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Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

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DRAFT GUIDANCE

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29

Preface

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Table of Contents

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Draft Guidance for Industry and Food and Drug Administration Staff

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140 *This draft guidance, when finalized, will represent the current thinking of the Food*
141 *and Drug Administration (FDA or Agency) on this topic. It does not establish any*
142 *rights for any person and is not binding on FDA or the public. You can use an*
143 *alternative approach if it satisfies the requirements of the applicable statutes and*
144 *regulations. To discuss an alternative approach, contact the FDA staff responsible for*
145 *this guidance as listed on the title page.*
146

147 ## 1. Introduction

148
149 The Food and Drug Administration (FDA) aims to promote safe and effective device use
150 in pediatric patients, while ensuring device approvals are based on valid scientific
151 evidence.[1] Currently, there is a paucity of scientific evidence available to substantiate
152 submissions for devices that are indicated for use in the diagnosis or treatment of
153 pediatric patients. FDA believes that leveraging relevant available clinical data, when
154 appropriate, may lead to more devices being approved for pediatric indications, which
155 will increase the availability of medical devices with appropriate labeling to support safe
156 and effective device use in pediatric patients. This approach will potentially streamline

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[1] Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. (21 CFR 860.7(c)(2))

157 the requirements for establishing a pediatric intended use claim, and enhance and
158 encourage pediatric device development programs.
159
160
161 FDA's guidance documents, including this guidance, do not establish legally enforceable
162 responsibilities. Instead, guidance documents describe the Agency's current thinking on a
163 topic and should be viewed only as recommendations, unless specific regulatory or
164 statutory requirements are cited. The use of the word "should" in Agency guidance
165 documents means that something is suggested or recommended, but not required.

2. Overview

166
167
168 The objectives of this guidance are: (1) to increase the availability of safe and effective
169 pediatric devices by leveraging relevant existing clinical data for use in pre-market
170 approval applications (PMAs) and humanitarian device exemptions (HDEs); (2) to
171 explain the circumstances in which FDA believes it may be appropriate to leverage
172 existing clinical data to support pediatric device indications and labeling; (3) to outline
173 the approach FDA uses to determine whether extrapolation is appropriate, and if so, to
174 what extent the data can be leveraged; and (4) to describe statistical methodology that can
175 be used to leverage the data in a way that increases precision for pediatric inferences.
176
177
178 For the purposes of this document, "extrapolation" refers to the leveraging process
179 whereby an indication for use of a device in a new pediatric patient population can be
180 supported by existing clinical data from a studied patient population. That is, when
181 existing data are relevant to a pediatric indication and determined to be valid scientific
182 evidence, we believe that it is scientifically appropriate in certain circumstances to
183 attempt to extrapolate such data to a pediatric use in support of demonstrating a
184 reasonable assurance of effectiveness and occasionally safety.
185
186 This draft guidance explains when and how existing clinical data in another studied
187 population (such as adults, or a different pediatric subpopulation) may be leveraged
188 ("extrapolated") to support marketing approval and labeling of medical devices for use in
189 pediatric patients. In order to make decisions about the effectiveness and safety of a
190 medical device in pediatric patients, FDA considers the totality of the evidence available.
191 As with any PMA or HDE, FDA will still consider clinical data (whether extrapolated or
192 not) alongside other forms of scientific evidence from assessments of device performance
193 (e.g., preclinical testing, engineering models, biocompatibility, virtual patient
194 simulations, statistical models, etc.) to determine whether the sponsor has demonstrated a
195 reasonable assurance of safety and effectiveness (or probable benefit for HDEs).
196
197 This guidance does not change the threshold for regulatory approval or valid scientific
198 evidence. Instead, the document seeks to provide clarity and predictability for device
199 sponsors and to ensure consistency within FDA regarding the specific criteria that should
200 be considered when deciding whether leveraging existing clinical data to support

201 pediatric claims is appropriate, and if so, to what extent. When considering
202 extrapolation, sponsors are encouraged to engage FDA early in product development
203 planning.
204
205 This guidance should be used in conjunction with other guidance documents for pediatric
206 medical devices and other applicable device-specific guidance documents to help ensure
207 that medical devices intended for use in the pediatric population provide reasonable
208 assurance of safety and effectiveness (or probable benefit, for HDE).
209
210 The scope of this draft guidance includes medical devices subject to the PMA and HDE
211 premarket requirements. For these premarket submissions, it may be appropriate to
212 extrapolate existing clinical data when the course of the disease or condition and effects
213 of the device are sufficiently similar in adults and pediatric patients, and the existing data
214 is determined to be valid scientific evidence. FDA believes that extrapolation should be
215 limited to circumstances in which endpoints used in the adult data sources are relevant to
216 the pediatric population, and the quality of these data is high. In this context, it is
217 important to note that the consideration of whether to borrow existing data to extrapolate
218 effectiveness for a pediatric population is independent from the consideration of whether
219 to extrapolate for safety. In other words, the criteria that govern the decision of whether
220 or not to extrapolate are considered separately for effectiveness and for safety.
221
222 This guidance facilitates efforts to address an unmet medical device need for pediatric
223 patients. The framework described herein is one tool to make optimal use of what is
224 already known about device effects in other populations to support indications in the
225 pediatric population

