLP facility. In these situations, FDA recommends that you provide a complete rationale  
304 for the selection of the test site and that you follow the highest levels of oversight, record-  
305 keeping, and reporting. The rationale should include the differences from GLP and  
306 include an explanation as to why those GLP deviations do not affect the integrity of the  
307 data. If the reason for non-compliance with GLP is the lack of a QAU, FDA  
308 recommends that you employ an independent auditor so that impartial quality assurance  
309 is provided. For example, the quality assurance auditor should monitor the study conduct  
310 against the study protocol and facility standard operating procedures. The standard  
311 operating procedures should be similar in scope and detail as those typically used for  
312 GLP studies.

313  
314 Finally, in situations where a study report and/or its appendices are lacking key data and  
315 information, if the study site has assurances such as USDA registration, AAALACi  
316 accreditation, and/or an approved Animal Welfare Assurance Statement with NIH, the scope and  
317 level of detail found in the test facilities' standard operating procedures may provide sufficient  
318 evidence to confirm the validity of statements in the final study report.

## 319 **C. Study Objectives**

320 FDA recommends that animal studies for medical devices be designed with the objective  
321 of studying the risks that are predicted from the design of the device, any known risks of  
322 the device type, and any new risks that may have emerged in prior investigations, such as  
323 bench testing or animal feasibility/pilot studies.

324  
325 Recommendations for evaluating specific types of risks are provided below.

### 326 **1. Performance and Handling**

327 FDA recommends that your animal study protocol simulate the clinical setting as  
328 much as possible. You should identify all steps required to deliver, implant, or use  
329 the device, and develop acceptance criteria for each of the steps. FDA recommends  
330 that you apply a semi-objective rating scale (e.g., Likert scale) to each acceptance  
331 criterion. If the device is delivered or used with ancillary equipment, the acceptance  
332 criteria should include elements evaluating system compatibility. Rating criteria  
333 should encompass steps between the preparation of the device through device  
334 placement or use, and also withdrawal and redeployment, if appropriate. If the device  
335 is surgically placed, all steps from entry through the body wall through the final  
336 device handling should be described.

### 337 **2. Device Safety**

#### 338 **a. Physiological Response**

339 Medical devices can cause mechanical or biologic stresses. FDA recommends  
340 that you identify key biologic response variables at regional sites, at locations  
341 adjacent to the implant site (if applicable), and along all paths to and from the  
342 point of implantation or use to develop active means of surveying the impact of  
343 your device on the body. FDA strongly recommends that you work with a

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344 pathology expert such as a veterinarian boarded by the American College of  
345 Veterinary Pathology to develop the study protocol.

#### 346 **b. Unexpected Morbidity and Mortality**

347 You should fully explain all observed instances of animal illness and death. The  
348 supporting rationale for any statements made regarding whether such events are  
349 or are not device-related should be thoroughly described. Retrospective  
350 testimonials or statements made by study directors, their designees, or their  
351 consultants that explain veterinary clinical outcomes should be supported by  
352 appropriate evidence, records, and reports. If the cause of death or illness could  
353 be indirectly attributed to the device, you should discuss the etiology of the  
354 condition. FDA recommends that you follow modern methods of animal health  
355 surveillance by having qualified veterinarians use problem-oriented veterinary  
356 medical records (POVMR)<sup>21</sup> for the purpose of detailing wellness or morbidity,  
357 including the development of key assessments for systemic effects of device use.  
358 These assessments include postoperative, interim, and terminal clinical pathology,  
359 including but not limited to: serum chemistry, hematology, and coagulation  
360 profiles with laboratory reference range values; imaging reports; and case report  
361 forms for specialized evaluations (e.g., electrophysiological, behavioral, and  
362 neurological assessments).

#### 363 **c. Downstream and Systemic Effects**

364 FDA recommends that you evaluate whether or not the device can have effects  
365 remote from the site of placement or use. If you believe that your device has the  
366 potential for this type of risk, you should ensure that your study includes  
367 objectives to evaluate other tissue beds (such as downstream tissue for blood-  
368 contacting devices or other relevant end organ tissue) for evidence of potential  
369 systemic problem(s) that might be part of the device and delivery system. Should  
370 these findings occur, you should develop a plan for assessing the quantity of  
371 tissue affected and whether there are any resulting functional disturbances.

### 372 **D. Study Schedule**

373 FDA recommends that you develop a schedule of key interventions and time points for  
374 your study based on your knowledge of the known risks and predicted outcomes of use of  
375 the device. These timepoints typically include:

- 376
- 377 • full characterization, implantation, and intermittent examination of device  
378 performance and/or animal response;
- 379
- 380 • explantation of the device (if an implant);
- 381
- 382 • full analysis of any explanted tissue;
- 383

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- 384 • preparation of the tissue; and
- 385
- 386 • preparation and sign-off of the final written reports.
- 387

388 We recommend that the QAU be aware of these key scheduling objectives so that interim  
389 study monitoring and inspections can be arranged. Because medical devices may involve  
390 some degree of invasiveness and predictable variability in animal survival, any  
391 anticipated change in the duration of study may necessitate adjustment of these  
392 parameters, depending on the interim data. For example, if adverse outcomes are  
393 detected at earlier time points than expected, you should consider enhancing the timetable  
394 for observation and device explantation so that useful terminal data are not lost. Also, we  
395 believe that the responsible use of animals optimizes the use of all animal tissue, and  
396 therefore recommend that complete gross and microscopic organ and tissue evaluations  
397 be performed on all animals and that tissue be freshly studied to avoid the potential for  
398 erroneous interpretation.

#### 399 **E. Test and Control Articles**

400 Under 21 CFR 58.105 and 58.107, you are required to fully characterize and account for  
401 all test and control articles used in the study. Since sponsors may often develop several  
402 iterations of the test article prior to clinical study initiation, we recommend that pivotal  
403 animal studies utilize test articles representing the final clinical design. If the final design  
404 was not used, you should provide a rationale for why the final clinical design presents no  
405 new risks to the patient compared to the design studied in animals. FDA also  
406 recommends that test and control articles be packaged, sterilized, and shipped to the  
407 research site in the same manner as would clinical product. You should develop and  
408 follow a method for tracking the test and control devices from their manufacture or  
409 procurement to final use.

#### 410 **F. Accessory Devices and Equipment**

411 Some test articles, such as vascular stents, are typically used in conjunction with specific  
412 or commercially-available accessory devices or components, such as guide catheters or  
413 guidewires. Such accessories are sometimes described as a part of the test system when  
414 their use is necessary to use the test article properly. We recommend that in such a case,  
415 you state if:

- 416
- 417 • any accessory devices used in the animal study are to be provided completely  
418 separate from the test article (i.e., commercially available), or if accessory devices  
419 will be marketed together with the test article (i.e., a kit); and
- 420
- 421 • whether the final labeling for the device will include instructions for accessory  
422 device selection or use.

423 **G. Test System**

424 The final study report must include a description of the test system (21 CFR 58.185). 21  
425 CFR 58.3(i) defines *test system* as, “any animal, plant, microorganism, or subparts  
426 thereof to which the test or control article is administered or added for study.”  
427 Additionally, FDA recommends that you provide a description of the following factors,  
428 as applicable, that may affect or influence the test system so that we can make a  
429 reasonable assessment of their contributions to the study outcome: the environment,  
430 including temperature, lighting, and physical structure; nutritional status; homeostatic  
431 controls, including electrolytes, blood glucose, maintenance of asepsis, and control of  
432 bleeding; ancillary diagnostic tools; and materials and methods used to define or describe  
433 the interaction between test or control article and the animal.