3. Background

228 When considering extrapolation of existing data for pediatric indications, it is important
229 to understand how pediatric subpopulations are identified. Section 520(m)(6)(E)(i) of the
230 Federal Food, Drug, and Cosmetic Act (FD&C Act)[2] defines "pediatric patients" as
231 persons aged 21 or younger at the time of their diagnosis or treatment (i.e., from birth
232 through the 21st year of life, up to but not including the 22nd birthday). Pediatric
233 subpopulations are defined in Section 520(m)(6)(E)(ii) (and adopted by reference in
234 Section 515A(c) of the FD&C Act) to be neonates, infants, children, and adolescents.
235
236 Age ranges for these pediatric subpopulations are as follows:
237
238 • Neonates: from birth through the first 28 days of life

239 • Infants: 29 days to less than 2 years

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[2] Available at
http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm

240   •   Children: 2 years to less than 12 years

241   •   Adolescents: aged 12 through 21 (up to but not including the 22nd birthday)

242

243 In 2004, FDA published a guidance document entitled "Premarket Assessment of
244 Pediatric Medical Devices" in an attempt to clarify the types of information needed to
245 provide reasonable assurance of safety and effectiveness of medical devices intended for
246 use in pediatric patients and to promote the development of these devices. This
247 document indicates that data can be extrapolated to support effectiveness and, on a
248 limited basis, safety for premarket approval applications (PMAs) when consistent with
249 scientific principles. The guidance states the following:

250

251   "If it is determined that clinical data are needed, it may be that the course of the
252   disease and the device's effects are similar in adult and pediatric patients. In such
253   a situation, the pediatric indication may be supported by the adult data with
254   limited additional safety data in the pediatric population."[3]

255

256 This guidance document was updated in 2014 to make clear that, as with other forms of
257 valid scientific evidence used to demonstrate effectiveness and safety for a device
258 intended for a pediatric population, the amount and type of extrapolated data necessary to
259 support a pediatric indication for a device varies:

260

261   "As is true for medical devices in general, FDA does not believe that clinical data
262   will be necessary to demonstrate effectiveness and safety for all devices intended
263   for pediatric populations. The agency recognizes that the amount and type of
264   evidence required will depend on a number of factors, including the nature of the
265   device, what is already known about the product in the adult population (if
266   relevant), what is known or can be extrapolated about the device to the pediatric
267   population, and the underlying disease or condition being treated. In some cases,
268   well-designed bench and animal testing will be sufficient to evaluate the device.
269   In others, clinical data may be needed to evaluate the safety and effectiveness of
270   the device."[3]

271

272 Congress was aware of the 2004 version of this guidance document when it passed the
273 Food and Drug Administration Amendments Act of 2007 (FDAAA). The House Report
274 (H.R. Rep. 110-225) states:

275

276   "FDA addressed premarket review of medical devices intended for pediatric
277   patients by issuing a guidance in May 2004 entitled 'Premarket Assessment of
278   Pediatric Medical Devices.' The guidance was published pursuant to the Medical
279   Device User Fee and Modernization Act, which contained several provisions
280   intended to promote the development of safe and effective pediatric devices. In

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[3] Available at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm

281   this guidance, FDA defined the age ranges for pediatric subpopulations,
282   **identified the types of information needed to provide reasonable assurance of**
283   **the safety and effectiveness of medical devices intended for use in the**
284   **pediatric population**, and described the protections that sponsors should consider
285   for pediatric subjects involved in clinical trials" (emphasis added).
286
287 Title III of FDAAA is the Pediatric Medical Device Safety and Improvement Act
288 (PMDSIA)[4] of 2007. PMDSIA specifically authorized the use of adult data to
289 demonstrate pediatric effectiveness[5], stating:
290
291   "If the course of the disease or condition and the effects of the device are
292   sufficiently similar in adults and pediatric patients, the Secretary may conclude
293   that adult data may be used to support a determination of a reasonable assurance
294   of effectiveness in pediatric populations, as appropriate."
295
296 In addition to allowing for the extrapolation of adult data to pediatric populations, the
297 provision indicates that, when appropriate, data can be extrapolated from one pediatric
298 subpopulation to another.[4]
299
300 While PMDSIA addresses the extrapolation of existing data to support a determination of
301 a reasonable assurance of effectiveness, it does not address safety data. However, we
302 believe there are also specific cases where it will be appropriate to consider extrapolation
303 of existing clinical safety data to support or enhance evidence for pediatric indications for
304 medical devices, including those defined in this guidance (e.g., the effects of the device
305 under consideration are identical when used in pediatric and adult populations and the
306 course of the disease or condition and associated risk factors are the same between the
307 two populations).
308
309 Given the potential for similarity in disease or condition, device attributes and treatment
310 effects between patient populations, and the availability of other nonclinical forms of
311 evidence to assess safe device performance, we believe that extrapolating for safety in
312 medical devices in specific circumstances could be appropriate and consistent with the
313 requirement to base approval decisions on valid scientific evidence. Because the
314 mechanism of action for devices is often well-characterized and fairly localized, non-
315 clinical forms of scientific evidence may provide information about device performance
316 characteristics related to safe device functioning (e.g., preclinical testing, engineering
317 models, computer modeling, or other nonclinical data). The potential availability of these

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[4] Available at
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf
[5] The term "effectiveness" is defined as follows: "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population**,** the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results" (21 CFR 860.7).

318 types of data for medical devices provides further support for the use of extrapolated
319 clinical data to demonstrate safety in pediatric patients. However, full extrapolation[6] of
320 safety data is expected to occur rarely. The appropriateness of extrapolation for
321 effectiveness and/or safety is considered independently on a *case by case* basis following
322 the decision tree described in Section 6.
323
324 This guidance does not change the threshold for regulatory approval or for valid scientific
325 evidence. When existing clinical data is relevant and appropriate for leveraging, the
326 amount of prospective clinical data in the pediatric population needed to demonstrate a
327 reasonable assurance of effectiveness and/or safety (or probable benefits outweigh risks,
328 for HDE) may be reduced. If not appropriate or insufficient to meet the threshold of
329 valid scientific evidence, data will not be extrapolated.

330 4. Why Extrapolate from Adult Data for Pediatric Use?
331
332 The extrapolation of adult data for pediatric use may benefit pediatric patients by
333 increasing the availability of medical devices with appropriate labeling to support safe
334 and effective pediatric use. Extrapolation, when appropriate, facilitates the use of
335 available relevant data by making use of existing clinical data that may be helpful for
336 understanding device performance in pediatrics. This is similar to the Bayesian concept
337 of borrowing from prior adult information to come to a posterior conclusion about
338 pediatric effectiveness or safety[7]. Extrapolation of adult data is limited to situations in
339 which the course of the disease or condition and the effects of the device are sufficiently
340 similar in adults and pediatric patients. For example, data from studies of devices that
341 create intracranial arteriotomies in adults may offer insights into their effectiveness in
342 pediatric patients between the ages of 13 and 21 because it is widely accepted that
343 cerebral vasculature of this age group is similar to that of adults.
344
345 There are many potential challenges involved in conducting pediatric clinical trials to
346 support pediatric indications for devices. For example:
347

348 • Small and diffusely scattered potential pediatric populations lead to small trial
349   sizes.

350 • Challenges exist in enrollment and consent procedures, which could increase the
351   length of time needed to determine safety and effectiveness.

352 • There are more variations in pathophysiology, physiology, anatomy, and human
353   factors in children and within pediatric subpopulations as compared to adults.

---

[6] See definition of "full extrapolation" in Section 5.1.
[7] See FDA's "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," available at
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071072.htm

354   • Reference samples may require an amount of blood too voluminous to obtain
355   safely from a neonate or small child.
356
357   At least in part because of these challenges, relatively few devices have pediatric-specific
358   indications and labeling. Yet off-label use of adult devices, without labeling information
359   to guide safe and effective use in pediatric patients, is not uncommon. The use of
360   existing clinical data when appropriate may reduce the need to prospectively conduct
361   large pediatric clinical trials by bolstering other scientific evidence supporting a
362   reasonable assurance of safety and effectiveness in a pediatric population. Extrapolation
363   encourages industry to provide performance data to support a pediatric indication, which
364   promotes proper labeling for use in pediatric patients even when limited pediatric data are
365   available. Informative labeling of a device which promotes safe and effective pediatric
366   use ultimately benefits patients.

5. Borrowing Strength from Adult Data

367
368
369   Extrapolation enables a sponsor to leverage adult data to support demonstration of a
370   reasonable assurance of effectiveness and possibly the safety of a medical device for
371   pediatric use. The quantitative information provided by existing adult data may be
372   important, and thus can be incorporated either by standing in for any potential pediatric
373   data or within a statistical model that also includes some pediatric data. The statistical
374   model would then estimate a device effect or adverse event in the pediatric population,
375   which can be potentially bolstered by the incorporation of additional data from adults.
376   This is known as "borrowing strength" in statistical literature (Carlin & Louis, 2009).
377   Such borrowing can bolster the sample size of a prospective pediatric study. The exact
378   model used to borrow strength may vary case by case. However, for all models, the
379   extent of leveraging depends, in part, on the similarity between borrowed data and any
380   pediatric data that will be collected.
381
382   The extent of borrowing may also be moderated by clinical judgments that are not
383   inherently implied by the statistical modeling. This may include consideration of the
384   particulars of the populations and studies, and whether such data are intended to
385   demonstrate either safety or effectiveness (or both). Effectiveness and safety often have
386   different endpoint assessments in a study. In addition, the study design could be different
387   for different endpoints, or there could be different considerations in the pediatric
388   population for safety versus effectiveness. Therefore, safety is considered independently
389   from effectiveness in deciding whether or not extrapolation may be appropriate. Section
390   6 provides more details about important information needed in the decision to
391   extrapolate.
392
393   Existing clinical data from adults and some non-clinical studies may provide information
394   about device safety which is relevant to risks in children.   For some devices, the
395   mechanism of action is expected to be similar in adults and pediatric patients. In these
396   cases, non-clinical forms of scientific evidence may provide some information about

397 many device performance characteristics related to safe device functioning (e.g.,
398 preclinical testing, engineering models, computer modeling, or other nonclinical data).
399 However, the sole use of non-clinical data as the basis for valid scientific evidence
400 regarding safety is expected to be exceedingly rare. Likewise, existing clinical data from
401 adults may provide information about device safety which is relevant to risks in children.
402 Based on the nature of the similarities and differences between target populations and on
403 the quality of the existing data, additional clinical studies in pediatric patients may be
404 warranted to supplement the existing data to provide valid scientific evidence about
405 device safety.
406
407 Types of existing data sources that may be considered for extrapolation include (but are
408 not restricted to) data from a variety of clinical investigations (e.g., randomized
409 controlled trials, single arm studies, and from any individual treatment arm), historical
410 clinical data, reference samples, and published literature.