434 **VI. Personnel**

435 Each test report must contain a section that lists key study personnel (21 CFR 58.185(a)(10)).  
436 We believe that this information is relevant to regulatory review because 21 CFR 58.29(a)  
437 requires that study personnel are appropriately trained and experienced to properly carry out their  
438 duties. This regulation underscores the importance of the training and expertise of animal study  
439 personnel. FDA recommends that the animal study team include skilled clinical veterinary staff  
440 in order to detect and resolve adverse outcomes; make decisions about the necessity to intervene,  
441 intervene accordingly, or deviate from the protocol in the interest of humane care; preserve  
442 valuable tissue; and assist in the determination of device associations with any adverse finding.  
443 Animal models may frequently impart the need for unique surgical approaches, anatomical  
444 limitations, and important features of wound closure that best argue for trained veterinary  
445 surgical expertise as part of the research team.

446  
447 FDA recommends that the animal study involve investigators with a combination of expertise,  
448 including human clinical, veterinary clinical, and veterinary pathologic fields. In keeping with  
449 the requirements in 21 CFR 58.29(b), you must maintain a current summary of the training and  
450 experience and job description of all personnel engaged in, or supervising the conduct of, animal  
451 studies. FDA recommends that any assessment of the competencies of key personnel be based  
452 on a rationale for why the individuals are suited for the type of studies being conducted.

453  
454 FDA notes that appropriate training and experience of study personnel are also addressed in  
455 other relevant guides, and other agency regulations and policies.<sup>1,1,4</sup>

456  
457 In addition to assembling a team of competent oversight personnel (including the study director,  
458 QAU, and attending veterinary and interventional staff), FDA recommends that you select the  
459 number of qualified personnel and their resources (including equipment, lateral and subordinate  
460 personnel, records and reports, and standard operating procedures) such that monitoring,  
461 treatments, and test sampling can be obtained at appropriate time points and to ensure that there  
462 is active surveillance at these periods for risks known or predicted in previous animal or bench  
463 testing, or possibly from previous experience with similar products. Finally, we recommend that  
464 you employ veterinary professionals with adequate training and experience to perform animal

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465 welfare audits of facilities, personnel, and methodology for those business entities that you may  
466 wish to contract from, such as contract animal research or holding facilities.

467 **VII. Facilities**

468 **A. Environment**

469 We recommend that you consult published guidelines involving the housing and well-  
470 being of animal research models.<sup>22-26</sup> The referenced guidelines address  
471 recommendations for minimum housing, husbandry standards, social and environmental  
472 enrichment, and the development of standard operating procedures that address timely  
473 and adequate veterinary medical care. FDA believes that following these guidelines and  
474 allowing animals sufficient access to resources such as food and water receptacles,  
475 enrichment devices (toys), clean and species-typical resting surfaces, provisions for  
476 postural adjustments, and adequate play and exercise are important. Comfort and  
477 familiarity with handlers can reduce background stress, thus potentially minimizing  
478 experimental confounding factors that could adversely affect the interpretation of your  
479 study results.

480  
481 In keeping with the standard of care, we recommend that the floors, walls, and ceilings of  
482 animal holding structures be non-porous in order to permit easy sanitization of surfaces.  
483 We recommend that there be adequate lighting and light controls to permit periods of  
484 normal daylight and opportunities for rest. We also recommend the utilization of  
485 facilities with appropriate environmental controls for temperature and humidity in order  
486 to prevent temperature stress and minimize respiratory infections.<sup>4</sup>

487  
488 Additionally, we note that laboratory animal guides have been developed, and other  
489 agencies have established regulations and principles of humane animal care, including  
490 assurances to state, national, and international authorities that a state of animal wellness  
491 is maintained during research as a well-controlled test system.<sup>1-3</sup>

492 **B. Animal Groupings**

493 FDA regulation 21 CFR 58.43 requires testing facilities to have a sufficient number of  
494 animal rooms or areas, as needed, to assure proper separation of species or test systems.  
495 However, outside of the post-operative monitoring period, we recommend housing social  
496 animals in conspecific groups. FDA cautions that the environmental conditions not  
497 interfere with the assessment of the study and that all animals have access to adequate  
498 resources such as food, water, and toys in order to prevent bullying and territorial stress.

499 **C. Primary and Secondary Enclosures**

500 Because many Class III devices and implants associated with surgical procedures  
501 necessitate frequent observations during certain predicted sub-acute periods, FDA  
502 recommends that your facilities include access to small recovery rooms or enclosures that  
503 can provide intensive care treatments such as oxygen, swivel systems for intravenous

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504 medications, remote ECG monitoring, and temperature and/or humidity adjustment. We  
505 also recommend that you consider whether your protocol should include periods of  
506 animal holding in high-level experimental facilities, with subsequent transport to more  
507 agricultural facilities following post-procedural stabilization.

508 **D. Transport Systems**

509 To minimize the stress animals can experience during transport, FDA recommends that  
510 you consider the use of transport cages with raised flooring, soft cushioning rest devices,  
511 carboys, hay nets, or other enrichment and food/water devices.<sup>26,27</sup> Transport vehicles  
512 should afford animals environmentally-controlled heating and air conditioning in order to  
513 further minimize shipping stress.<sup>1,4</sup> FDA notes that proper care in transport of animals is  
514 also addressed in other agency regulations.<sup>1</sup>

515 **VIII. Study Methods and Conduct**

516 FDA recommends that the methods and materials utilized for the assessment of medical devices  
517 in research animals be similar to those utilized in modern veterinary and human hospitals.  
518 Monitoring and intervention strategies should be based on the previous experience of key  
519 veterinary and scientific professionals. Once the failure modes and effects that can be addressed  
520 in an animal study have been identified, you should develop an animal study protocol that  
521 addresses each of the identified risks and that prescribes the frequency and type of monitoring,  
522 interventions, and outcome assessments.

523 **A. Research Controls**

524 Evaluation of device safety is often based on animal studies that provide valid scientific  
525 evidence (21 CFR 860.7(d)), and whether or not a facility has adequate standard  
526 operating procedures to ensure the quality and integrity of the data (21 CFR 58.81). FDA  
527 recommends that animal studies include adequate controls to minimize experimental  
528 variability and error. Such research controls include, but are not limited to, the  
529 minimization of anything given to or affecting the test animal in the course of an  
530 experiment that would impact the comparison between the test animals (i.e., animals  
531 receiving the test article) and control animals (i.e., animals receiving the control article).  
532 Variables that may impart change to the test animals may be devices other than the test  
533 article, or they may consist of background factors such as environmental factors,  
534 concomitant medications, or co-morbidities. You should minimize these confounding  
535 factors because they may hinder the ability of the investigator and FDA to clearly  
536 associate adverse or positive outcomes with the device and/or its effects.

537  
538 With this consideration in mind, we recommend the use of personnel, consumable  
539 equipment, and practices that enable test article-associated outcomes to be clearly  
540 understood. A reference of key controls recommended for animal research studies is  
541 included in Appendix C.

542 **B. Study Equipment**

543 Given that a medical device animal study is typically sophisticated in its components, and  
544 in recognition of the shift from the use of sponsor-owned to contract study facilities, FDA  
545 recommends that study sponsors, their consultants, and the study director carefully assess  
546 the care, maintenance, and knowledge about the contract equipment used in the study.  
547 We encourage early and frequent interaction between personnel involved in the planning  
548 of the animal study and those who will actually perform the study. We believe this  
549 dialogue is especially important to ensure that the study facilities have the proper  
550 ancillary equipment, supplies, and resources for the study. For example, imaging  
551 equipment and personnel may need to be as advanced as those found in human  
552 interventional suites or operating rooms to properly emulate the clinical situation.