5.1   Full and Partial Extrapolation

411

412

413 Existing clinical data may be leveraged either fully or partially via statistical modeling, to
414 support a reasonable assurance of safety or of effectiveness in a pediatric patient
415 population. The following are the differences between full and partial extrapolation:

416

417 • **Full Extrapolation**: Existing clinical data are used directly (i.e., as a complete
418   substitute) for prospective pediatric clinical data in support of a determination of a
419   reasonable assurance of effectiveness or of safety for a pediatric device. No
420   prospective pediatric clinical data are anticipated for the endpoint being fully
421   extrapolated. However, as with any PMA or HDE, FDA will consider this
422   alongside other data sources, such as virtual patient simulations, bench data,
423   mechanical models, literature studies or case reports, as further valid scientific
424   evidence supporting a reasonable assurance of safety and effectiveness in the
425   intended pediatric population. Given the range of potential differences between
426   adult and pediatric patients, full extrapolation of existing clinical data to
427   demonstrate safety is expected to be rare.

428 • **Partial Extrapolation**: Existing data are combined via a statistical model with
429   pediatric data sources or prospective pediatric clinical data in support of
430   demonstrating a reasonable assurance of effectiveness or of safety for a pediatric
431   device. The construction of such a statistical model is anticipated to require the
432   availability of measured variables that will help connect the adult outcomes to the
433   pediatric outcomes. If necessary variables are not available in the data sources,
434   partial extrapolation may not be appropriate. If the model is determined to be
435   appropriate, then the inferences obtained from it may be used to support a
436   pediatric indication.

437

438 Full extrapolation requires a significant amount of trust in the relevance and quality of the
439 adult data because they will constitute the sole clinical data to support effectiveness and
440 possibly safety of the device in pediatric patients. Partial extrapolation also requires trust

441 in the adult data, specifically, the trust that the adult data are similar to what is expected
442 to occur in pediatric patients. Furthermore, because the *actual* extent of partial
443 extrapolation (or borrowing) will be determined *after* the pediatric data are gathered,
444 there is some verification of whether extrapolation is ultimately appropriate. If
445 extrapolation is ultimately not appropriate, then the pediatric data will need to be
446 sufficient alone to support marketing approval. Section 6 of this document describes the
447 approach that is used to determine whether existing clinical data sources are candidates
448 for borrowing either fully or partially to extrapolate either effectiveness, safety, or both to
449 a pediatric population.

450 ## 5.2   Extrapolation for Effectiveness vs. Safety

451
452 FDA believes that existing clinical data can be extrapolated when appropriate to support
453 either effectiveness or safety or both in medical devices. However, since the endpoints
454 related to effectiveness are likely different from those for safety in a given study, and
455 because the quality of data may differ in some circumstances, the decisions of whether to
456 extrapolate existing data for safety or effectiveness (or both) are made independently.
457 For example, in medical devices, there may be circumstances where FDA may conclude
458 (based on the flowchart in Section 6.1) that full extrapolation of adult data is appropriate
459 for effectiveness, but there is still a need for a safety study in a pediatric population.
460
461 Because of the physiological differences between adult and pediatric patients that may
462 affect device safety and the inherent difficulties in designing and powering clinical
463 studies that provide comprehensive assessments of safety, extrapolation for safety is
464 expected to be rarer than extrapolation for effectiveness. However, we believe that there
465 are cases where extrapolation for safety is appropriate in some cases to support a
466 pediatric indication. Again, these data will be considered with the totality evidence to
467 either support or not support a reasonable assurance of safety and effectiveness (or
468 probable benefit in HDEs).

469 # 6. Pediatric Extrapolation Decision Process

470
471 The extrapolation approach described in this guidance document provides a framework
472 for considering whether or not the extrapolation of existing clinical data is appropriate to
473 support a pediatric indication, and if so, to what extent.
474
475 Extrapolation of adult data may be used, as appropriate, to support a pediatric indication
476 if the course of disease or condition and the effects of the device are sufficiently similar
477 in adults and pediatric patients. The appropriateness of extrapolation largely depends on
478 three main factors: (1) the similarity of the existing adult response data and/or population
479 characteristics to the intended pediatric population, the (2) the quality of the adult data in
480 terms of study design, data collection, and measurement, and (3) whether extrapolated
481 data may be used to fairly and responsibly decide whether there is a reasonable assurance
482 of the safety and effectiveness (or probable benefit for HDEs) of a medical device (i.e.,

483 constitute valid scientific evidence).   Broadly, factors that can affect data quality include
484 study design, data collection and measurement, and the applicability of these data with
485 consideration of the current standard of practice for the disease or condition being treated.
486
487 When both similarity and quality are determined to be sufficiently high, there is a greater
488 level of certainty that the existing data can be appropriately considered for extrapolation
489 to the intended pediatric subpopulation. If neither similarity nor data quality are high,
490 then the existing adult data may be inappropriate to use for extrapolation purposes.
491

6.1 Pediatric Extrapolation Decision Tree

493

494 The following decision tree (see Figure 1 below) can be used by sponsors and FDA
495 review staff as a tool to help determine whether extrapolation of existing clinical data is
496 appropriate and, if so, whether extrapolation should be full or partial.
497

498 Please note that the approach described in the decision tree is intended as an aid to decide
499 whether or not extrapolation can be considered in a specific situation. A conclusion from
500 the decision tree that extrapolated data may be used does not necessarily mean that these
501 data will support an approval decision for the PMA or HDE. If it is determined that
502 existing data can be extrapolated in some manner to support a pediatric indication, the
503 extrapolated data would be considered in conjunction with the totality of evidence that
504 will either support or not support a reasonable assurance of safety and effectiveness (or
505 probable benefit, for HDE).
506