553 **C. Animal Identification**

554 You should include a table of information pertaining to animal identification, allocation  
555 to study sub-groups, type of procedure performed, and the fate or disposition of each  
556 animal. For example, if animals are purchased with a USDA identification number but  
557 then subsequently identified with an institutional identification number and then further  
558 described by a group number, this information should be clearly understood and equally  
559 well presented to FDA so that a chain of custody of any individual test or control animal  
560 is possible.

561 **D. Animal Quarantine and Conditioning**

562 FDA recommends that you implement standard operating procedures that permit for  
563 adequate periods of quarantine and acclimation, as well as a program of socialization.<sup>4</sup>  
564 Background levels of disease and psychological stress should be controlled as much as  
565 possible. Farm animals are particularly prone to intestinal parasites, which commonly  
566 present sub-clinically but can cause clinical syndromes under the stress of surgery and  
567 during recovery. To minimize this confounding factor, we recommend that you initiate  
568 early and frequent dialogue with the attending veterinarian about ways to detect and  
569 eliminate clinical and sub-clinical disease to ensure optimal animal wellness. We note  
570 that the laws and policies of other agencies, e.g., the Animal Welfare Act (7 U.S.C.  
571 §§ 2131-2159) and Public Health Service (PHS) “Policy on Humane Care and Use of  
572 Laboratory Animals,” have resulted in important changes in the use of environmental and  
573 socialization protocols that are routinely implemented to control background stress.<sup>1-2</sup> We  
574 believe that following these laws and policies enhances the opportunity for and intensity  
575 of observations and can potentially result in other useful findings for the investigators.

576 **E. Animal Allocation to Experimental Grouping**

577 FDA recommends including a control group within the animal study design, or an  
578 explanation why a control group was not included. Additionally, when considering the  
579 number of animals needed to generate sufficient data that can support the safety and  
580 performance of a medical device, it is important to utilize sufficient animal numbers to  
581 obtain predictive outcomes. We believe that this determination can best be made after



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582 bench testing is complete and the device iterations are finalized. We strongly recommend  
583 that you conduct definitive animal studies on the market ready device except as required  
584 to scale, if needed, to implant in the animal model. The number of animals in the study  
585 should be based on sound scientific justification with consideration for the difficulty of  
586 the model and whether one or more test article(s) and/or control article(s) can be  
587 reasonably studied in a single animal. For example, FDA believes that deployment and  
588 handling studies can often be performed multiple times in the same test subject, or  
589 incorporated into a chronic safety study. By contrast, studies involving high-risk  
590 implants such as prosthetic joints can involve a high degree of expertise and some  
591 expected morbidity, such that a relatively large number of animals may be appropriate in  
592 order to establish device safety. Based on our experience, typical animal studies in a  
593 higher species (e.g., sheep, goat, nonhuman primate) generally have 3-9 animals per  
594 group/time point. However, in all cases a scientific justification should be provided in  
595 the protocol for the numbers used. We encourage you to discuss proposed animal studies,  
596 including the number of animals to be involved, prior to implementation through the Pre-  
597 Submission process.<sup>13</sup>

598 **F. Food, Water, and Basic Husbandry**

599 FDA recommends that sponsors expressly communicate with subordinate and contract  
600 personnel the type and quantity of food that will be offered, and also to pre-specify that  
601 cage sizes, and the location and quantity of food receptacles should be ample in pen-  
602 housed situations. You should also consider following other research standards that more  
603 specifically prescribe housing limitations.<sup>4</sup>

604  
605 We find weight loss challenging to interpret, making it difficult to attribute whether  
606 weight loss is or is not device related. As such, you should ensure that individuals  
607 monitor animals to document specifics regarding appetite, food and water intake, and  
608 micturition and bowel movements, particularly when animals are pen-housed. Bullying  
609 and resource coveting are commonly associated with weight loss due to inadvertent  
610 reduced caloric or fluid intake.

611  
612 Animals (i.e., small ruminants) enrolled in chronic studies are often transferred to a more  
613 typical agricultural setting where animals are allowed to graze on open pasture and/or are  
614 fed hay as a component of their diet. The sponsor/test facility should ensure that the  
615 pasture is free of potentially poisonous plants, parasite ova and other potential  
616 contaminants, and that the condition (soil, grass) of the pasture meets the animal's  
617 nutritional requirements, including minerals. Some species may be sensitive to  
618 imbalances in organic metals in the soil (e.g., sheep are sensitive to copper and  
619 molybdenum imbalances) which may inadvertently lead to toxicities (copper toxicity in  
620 sheep). Growth-enhancing additives, such as monensin, are another common source of  
621 inadvertent toxicity due to errors in ration preparation or feeding a ration for one species  
622 to another. Feed and water used for the animals must be analyzed periodically to ensure  
623 that contaminants known to be capable of interfering with the study and reasonably  
624 expected to be present in such feed or water are not present at levels above those  
625 specified in the protocol (21 CFR 58.90(g)). The sponsor/test facility should be

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626 cognizant of these potential problems and judicious in writing standard operating  
627 procedures that address periodic tests of water and feed for potential contaminants, the  
628 pasture soil and crop for nutritional balance, training employees on the importance of  
629 reading ration labels, feeding species-specific rations, etc. Local farm extension services  
630 provide invaluable assistance for this purpose.

631 **G. Periods of Observation**

632 FDA recommends that standards of veterinary care be followed.<sup>1-3,7,28-31</sup> For example,  
633 study animals should be monitored at a frequency and intensity that adequately assess for  
634 known risks posed by the device, and you should work with attending veterinary staff at  
635 the study facility to develop these monitoring parameters. We believe that such  
636 monitoring is appropriate not only for humane reasons, but also because well-monitored  
637 animals help us sort common spontaneously occurring conditions from conditions that  
638 might be attributed to the device. To best characterize the device effects on the animal,  
639 FDA recommends that the process be active and specific, rather than passive and general.  
640 Important attributes to consider for evaluation include, but are not limited to:

- 641
- 642 • respiratory rate, pattern, and depth;
- 643
- 644 • blood pressure;
- 645
- 646 • heart sounds and pulse character;
- 647
- 648 • mucus membrane color at rest and under exertion;
- 649
- 650 • attitude;
- 651
- 652 • mentation;
- 653
- 654 • gait; and
- 655
- 656 • presence or absence of abdominal, bladder, or bowel distension.
- 657

658 To best assist FDA's assessment of test article safety, we recommend that you follow  
659 current standards of record-keeping in veterinary medicine, such as the  
660 subjective/objective assessment and plan (SOAP) format. Additionally, these records  
661 should be readily available to all key support personnel in order to optimize data entry.  
662

663 Specific recommendations for animal study monitoring are provided below.

664 **1. Intraoperative Monitoring**

665 Good surgical technique alone is not sufficient to ensure a successful outcome for  
666 complex procedures required for medical device implants. Intraoperative and

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667 postoperative monitoring of heart rate, electrocardiogram, blood pressure, and  
668 blood gases are essential contributors to a positive outcome.

## 669 **2. Acute Studies**

670 If the study is acute and the device-associated trends are expected to be transient  
671 during the period of acute observation and harvest, we recommend that you track  
672 and record vital signs such as cardiac rhythm, respiratory rate, pulse oximetry,  
673 and blood pressure on operative records. This information should be correlated  
674 with the timing of insertion, implantation, deployment, or use of the device,  
675 contrast agent, or other device-associated materials, and noted on the anesthetic  
676 and/or operative records.

## 677 **3. Chronic Studies**

### 678 **a. Post-Operative Period**

679 FDA recommends that you follow the current standard of care for laboratory  
680 research animals by ensuring that investigators manage normal body  
681 temperature, minimize pain and infection, and provide adequate fluids and  
682 electrolytes.<sup>4,30-34</sup> You should capture physiological information similar in  
683 quality to that obtained in human care and recovery areas. In addition, you  
684 should control stress variables by establishing a standard assessment paradigm  
685 for the monitoring of pain and body temperature, and directing the  
686 administration of additional warmth and pain killers based on interim  
687 outcomes.

### 688 **b. Interim Periods of Observation**

689 During periods where animals have recovered from initial surgical procedures  
690 but are to be monitored for device-associated risks, FDA recommends that  
691 you monitor them at least twice daily at feeding times so that they may be  
692 observed when active. We also recommend that you consult your veterinarian  
693 and develop a weight monitoring plan. You should consider inclusion of body  
694 scoring as an adjunct to your periodic observations of the animal.<sup>7,35-38</sup>

695  
696 If your study involves the collection of clinical chemistry data or more  
697 advanced diagnostics, we recommend that you develop standard operating  
698 procedures that prescribe, when needed, a method of chemical restraint that  
699 does not interfere with the device. In our experience, some animals, such as  
700 dogs and sheep, may be conditioned to be compliant for these activities, while  
701 swine rarely are.

### 702 **c. Terminal Study Period**

703 FDA recommends that the study protocol include details of the terminal study  
704 and include all methodology for the examination, collection and processing of  
705 tissue. This section of the protocol should include the following information:  
706

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- 707
- 708
- 709
- 710
- 711
- 712
- methods for end-period examination;
  - (if applicable) a statement that in-life radiographic analysis and/or imaging will be completed; and
  - methods for establishing end weight and/or body score.

713 **d. Necropsy and Post-Mortem Evaluation**

714 Adverse events may present clinically or subclinically; therefore, we  
715 recommend that you include a comprehensive systematic necropsy in your  
716 study, including tissue collection and preservation for possible processing for  
717 histopathology examination as the resulting information can help FDA to  
718 determine whether observed adverse events are device-related. FDA  
719 generally recommends that you describe the rationale and process for how  
720 sectioning of organs is performed and the training and experience of the  
721 prosector in order to assure an objective process in the sampling of gross  
722 tissue for microscopic evaluation. You should support any statements  
723 regarding whether any adverse outcomes are device-related with appropriate  
724 evidence from the necropsy or histopathology report and from in-life  
725 observations. In the event of an unscheduled death, you should be able to  
726 provide evidence that supports your statement regarding cause of death.

727 **H. Post-Mortem Imaging and Assessment Methods**

728 **1. Explant Imaging (i.e., radiography, microCT)**

729 Prior to preparing devices for histomorphometric analysis, you should consider  
730 whether an analysis of the structural integrity of the device would assist in the  
731 determination of device safety.

732 **2. Scanning Electron Microscopy (SEM)**

733 FDA recommends the use of Scanning Electron Microscopy to fully characterize  
734 the implant device surface after explant of the device from animals.

735 **3. Histomorphometric Analysis**

736 Because proper interpretation of acute and chronic biologic responses is critical to  
737 FDA's evaluation of safety, especially in the absence of clinical data, we  
738 recommend that you seek the expertise of board-certified veterinary or clinical  
739 pathologists when developing and executing methods for preparing tissues for  
740 histomorphometric analysis. We also recommend that you identify appropriate  
741 expertise to develop pre-specified objective methods for scoring and analyzing  
742 observations of injury and inflammation of all tissue. Specific assessments such  
743 as inflammation, vascularization, calcification, proteoglycan/collagen, and  
744 fibrin/thrombus, etc. should be considered in your evaluation.  
745

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746 FDA recommends that you report any non-standard tools and methods used to  
747 collect the tissues that contain the device as well as the methods of fixation,  
748 cutting, and staining. The reports should also include diagrams indicating the  
749 location of implants. The sectioning methods, including tissue and device  
750 orientation, should be detailed. When discussing the study results, you should  
751 include well-marked high resolution color images, each indicating the animal  
752 number, study group, tissue section, magnification, stain, and other important  
753 identifiers. Some sponsors find the use of pathology keys that further detail their  
754 grading system useful. Other important identifiers are experimental animal  
755 number and cohort as well as a scale on the photomicrograph.

#### 756 **4. Local and Downstream Tissue Assessment**

757 FDA believes that most devices, including both implant and delivery system  
758 components, have the ability to embolize particulates or microthrombi from  
759 devices' structural elements or coatings, resulting in adverse observations such as  
760 pressure necrosis and inflammation in surrounding tissue or upstream/downstream  
761 tissue if the device is in contact with blood. The calvarium should be opened and  
762 the brain sectioned if there is a risk of upstream emboli. If your risk analysis  
763 identifies this potential risk for your device, we recommend that your pathologic  
764 study include systematic descriptive evaluation of upstream/downstream and  
765 surrounding tissue. If foreign bodies are observed, you should provide a  
766 discussion of the amount of surface area affected as well as the methods utilized  
767 to calculate this affected area.

## 768 **IX. Records and Reports**

769 A final report must be prepared, and any changes to the final study report must be documented as  
770 report amendments in accordance with 21 CFR 58.185. All raw data, documentation, protocols,  
771 final reports, and specimens (with certain exceptions) generated as a result of the animal study  
772 must be retained (21 CFR 58.190). FDA recommends that you prepare the records and reports  
773 for your animal studies such that we can most efficiently evaluate device safety and  
774 performance. You should consider whether the data are best suited for statistical analysis or  
775 better presented "raw." When raw data are requested by the Agency, you should include  
776 individual animal recordings and key study attributes as appendices to the final study report, and  
777 organize their format and content with the goals of explaining all study outcomes to minimize  
778 ambiguity. We recommend that the protocol also contain information about how the records will  
779 be organized and stored; who will make entries for each attribute; and when interim inspection of  
780 the records will be performed. We also recommend time and date stamping for study  
781 observations, as this helps to capture events accurately, which aids in the assessment of the inter-  
782 observational differences between study subjects. The final study report must include the  
783 information specified in 21 CFR 58.185, including a description of all circumstances that may  
784 have affected the quality or integrity of the data.  
785

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786 Under 21 CFR 58.190, you are required to retain all raw data, documentation, protocols, final  
787 reports, and specimens generated as a result of a non-clinical laboratory study for the durations  
788 specified under 21 CFR 58.195.

## 789 **X. Preparation of Regulatory Submissions**

790 When preparing regulatory submissions, including IDE, 510(k), HDE, and PMA submissions  
791 and *de novo* requests, we recommend that you include all relevant information collected as part  
792 of your animal studies. The summary of nonclinical studies in your submission should discuss  
793 the number of animal studies conducted, and include the following information for each of the  
794 studies:

- 795
- 796 • the rationale for the model selected;
- 797
- 798 • the similarity of the selected model compared to humans;
- 799
- 800 • the general animal study methodology you used;
- 801
- 802 • whether there were standard operating procedures in place and followed during the study;
- 803 and
- 804
- 805 • how the quality assurance unit is independent and impartial with respect to the inspection
- 806 of the data and the reporting of the results.
- 807

808 In addition, you should include your rationale for your transition from pilot, validation, or proof  
809 of concept animal studies to pivotal animal studies, or from one pivotal study to the next, as this  
810 information assists us in understanding how you comprehensively assessed device safety, and  
811 performance and handling across multiple studies. You should also describe any design changes  
812 to the device that were implemented after completion of all animal studies.