507 The general approach of the decision tree is to first consider whether the treated condition
508 occurs at all in the intended pediatric population and whether available adult data related
509 to that condition and effect of the device are relevant to the intended pediatric population.
510 One potential (and perhaps readily available) source of relevant data includes prior
511 clinical studies done for approval of the device in adults. If these adult studies use an
512 endpoint that is similar to the primary endpoint of interest in the pediatric population,
513 then they may be relevant for extrapolation. If no *relevant* data are available from any
514 prior adult studies, then extrapolation should not be used. Second, consider to what
515 extent the adult data are similar to what may be seen in the pediatric population. For
516 example, are there expected differences in the device characteristics, patient
517 characteristics, or disease characteristics between the identified adult population and the
518 intended pediatric (sub)population(s)? If there are expected differences, extrapolation
519 might not be appropriate. The differences could contribute to a high level of uncertainty
520 regarding the expected device effect such that the adult data cannot support a pediatric
521 indication. On the other hand, if such differences are minimal and can be accounted for
522 with the measurement of covariates or surrogate variables within a statistical model,
523 partial extrapolation may be appropriate. If there are *no* expected differences, then full
524 extrapolation could be an option if the quality of the adult data is such that *substituting*
525 adult data for pediatric data is considered appropriate.
526

527   The decisions to extrapolate for safety or effectiveness are made by going through the
528   tree independently for each of these factors. In the tree, there will be items that will
529   remain constant for either decision. For example, when considering whether to
530   extrapolate for safety, effectiveness or both, the considerations related to the similarities
531   or differences in disease progression and device characteristics between the adult and
532   pediatric populations may be the same. However, endpoints and the quality of data
533   relating to these endpoints may differ when considering the safety or effectiveness
534   components of a prior study.
535
536   **Figure 1. Pediatric Extrapolation Decision Tree**
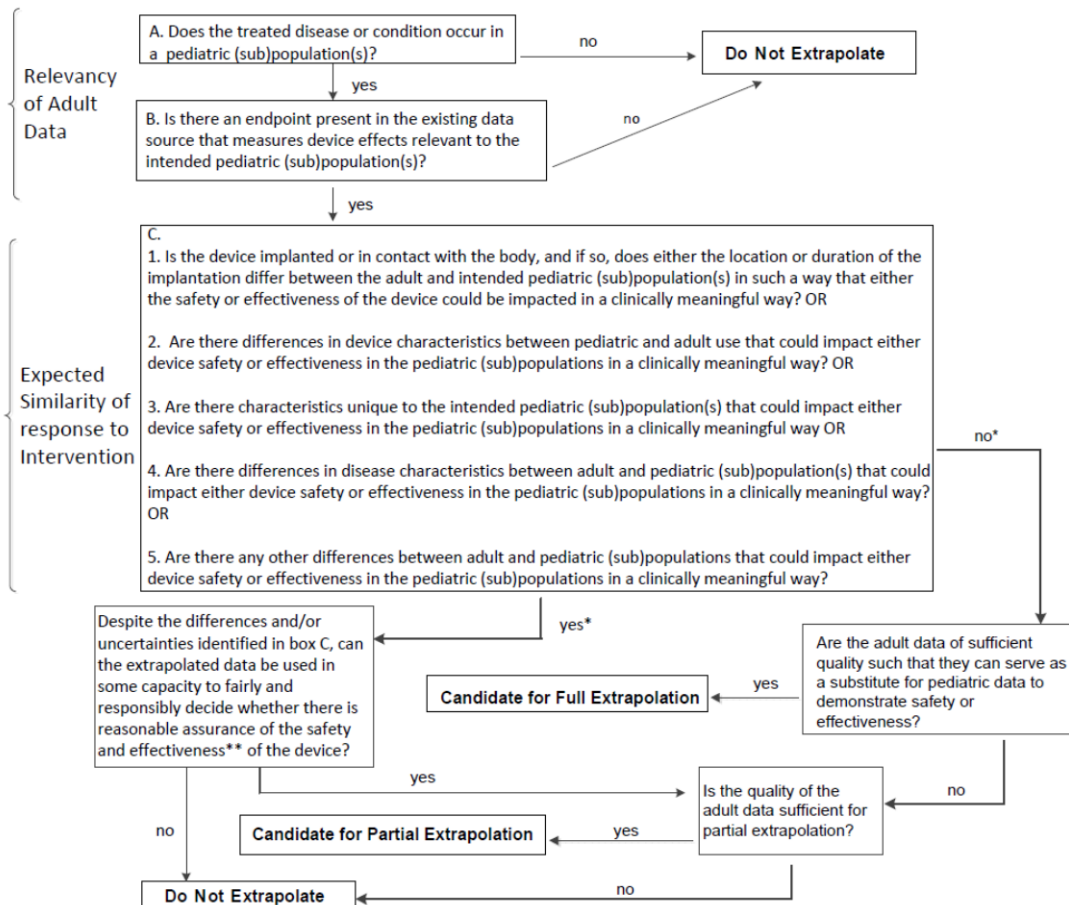
537
538   * Note that if all five questions in Box C are answered "no", the direction from C is "no". If at least one of
539   the five is answered "yes", the direction from C is "yes".
540   **"The agency relies upon only valid scientific evidence to determine whether there is reasonable assurance
541   that a device is safe and effective. Valid scientific evidence is evidence from well-controlled investigations,
542   partially controlled studies, studies and objective trials without matched controls, well-documented case
543   histories conducted by qualified experts, and reports of significant human experience with a marketed device,
544   from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance
545   of the safety and effectiveness of a device under its conditions of use. 21 CFR 860.7(c)(1)&(2)."