813

814 We recommend that you also provide a tabular representation of key parameters for each study,  
815 including the following information:

- 816
- 817 • the study groups;
- 818
- 819 • the number of animals in each group;
- 820
- 821 • identification of animals corresponding to study group allocation;
- 822
- 823 • study duration;
- 824
- 825 • the device design iteration used; and
- 826
- 827 • a summary of study outcomes.
- 828

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829 A signed and dated copy of the final study report should be included in your submission with  
830 changes to the final study report documented as report amendments. You may also submit an  
831 overall report of the study. In addition, you should provide an attachment to each final study  
832 report for each animal study that includes study details, including signed and dated individual  
833 scientific reports (e.g., the study director, the clinical veterinarian, the pathologist, and the  
834 radiologist), accompanying test protocols, and raw data. These attachments should also identify  
835 key study personnel and facilities, describe the overall results of the study, and discuss how the  
836 results met the objectives of the study and demonstrated that the device is safe for human use.  
837 To aid with the presentation of this information, FDA recommends that your overall animal  
838 study summary identify and present the individual test reports in a tabular format, and provide  
839 the locations of relevant appendices and attachments to the final study report within the  
840 submission.

841  
842 When compiling more than one study into a group of attachments to the final study report, FDA  
843 recommends that you do so in the order in which the studies were performed so that we can  
844 follow the device history and *in vivo* performance from the first to the last study, and evaluate the  
845 means by which you assessed device safety and performance and arrived at your final  
846 conclusions. A sample organizational template for relevant content of an animal study report for  
847 regulatory submissions is provided in Appendix D.

848  
849 In addition to these considerations, we recommend that you review any available FDA guidance  
850 documents specific to your device type for more detailed animal study recommendations.  
851

852 **Appendix A: List of Common Acronyms Related to Animal Studies**

- 853 AAALACi: Association for Assessment and Accreditation of  
854 Laboratory Animal Care, International  
855  
856 ACVIM: American College of Veterinary Internal Medicine  
857  
858 ACVECC: American College of Veterinary Emergency and Critical Care  
859  
860 ACLAM: American College of Laboratory Animal Medicine  
861  
862 APHIS: USDA Animal and Plant Health Inspection Service  
863  
864 CDRH: Center for Devices and Radiological Health  
865  
866 CFR: Code of Federal Regulations  
867  
868 FDA: United States Food and Drug Administration  
869  
870 GLP: Good Laboratory Practice (21 CFR Part 58)  
871  
872 IACUC: Institutional Animal Care and Use Committee  
873  
874 NHP: Nonhuman Primate  
875  
876 PHS: Public Health Service  
877  
878 QAS: Quality Assurance Statement  
879  
880 QAU: Quality Assurance Unit  
881  
882 SOAP: Subjective/Objective Assessment and Plan  
883  
884 USDA: United States Department of Agriculture  
885  
886 US: United States  
887



888 **Appendix B: Sample Decision Tree for Medical Device Animal Studies**

- 889 1. Have you completed a risk analysis that considered all sources of relevant information,  
890 including your own knowledge of risks and failure modes that you believe exist with your  
891 device, risks commonly attributed to this general device type, and post-market  
892 information for similar marketed devices? Postmarket information can be obtained from  
893 the published literature and the CDRH Manufacturer and User Facility Device  
894 Experience (MAUDE) database  
895 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM>).  
896  
897 a. If yes, go to step 2.  
898  
899 b. If no, we recommend that you complete the risk analysis and go to step 2.  
900  
901 2. Have all of the evaluable risks been tested on the benchtop, to the extent feasible, using  
902 the **final design** iteration (i.e., proposed market-ready device)?  
903  
904 a. If yes, go to Step 3.  
905  
906 b. If no and if feasible, we recommend completion of bench testing with the final  
907 device design before proceeding to step 3.  
908  
909 3. Did the risk analysis suggest that an animal study is necessary to assess potential safety  
910 problems?  
911  
912 a. If yes, go to Step 4  
913  
914 b. If no, consider submitting a Pre-Submission<sup>13</sup> and request FDA feedback.  
915  
916 4. Is there an established animal model for the type of device you are testing (i.e., one that  
917 has been described in the literature or used to support the clearance or approval of a  
918 similar device for the same indications for use)?  
919  
920 a. If yes, go to Step 5.  
921  
922 b. If no, have you assessed the anatomy and physiology (e.g., angiographic,  
923 radiographic, CT screening) of commonly utilized laboratory animal species (e.g.,  
924 small hoofed stock, dogs, and nonhuman primates) for size and procedural  
925 approach features?  
926  
927 i. If yes, and you can identify an animal model that would work, go to Step 5.  
928  
929 ii. If yes, and you identify significant challenges that prohibit the use of a  
930 reasonable animal model for all or some of the animal studies recommended  
931 by the risk analysis, FDA recommends that you contact the Agency for a

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932 discussion of these challenges and alternative approaches for collecting  
933 evidence to demonstrate satisfactory device safety and performance prior to  
934 clinical use via the presubmission process. Please note that FDA believes  
935 such situations to be unusual. As part of this discussion, you should include  
936 any available evidence that animal studies would not be feasible, propose  
937 alternative solutions, including any available simulations, cadaveric studies,  
938 and clinical information collected outside the United States. Please also note  
939 that FDA generally does not consider high cost as sufficient justification for  
940 not conducting animal studies.

941  
942 iii. If no, FDA recommends that you consult an experienced laboratory animal  
943 veterinarian to determine the availability and utility of common laboratory  
944 species before proceeding to Step 5 or Step 4.b.ii.  
945

- 946 5. Are there any particular features of the device that would result in study endpoints that  
947 differ from those previously used in studies for other devices of the same type for the  
948 same proposed indications, or are there new indications that suggest the use of different  
949 or additional evaluation time points or methods?  
950
- 951 a. If yes, you should identify the new endpoints, time points and methods, and  
952 proceed to Step 6.  
953
  - 954 b. If no, FDA recommends that you use the endpoints, time points, and methods  
955 reported for similar devices, and proceed to Step 6.  
956
- 957 6. Is there anything known about the device that would indicate high variability  
958 of animal responses, due to factors such as investigator training and familiarity with the  
959 device or inherent challenges in the placement or tolerance of the device?  
960
- 961 a. If you have investigated this issue and have determined that there is not a  
962 significant learning curve or predicted animal response variability, proceed to  
963 Step 7.  
964
  - 965 b. If evidence exists from either *in vivo* or *in vitro* studies that a significant learning  
966 curve exists that would significantly increase animal response variability, FDA  
967 recommends conducting pilot or proof of concept animal studies to evaluate this  
968 issue prior to conducting pivotal animal studies and before proceeding to Step 7.  
969
- 970 7. If, after consideration of all these issues, you would like FDA feedback on your proposed  
971 animal study strategy, FDA recommends that you submit a Pre-Submission<sup>13</sup> that  
972 includes a proposal for your pivotal animal studies. This proposal should detail all  
973 methods of assessment for identified risks that may be observed dynamically in life and  
974 with gross pathology and histopathology, and include any specific questions for which  
975 you would like FDA input.  
976  
977

978  
979

## **Appendix C: Recommended Animal Study Research Controls to Consider**

980 The requirements in 21 CFR Part 58 (e.g., adequate calibration and maintenance of experimental  
981 equipment in accordance with standard operating procedures, 21 CFR 58.63 and 58.81(b)(11),  
982 and proper identification of the test system, test article, control article, and all specimens  
983 collected from the test system to preclude error in data recording and storage, 21 CFR 58.105,  
984 58.107(c), 58.120(a)(5), and 58.130(c)) are intended to ensure the quality and integrity of the  
985 data generated from the study. In addition to these requirements, we recommend that you  
986 consider implementing the following controls to help keep the study focused, with clear goals,  
987 and minimize problems that can interfere with a successful study.