546

547   The questions in the Pediatric Extrapolation Decision Tree are a guide for what to
548   consider when determining the appropriateness of extrapolation of adult data for pediatric
549   indications. These questions are designed to promote discussion between FDA review

550   staff and sponsors while facilitating consistency among FDA review staff. Considerations
551   of extrapolation of any type should be discussed with FDA staff throughout the device
552   protocol planning stages. It is highly recommended that the pre-submission pathway be
553   used to explore such options.[8] A 522 post-market surveillance study may be required,
554   particularly in situations where full extrapolation of safety data is agreed upon by FDA
555   staff and device manufacturers.[9]

6.2   Questions in the Pediatric Extrapolation Decision Tree

556

557

558   This section provides more detail about using the questions in the Pediatric Extrapolation
559   Decision Tree to make a decision regarding the appropriateness of extrapolation. The first
560   two questions are asked to determine whether extrapolation should be considered at all.
561   Within the tree, these are referred to as "Relevancy" Questions because they pertain to
562   whether adult data are relevant for extrapolation.

563

564   Question A: Does the treated disease or condition in question occur in pediatric
565   (sub)populations?

566

567   If the answer is no, extrapolation of adult data is not appropriate. If the answer is yes,
568   proceed to question B.

569

570   Question B: Is there an endpoint present in the existing data source that measures device
571   effects relevant to the intended pediatric (sub)population(s)?

572

573   In order to borrow confidently from adult data there should be either: (1) the same
574   variable measured in the adult data as would be expected to be measured as the primary
575   endpoint in the intended pediatric population, or (2) a variable measured in the existing
576   adult data that is *sufficiently related* to the primary endpoint expected to be measured in
577   the pediatric population. For the latter case, a reliable and valid model might be used to
578   predict the endpoint from the pediatric population using the endpoint from the adult
579   population. Reliability and validity of the model should be established from prior
580   investigations. One possibility is to use a validated surrogate endpoint in the adult data
581   set(s) that has been shown to predict a different (perhaps, longer term) endpoint of
582   interest. For example, a device that is used to treat diabetes may rely on validated adult
583   and pediatric surrogate endpoints such as serum glucose levels or HbA1c to measure
584   actual device outcomes.

585

586   If the answers to questions A. and B. are yes, continue along the decision tree. The next
587   five questions are addressed as a set (Questions C.). Within the tree, we label these

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[8] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

[9] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm

588 questions as pertaining to "Similarity". The questions in box C essentially ask whether
589 there are differences between the adult and pediatric populations, or the devices used in
590 each population, that could impact the safety and effectiveness of the device in pediatric
591 (sub)population(s). In other words, the questions in Box C serve to address whether or
592 not the course of the disease and the effects of the device are sufficiently similar in adults
593 and pediatric patients, and if so, to define what those similarities (as well as differences)
594 are.
595
596 To determine that the effectiveness and safety of the device is similar across adult and
597 pediatric populations, a basic consideration is that the direction of benefit from the device
598 on the outcome should be the same across populations. That is, if the device has a
599 positive effect on adults, then it should also have a positive effect on the intended
600 pediatric population, for the endpoint under study. Some devices are intended to benefit
601 an adult population but are not expected to benefit a pediatric population, and might even
602 worsen the pediatric patient's condition. For example, a device used for damaged joints
603 in adults is considered for the same indication in children; however, because children do
604 not have closed growth plates, the device could cause significant problems for children
605 who are still actively growing. Therefore, the direction of benefit is not the same. The
606 *magnitude* of the device effect should also be similar. Evaluating the extent of similarity
607 of the magnitude across populations may involve research into published literature, and
608 should be considered on a case by case basis.
609
610 The questions in C. should be used to help answer whether the device is expected to have
611 a similar effectiveness and/or safety result across populations. Differences tend to
612 increase the amount of uncertainty in statistical inference when extrapolating from adult
613 to pediatric patients. If all of the five questions are answered "no" for either safety or
614 effectiveness or both, then full extrapolation can be considered if the adult data are of
615 sufficiently high quality. If any of the questions in C. are answered "yes", then the review
616 team should determine whether the adult data provide useful information for partial
617 extrapolation by revisiting answers to the questions within C. as well as any additional
618 important information.
619
620 Questions Box C.
621
622 Question C-1: Is the device implanted or in contact with the body, and if so, does either
623 the location or duration of implantation differ between the adult and intended pediatric
624 (sub)population(s) in such a way that the safety and effectiveness of the device could be
625 impacted in a clinically meaningful way?
626
627 If the location or duration of implantation differs and the difference is expected to impact
628 device safety or effectiveness, then full extrapolation is probably not feasible. However,
629 partial extrapolation may still be viable if the quality of adult data is sufficiently high
630 such that statistical and clinical modeling can account for the difference, and FDA can
631 fairly and responsibly use such data to conclude that there is reasonable assurance of
632 effectiveness and/or safety of the device.
633