- 988
- 989 • Whenever possible, use pilot studies to best aid in the selection of time points, animal  
990 numbers, and interventions that minimize confounding and optimize animal use. The number  
991 of animals to be used in the study should be stated with clear reasoning.  
992
  - 993 • In addition to defining the study objectives as required under 21 CFR 58.120(a), we  
994 recommend that you include *a priori* acceptance criteria for success that are based on  
995 clinically relevant risks (often identified in your Risk Assessment Plan). A plan for analysis  
996 of these criteria should be defined and should include, where appropriate, the statistical  
997 methods that are to be used with definitions of success and failure. If using a semi-  
998 quantitative rating scale, define the score required that constitutes “success/pass” and provide  
999 your scientific rationale.  
1000
  - 1001 • Ensure selection of normal healthy animals based on timely interpretation of laboratory work  
1002 and veterinary medical examination prior to study enrollment.  
1003
  - 1004 • In addition to the requirement in 21 CFR 58.90(g) to analyze feed and water periodically for  
1005 known contaminants, incorporate methods that permit nutritional adequacy for the species  
1006 under study, such as:  
1007
    - 1008 ○ regularly scheduled interim weight measurements
    - 1009
    - 1010 ○ provision of adequate number of feeders in pen-housed animals
    - 1011
    - 1012 ○ consultation with attending veterinary staff regarding provision of special feeds or special  
1013 nutritional supplements during periods when you may expect finicky eating behavior,  
1014 such as the peri-procedural time frame.  
1015
  - 1016 • Consider use of an acclimation period after the source animals arrive at the test facility, such  
1017 as 7 to 10 days, prior to study enrollment.  
1018
  - 1019 • Incorporate appropriate baseline assessments of animal health and behavior prior to study  
1020 enrollment, including timely veterinary interpretation (e.g., fecal examination for parasites,

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- 1021 hemogram, and blood chemistry accompanied by the laboratory reference values). Under 21  
1022 CFR 58.90(c), at the initiation of the study, animals must be free of any disease or condition  
1023 that might interfere with the purpose or conduct of the study. Therefore, screen animals out  
1024 or treat and verify medical readiness for study, thereby minimizing the inability to associate  
1025 clinical pathology with the device vs. a pre-existing condition.  
1026
- 1027 • Ensure proper aseptic surgical technique, and monitoring and intervention to control  
1028 unintended infections.  
1029
  - 1030 • Incorporate practices and procedures, as appropriate, in addition to those required under 21  
1031 CFR Part 58, that ensure the animal facility staff are providing adequate sanitation and  
1032 environmental controls to prevent unintended injury and infection.  
1033
  - 1034 • Incorporate practices to ensure that training in the planned experimental methods have  
1035 exceeded the device learning curve, such that there is low to non-existent inter-procedural  
1036 variability.  
1037
  - 1038 • Under 21 CFR 58.29(c), there must be a sufficient number of personnel for the timely and  
1039 proper conduct of the study according to the protocol. Therefore, you should incorporate  
1040 practices to ensure that there is adequate personnel and staffing to make certain that animals  
1041 are appropriately monitored throughout the duration of study and at the appropriate intensity  
1042 and duration that would reasonably detect the predicted failure modes as well as any common  
1043 experimental outcomes.  
1044
  - 1045 • Ensure that the protocol includes appropriate monitoring and timely postoperative monitoring  
1046 and intervention to detect, control, and report common physical and physiological outcomes  
1047 such as vascular spasms, arrhythmias, respiratory difficulty, seizures, gait disturbances,  
1048 cognitive dysfunction, pain, and distress.  
1049
  - 1050 • Incorporate practices to ensure that transportation and shipping stress is minimized when  
1051 moving peri-procedural animals to remote holding sites.  
1052
  - 1053 • Incorporate practices and procedures that enable animals in group settings to consume  
1054 adequate amounts of water and food and to minimize inter-species injury.  
1055
  - 1056 • Incorporate practices that encourage adequate and timely intervention to obtain complete  
1057 necropsies (gross and histopathology) when animals die unexpectedly in order to establish  
1058 whether the cause of death is or is not device-related.  
1059
  - 1060 • Incorporate practices that encourage proper handling, storage, and preparation of tissue for  
1061 chemical analysis and histological processing.  
1062
  - 1063 • Consider steps to minimize bias or the perception of bias including, but not limited to:  
1064
    - 1065 ○ Contributing Scientists with no financial conflicts,

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- Blinding, and
- The utilization of more than one observer.
- Incorporate programs that will provide physiologic homeostasis, such as adequate thermoregulation, and electrolyte, blood glucose, and caloric balance.
- Incorporate a program to maximize animal wellness through the provision of species-specific social adequacy and environmental enrichment.
- Incorporate procedures that standardize the timely methods for the collection, handling, and shipment of tissue specimens.

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1081 **Appendix D: Sample Organization of Animal Study Test Report [Including**  
1082 **Raw Data (as defined by 21 CFR 58.3(k))] Components to Facilitate Review**

1083 The list below is intended as an example of the organization of a test report for recommended  
1084 and required content. This sample does not include all of the requirements of 21 CFR 58.185.  
1085 For more information on required content necessary to be in compliance with Part 58 reporting  
1086 requirements, please see 21 CFR 58.120 and 58.185.

- 1087
- 1088 1. Report numbers (as applicable)
- 1089
- 1090 a. Institutional Animal Care and Use Committee/Ethics Committee protocol number
- 1091
- 1092 b. Study director protocol number(s)
- 1093
- 1094 c. Test Facility protocol number(s), if applicable
- 1095
- 1096 2. Title of the report
- 1097
- 1098 3. Description of compliance with GLP regulations. If not in compliance, your statement  
1099 provided in your submission explaining the reasons why the study was not in  
1100 compliance with GLP regulations should also describe in detail all deviations from the  
1101 regulations. The statement should include information that will help FDA reconstruct  
1102 the study, explain any confounding variables, and demonstrate that authentic and  
1103 complete test data have been collected and reported.
- 1104
- 1105 4. Contact information (e.g., mailing address, street address, city, state, country and zip  
1106 code for each contact)
- 1107
- 1108 a. Sponsor
- 1109
- 1110 b. Sponsor representative
- 1111
- 1112 c. Test facility name(s); provide additional information, if available:
- 1113
- 1114 i. USDA registration (yes/no)
- 1115
- 1116 ii. AALACi accredited (yes/no)
- 1117
- 1118 iii. PHS Assurance (yes/no)
- 1119
- 1120 d. Study director
- 1121
- 1122 e. Quality Assurance director
- 1123
- 1124 5. Final report signature

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- 1125
- 1126 a. Study director's signature
- 1127
- 1128 b. Quality Assurance Statement and signature
- 1129
- 1130 6. Copy of the protocol reviewed by the Institutional Animal Care and Use Committee
- 1131 (IACUC), and signed by the IACUC chairperson and attending veterinarian
- 1132
- 1133 7. Executive summary
- 1134
- 1135 a. Overview of animal study
- 1136
- 1137 i. Study Schedule
- 1138
- 1139 ii. Objective of the study
- 1140
- 1141 iii. Acceptance criteria
- 1142
- 1143 iv. Rationale for selection or exclusion of animals, including supporting
- 1144 discussion and rationale if the proposed animal model could not be used
- 1145
- 1146 v. Characterization of test and control articles
- 1147
- 1148 a) Design iteration of device used
- 1149
- 1150 b) Referenced serial or model numbers
- 1151
- 1152 vi. Brief discussion of methods used, including insertion, approach, incision,
- 1153 monitoring, intervention, imaging, necropsy, and histology as appropriate
- 1154
- 1155 vii. Brief overview of results
- 1156
- 1157 a) Morbidity/mortality
- 1158
- 1159 (i) Gross necropsy information
- 1160
- 1161 (ii) *In situ* photography
- 1162
- 1163 (iii) Descriptive findings
- 1164
- 1165 b) Biologic response to the device to include such things as
- 1166
- 1167 (i) Inflammation
- 1168
- 1169 (ii) Resorption (if applicable)
- 1170