634   Question C-2: Are there differences in device characteristics between pediatric and adult
635   use that could impact either device safety or effectiveness in the pediatric
636   (sub)population(s) in a clinically meaningful way?
637
638   For instance, sometimes device modifications (e.g., design, materials, and mechanisms of
639   use) must be made in order to use a device in a pediatric population. To the extent these
640   modifications could impact device safety or effectiveness in a clinically meaningful way,
641   the answer to this question will be yes. Possible differences might include, but are not
642   limited to, differences in human factors issues (e.g., self-administration versus
643   administration by a guardian), reference or normal values, size, scaling of the device,
644   blood sampling or sample quantity issues for in vitro diagnostic devices, energy, delivery,
645   device function, or device materials. This question is also related to whether conditions
646   for preclinical or clinical testing differ between adult and intended pediatric
647   (sub)population(s) and whether the device needs to change over time to accommodate
648   growth and development. Sometimes device characteristics and patient characteristics
649   are intertwined. For example, if the normal value (for diagnostics) or performance (for
650   therapeutics) of the device depends on a body measurement or unique physiology that
651   differs between adult and intended pediatric (sub)population then the device
652   measurement could differ.
653
654   If the answer to question 2 is "yes", then full extrapolation is not feasible. However, as
655   described above, partial extrapolation may still be viable in certain circumstances.
656
657   Question C-3: Are there characteristics unique to the intended pediatric
658   (sub)population(s) that could impact either the effectiveness or safety of the device when
659   used in the pediatric (sub)population(s) in a clinically meaningful way?
660
661   Some devices might require special considerations that affect only pediatric patients; for
662   example:
663
664   • Growth of the child during the device performance period

665   • Specimen sample size or quantity

666   • Reference or normal values

667   • For serologic in vitro diagnostic devices, specific challenges in certain subgroups
668   due to differing immune status

669   • Analytical issues which affect interfering substances for in vitro diagnostic
670   devices

671   • Drug dose or metabolic differences for therapeutic drug monitoring devices

672   • Pediatric human factors

673   • Increased impact of time exposure to younger subjects (e.g., long-term toxicity
674   differences between populations)
675

18

676 The kinetics or physiology might differ between adults and children, which might then
677 influence the interpretation of test results or treatment modality, ultimately impacting the
678 effectiveness or safety of the device across populations.
679
680 An example where patient characteristics might affect interpretation of data concerning
681 device effectiveness is a device indicated for weight loss. In this case, an adolescent and
682 an adult may have different body sizes and/or masses that may impact evaluation of a
683 device's effectiveness. For an adolescent study subject, weight gain could be attributed to
684 normal growth, whereas for an overweight adult, weight gain would more likely
685 demonstrate the failure of the device to have its intended effect.
686
687 If the answer to question C-3 is yes, full extrapolation is probably not feasible. However,
688 as described above, partial extrapolation may still be viable in certain circumstances.
689
690 Question C-4: Are there differences in disease characteristics between adult and pediatric
691 (sub)population(s) that could impact either device safety or effectiveness in the pediatric
692 (sub)population(s) in a clinically meaningful way?
693
694 For some devices, there might be differences in disease characteristics between adults
695 and children, which are highly likely to affect how the device performs or how test results
696 are interpreted. The prevalence or severity of disease characteristics might differ between
697 adults and children, or the natural course of the disease might differ. For example, a
698 diagnostic device could indicate the need for medical intervention differently for children
699 than for adults because analyte levels considered safe may differ for each population.
700
701 If the answer to question C-4 is yes, full extrapolation is probably not feasible. However,
702 as described above, partial extrapolation may still be viable in certain circumstances.
703
704 Question C-5: Are there other differences between adult and pediatric (sub)population(s)
705 that could impact either device effectiveness or safety in the pediatric (sub)population in
706 a clinically meaningful way?
707
708 This question allows for consideration of other differences that are not addressed by the
709 first four questions.
710
711 If the answers to questions Box C are all "no", and if the adult data are of sufficiently
712 high quality, then full extrapolation could be considered, and it is possible that no
713 pediatric data would be needed to achieve approval for the pediatric indication
714
715 Study design and sampling plan are factors that could influence data quality. A registry or
716 single-arm study is of lower quality than a randomized controlled (and blinded) trial.
717 Responses from registries or single-arm studies may be biased in favor of the device
718 because the subjects know they are receiving a new treatment that they hope to be better
719 than the current standard of care. Allowing study subjects to choose their own treatment
720 arms instead of randomly assigning them to treatments may be similarly biased. The
721 "Guidance for Industry, Clinical Investigators, and Food and Drug Administration

19

722 Staff—Design Considerations for Pivotal Clinical Investigations for Medical Devices,"[10]
723 issued in 2013, compares study designs in terms of general quality, and represents the
724 agency's proposed approach on this topic.
725
726 If the answer to any or all of questions in Box C is "yes", then the decision on whether
727 partial extrapolation is appropriate will depend on whether some prospectively collected
728 pediatric data can be obtained and/or whether an appropriate statistical model can be
729 constructed such that pediatric outcomes can be predicted reliably by borrowing strength
730 from the adult data. As stated above, statistical models may be used to combine relevant
731 adult data with pediatric data in order to increase precision in inferences made from a
732 pediatric study. These models can then potentially account for differences identified in
733 the decision tree (see Section 7 and Appendix B for a discussion). In this way, the
734 borrowed or extrapolated data have the potential to be used in some capacity to fairly and
735 responsibly conclude that there is reasonable assurance of the effectiveness and/or safety
736 of the device. If it determined that existing clinical data cannot be fairly and responsibly
737 used in some capacity to conclude that there is a reasonable assurance of effectiveness
738 and/or safety, extrapolation should not be considered.
739
740 It is important to reiterate that any anticipated differences between adult and pediatric
741 populations may not be realized until after the pediatric study is finished, if a study is
742 recommended. Therefore, the *realized* extent of partial extrapolation is determined *after*
743 data become available, and the statistical model is fit to the adult and pediatric data.
744
745 If there are other device- or disease-specific questions not addressed in the Pediatric
746 Extrapolation Decision Tree that could assist the FDA review team in its review, those
747 questions may also be considered under Question C-5 in the tree. These situations may be
748 more complex and require thoughtful collaboration between the FDA review team and
749 the sponsor to determine whether extrapolation might be feasible. Borrowing of data may
750 be achieved for some areas, while the sponsor may need to collect data in other areas. See
751 Appendix A for examples.