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- 1171 (iii) Injury  
1172  
1173 (iv) Healing  
1174  
1175 (v) Integration  
1176  
1177 c) Impact of animal on device  
1178 (i) Device structural integrity  
1179 (ii) Device functional integrity  
1180  
1181  
1182 d) Deployment/surgical success, positioning, and overall handling  
1183  
1184 e) System compatibility, if routinely used with other ancillary devices  
1185  
1186 f) Imaging characteristics  
1187  
1188  
1189 viii. Conclusions  
1190  
1191 a) Conformity with controls  
1192  
1193 b) Success in meeting acceptance criteria  
1194  
1195 c) Identification of related studies that were conducted or are  
1196 scheduled to be completed that explain any outstanding issues  
1197  
1198 8. Indexed Secondary Attachments (raw data and individual test reports)  
1199  
1200 a. Vendor reports  
1201  
1202 b. Baseline and interim health examinations  
1203  
1204 c. Surgery and anesthesia reports  
1205  
1206 d. Imaging reports  
1207  
1208 e. Clinical pathology results  
1209  
1210 f. Electromechanical results  
1211  
1212 g. Copies of animal medical records  
1213  
1214 h. Signed and dated Contributing Scientist(s) reports (e.g., interventionalist, surgeon,  
1215 radiologist, clinical veterinarian, clinical pathologist, pathologist etc.). These  
1216 reports may need:



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- i. Images (e.g., explant radiography images, *in situ* photography, gross and histopathology, angiography)
- ii. Cinematography
- iii. Electrophysiology strips
- iv. If applicable and part of the raw data, consider providing case report forms.

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**Appendix E: Tabulated Summary of Relevant Federal Regulations and Guides (the list below is not intended to be exhaustive)**

<b>Topic</b>	<b>Regulatory Citation</b>
GLP Animal Care	21 CFR 58.90
Protocol	21 CFR 58.120 and 58.130
Quality Assurance Unit	21 CFR 58.35
Test and Control Articles	21 CFR 58.105 and 58.107
Records and Reports	21 CFR 58.185, 58.190, and 58.195
Test System	21 CFR 58.3(i)
Federal Animal Biomedical Research Standards	9 CFR Chapter I, Part 3
Housing and Well-Being of Dogs	The care, exercise, and housing of dogs are described in 9 CFR Chapter I, Part 3 Standards, Subpart A. Housing, animal management, and species-specific space recommendations are provided in the National Research Council (NRC) publication, “Guide for the Care and Use of Laboratory Animals,” <sup>4</sup> which is the recommended reference to which metrics are applied by AAALAC and the PHS.
Sanitization and Husbandry	9 CFR Chapter I, Part 3 Standards and in the “Guide for the Care and Use of Laboratory Animals.” <sup>4</sup>
Environmental Control of Transportation	9 CFR Chapter I, Part 3 Standards and in the “Guide for the Care and Use of Laboratory Animals” <sup>4</sup>
Animal Identification Systems	Identification of warm-blooded animals (except suckling rodents) is discussed in 21 CFR 58.90, and also, with respect to dogs and cats and all other animals used in research, within 9 CFR Chapter 1, Part 2, Subpart E.
Animal Quarantine and Conditioning	21 CFR 58.90 and in the NRC “Guide for the Care and Use of Laboratory Animals,” <sup>4</sup> Page 110. The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes <sup>39</sup> provides similar guidance to European member state facilities.
Social and Environmental Research Standards	9 CFR 3.7 and 3.8, and in the NRC “Guide for the Care and Use of Laboratory Animals,” <sup>4</sup> pages 52-56, 63-65, 82-84.

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1232 **Appendix F: Additional Resources on Animal Care and Research**

- 1233 1. FDA Guidance for Industry (2007). [Good Laboratory Practices - Questions and](#)  
1234 [Answers](#).  
1235 ([http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm](http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133748.pdf)  
1236 [133748.pdf](http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133748.pdf))
- 1237 2. Hasenfuss G (1998). Animal models of human cardiovascular disease, heart failure and  
1238 hypertrophy. *Cardiovascular Research*, 39(1) 60-76.
- 1239 3. National Research Council Board on Agriculture Subcommittee on Dog Nutrition.  
1240 [Nutrient Requirements of Dogs](#), Revised. (1985). Washington, D.C.: National Academy  
1241 Press. ([http://www.nap.edu/openbook.php?record\\_id=15&page=R1](http://www.nap.edu/openbook.php?record_id=15&page=R1))
- 1242 4. National Research Council Board on Agriculture and Renewable Resources  
1243 Subcommittee on Goat Nutrition. [Nutrient Requirements of Goats: Angora, Dairy, and](#)  
1244 [Meat Goats in Temperate and Tropical Countries](#). (1981). Washington, D.C.: National  
1245 Academy Press.
- 1246 5. National Research Council Board on Agriculture Subcommittee on Sheep Nutrition.  
1247 [Nutrient Requirements of Sheep](#). 6<sup>th</sup> rev. ed. (1985). Washington, D.C. National  
1248 Academy Press. ([http://www.nap.edu/openbook.php?record\\_id=614&page=R1](http://www.nap.edu/openbook.php?record_id=614&page=R1))
- 1249 6. National Research Council Board on Agriculture Subcommittee on [Nutrient](#)  
1250 [Requirements of Horses](#). 6<sup>th</sup> rev. ed. (2007). Washington, D.C. National Academy Press.  
1251 ([http://www.nap.edu/openbook.php?record\\_id=11653&page=R1](http://www.nap.edu/openbook.php?record_id=11653&page=R1))
- 1252 7. Flecknell P.A. (1996) *Laboratory Animal Anesthesia*, San Diego, CA: Academic Press  
1253 Inc.
- 1254 8. Carr, John. 1998. [Garth Pig Stockmanship Standards](#). Iowa, 5M Enterprises, LTD  
1255 Sheffield, UK. Website with condition images.  
1256 (<http://www.thepigsite.com/stockstds/23/body-condition-scoring/>. Accession date  
1257 [11/14/08](http://www.thepigsite.com/stockstds/23/body-condition-scoring/))

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<sup>1</sup> United States Department of Agriculture, 9 CFR Parts 1, 2, and 3 (Animal Welfare).

<sup>2</sup> United States Public Health Service (2002). [Policy on Humane Care and Use of Laboratory Animals](#). Office of Laboratory Animal Welfare, National Institutes of Health. Bethesda, MD. (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>)

<sup>3</sup> United States Government Health Research Extension Act of 1985, Pub. L. 99-158; and [US Government Principles for the Utilization of and Care of Vertebrate Animals Used in Testing, Research, and Training](#).

(<http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples>)

<sup>4</sup> [National Research Council Guide for the Care and Use of Laboratory Animals](#), 8<sup>th</sup> ed. (2011). Institute of Laboratory Animal Resources Commission on Life Sciences, Washington, D.C. National Academies of Science Press. ([http://www.nap.edu/catalog.php?record\\_id=12910](http://www.nap.edu/catalog.php?record_id=12910))

<sup>5</sup> The FDA maintains an intergovernmental [Memorandum of Understanding \(MOU\)](#) between NIH, FDA, USDA regarding common areas of regulatory interest in animal care and use. (<http://grants.nih.gov/grants/olaw/references/finalmou.htm>)

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- <sup>6</sup> Tsonis, P.A. (ed).(2008) *Animal Models in Eye Research*, 1<sup>st</sup> ed. Academic Press: Burlington.
- <sup>7</sup> Ma, C. and J-M Zhang (eds) (2011). *Modeling Pain in Laboratory Animals: A Collection of Protocols*. 1<sup>st</sup> Ed. Humana Press: New York.
- <sup>8</sup> Howells DW, MJ Porritt, SSJ Rewell, V O'Collins, et. al. Different strokes for different folks: the rich diversity of animal models of focal cerebral ischemia. *J Cerebral Blood Flow Metab* 2010; 30 (May 19): 1413-1431.
- <sup>9</sup> Rink C, G Christoforidis, A Abduljalil, M Kontzialis, et. al. Minimally invasive neuroradiologic model of preclinical transient middle cerebral artery occlusion in canines. *PNAS* 2008 (Sept 16); 105(37):14100-14105.
- <sup>10</sup> Potes JC, J ca Costa Reis, F Capela e Silva, C Relvas, et. al. The Sheep as an animal model in orthopaedic research. *Exper Pathol Health Sciences* 2008; 2(1): 29-32.
- <sup>11</sup> Pearce AI, RG Richards, S Milz, E Schneider, and SG Pearce. Animal models for implant biomaterial research in bone: A Review. *Eur Cells Materials* 2007; 13: 1-10.
- <sup>12</sup> An YH and RJ Friedman (eds.). (1999) *Animal Models in Orthopaedic Research*. CRC Press, LLC., Boca Raton, Fl.
- <sup>13</sup> For more information on Pre-Submissions, see the FDA guidance, [Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf) (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>).
- <sup>14</sup> The Interagency Coordinating committee on the Validation of Alternative Methods (ICCVAM) provides many websites for decisions related to animal care and use, refinements, reductions, and replacement of animal models and validated models (<http://iccvam.niehs.nih.gov/about/accept.htm>).
- <sup>15</sup> The European Centre for the Validation of Alternative Methods (ECVAM) is a useful web link to validated European alternative animal models. ([http://www.bfr.bund.de/en/european\\_centre\\_for\\_the\\_validation\\_of\\_alternative\\_methods\\_ecvam\\_-4411.html](http://www.bfr.bund.de/en/european_centre_for_the_validation_of_alternative_methods_ecvam_-4411.html))
- <sup>16</sup> The Japanese Convention on the Validation of Alternative Methods is a resource for those animal models and animal welfare items of interest from Japan. (<http://jacvam.jp/en/>)
- <sup>17</sup> The Johns Hopkins Center for Alternatives to Animal Testing (CAAT) is a comprehensive web resource for all subjects related to global animal care and use, animal welfare, and animal alternatives. (<http://caat.jhsph.edu/>)
- <sup>18</sup> The National Center for 3Rs is a comprehensive web link for animal care and use and animal refinement and replacement questions. (<http://www.nc3rs.org.uk/>)
- <sup>19</sup> AltTox Forum (sponsored by Proctor and Gamble and The Humane Society of the United States) provides information about validated animal alternatives. ([http:// alttox.org/](http://alttox.org/))
- <sup>20</sup> Tox Net is an NIH-sponsored website of available literature on alternatives. (<http://toxnet.nlm.nih.gov/altbib.html>)
- <sup>21</sup> Bassert, Joanna M. *Medical Records*. Chapter 5. IN: McCurnin, Dennis M and Joanna M Bassert (eds). 2010. *Clinical Textbook for Veterinary Technicians*, 7<sup>th</sup> edition. Saunders, St. Louis, MO.
- <sup>22</sup> Reinhart, V. (2002). *Comfortable quarters for laboratory animals ninth ed*. Washington, D.C. United States Department of Agriculture Animal Welfare Information Center

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- <sup>23</sup> Fisher, T. F. (1993). Miniature swine in biomedical research: Applications and husbandry considerations. *Lab Animal* 22(5), 47-50
- <sup>24</sup> Guide for the Care and Use of Agricultural Animals in Research and Teaching, 3rd edition 2010, Federation of Animal Science Societies (FASS).  
(<http://www.fass.org/page.asp?pageID=216&autotry=true&ULnotkn=true>)
- <sup>25</sup> Panepinto, L.M. (1986). Character and management of miniature swine. In H. C. Stanton and J. H. Mersmann (Eds.) *Swine in Cardiovascular Research, (1) (pp. 11-24)*. Ames, IA: Iowa State University Press.
- <sup>26</sup> National Research Council Institute for Laboratory Animal Research Committee on Guidelines for the Humane Transportation of Laboratory Animals (2006). Institute of Laboratory Animal Resources Division on Earth and Life Studies, Washington, D.C. National Academies of Science Press. ([http://www.nap.edu/openbook.php?record\\_id=11557&page=R1](http://www.nap.edu/openbook.php?record_id=11557&page=R1))
- <sup>27</sup> National Research Council Institute for Laboratory Animal Research Committee on Guidelines for the Humane Transportation of Laboratory Animals (2006). Nutrient Requirements of Beef Cattle. 7<sup>th</sup> rev. ed. Washington, D.C.: National Academy Press.  
(<http://www.nap.edu/openbook.php?isbn=0309069343>)
- <sup>28</sup> Hampshire, V.A., Davis, J.A. (2008). Postprocedural Care of Commonly Utilized Research Animal Subjects. In R.E. Fish, M.B. Brown, P.J. Danneman & A.Z. Karas (Eds.) *Anesthesia and Analgesia in Laboratory Animals 2<sup>nd</sup> ed* (pp. 219-237), London: Elsevier
- <sup>29</sup> Flecknell P.A, Waterman-Pearson A. (2000). *Pain Management in Animals*. London: Harcourt Publishers Ltd.
- <sup>30</sup> Peterson N.C. (2004). Assessment of Pain Scoring. *Contemp Top Lab Anim Sci*,43(1):74-76
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- <sup>34</sup> Rudloff E, Kirby R. (1998). Fluid Therapy: Crystalloids and Colloids. In Dibaratola, S.P. (Ed). *Vet Clin North Am Small Anim Pract*. 28(2),297-328.
- <sup>35</sup> Keown, J. F. (2005). How to Body Condition Score Dairy Animals. The University of Nebraska Extension-Lincoln Institute of Agriculture and Natural Resources.  
(<http://www.ianrpubs.unl.edu/epublic/live/g1583/build/g1583.pdf>)
- <sup>36</sup> State of Maine. Extension Programs and Resources. Bulletin #1010, Body Condition Scoring for your Horse. Retrieved from: <http://umaine.edu/publications/1010e/>
- <sup>37</sup> Ohio State University College of Veterinary Medicine on-line learning system: How to Assess Body Score in Dogs and Cats. (<http://vet.osu.edu/1851.htm>)
- <sup>38</sup> Michel, K.D., Sorenmo, K., Shofer, F.S. (2004). Evaluation of Body Condition and Weight Loss in Dogs Presented to a Veterinary Oncology Service. *J Vet Intern Med*, 13(5),692-5.
- <sup>39</sup> The European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes is a useful web resource for European principles relating to animal care and use in certain member states.  
(<http://conventions.coe.int/treaty/Commun/QueVoulezVous.asp?NT=123&CM=0&CL=ENG.>)