752 # 7. Factors That Could Limit Extrapolation
753
754 This section provides a series of general factors that can aid in responding to the
755 questions posed by the decision tree and determining whether, and to what extent,
756 extrapolation is appropriate.
757
758 Factors that may preclude extrapolation of any adult data include but are not limited to
759 the following:
760

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[10]Available at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm.

761 • There is little knowledge of the disease or condition in pediatrics.

762 • The device is not FDA approved or cleared for adults.

763 • Endpoints cannot be directly borrowed.

764 • Statistical models cannot account for differences.

765 • Human factors and growth can affect safety in pediatric patients (these factors
766   don't exist in adults).

767 • Appropriate labeling cannot be written for the pediatric population or
768   subpopulation(s) targeted.

769 • The practice of medicine has changed since the device was initially approved to
770   such an extent that historical data would likely be different than prospectively
771   collected data.

772 • Appropriate risk mitigation cannot be assured.
773

774 Factors that may limit extrapolation to a partial extent and thus require conducting a
775 prospective study of pediatric patients include, but are not limited to, the following:
776

777 • The age difference between the pediatric (sub)population and the available adult
778   data is too great, making it difficult to infer similarity in risk or effectiveness. In
779   such cases, it may be more appropriate to extrapolate to a pediatric age that is
780   closer to the mean age of the adult population. For example, it might be more
781   appropriate to extrapolate young adult data to an adolescent indication than to a
782   neonate indication.

783 • Other supportive pediatric data are outdated and may not properly represent
784   current treatment trends and practices.

785 • There are important differences between the adult and pediatric
786   (sub)population(s) such that the adult data cannot substitute for data from a
787   potential pediatric study to fairly and responsibly conclude that there is reasonable
788   assurance of the safety and effectiveness of the device in the pediatric population.
789

790 Whether any of these factors would preclude extrapolation or limit it to a partial extent
791 depends on how the differences are expected to influence potential conclusions of the
792 new study.

793 # 8. Uncertainty in Extrapolating Data
794

795 Extrapolation does add uncertainty into FDA's assessment of the effectiveness and safety
796 of a device. Whether extrapolating partially or in full, there remains some uncertainty
797 even though statistical modeling may be used to account for observed differences and
798 increase precision of inferences. The extent of this uncertainty depends on the

799 differences between the two populations and the quality of the data. FDA considers this
800 uncertainty as a factor when making benefit-risk determinations.
801
802 The Benefit-Risk Guidance[11] should be consulted for understanding how extrapolated
803 data might be weighed within a benefit-risk framework when considering device
804 approval. Because there may be greater uncertainty when using borrowed data, it may
805 not carry the same weight as stand-alone pediatric studies.
806
807 Regardless of the method used, extrapolation will only be permitted when it can be done
808 in a manner that supports reasonable, scientifically sound conclusions about medical
809 device effectiveness and safety based on valid scientific evidence.

9. Statistical Methodology for Extrapolation

810
811
812 When the use of extrapolation is determined to be appropriate, a sponsor may have
813 several options for how to extrapolate the adult data. Available options could depend on
814 whether a prospective study of pediatric patients is needed and feasible, and/or whether
815 sufficiently robust pediatric data can be obtained in other ways such as from prior studies
816 run by the sponsor, studies in the literature, or pediatric registries.
817
818 Many of the methods available for borrowing strength across studies employ the
819 Bayesian approach to statistics, which espouses learning from evidence as it accumulates.
820 Bayesian statistics use Bayes' theorem to combine prior information with current
821 information on a quantity of interest such as the primary endpoint. The idea is to consider
822 the prior information and the current study results as part of a continuous data stream in
823 which inferences are being updated each time new data become available. Prior
824 information typically comes from results of previous comparable studies. Therefore,
825 Bayesian methods are quite applicable for partial extrapolation from prior adult studies.
826 Refer to FDA's "Guidance for the Use of Bayesian Statistics in Medical Device Clinical
827 Trials,"[12] issued in 2010, for an introduction and more details on Bayesian statistics in
828 medical device studies, including Bayesian hierarchical modeling, described briefly
829 below.

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[11] Available at
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf.

[12] Available at
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071072.htm

9.1 The Bayesian Hierarchical Model and Exchangeability of Studies

Bayesian hierarchical modeling may allow an increase in effective sample size in a new study by "borrowing strength" (information) from prior studies. With a hierarchical model, as the differences among the study results decrease, more information is borrowed among studies, and a smaller sample size is needed for the new (pediatric) study. A typical hierarchical model might have two levels: a patient level and a study level. In a two-level structure, studies have different but related treatment effects (e.g., mean differences between treatment and control group) or mean outcomes. The relationship among the studies is referred to as "exchangeable studies", and has a mathematical definition described in more detail in the FDA Guidance document referenced above. Practically speaking, when two or more studies are exchangeable with one another, it means one could not distinguish the studies only by looking at the study results because there is nothing known a priori that would imply one study achieved a better average outcome from the device than any other study. For a two-level hierarchical model, study treatment effects or means are exchangeable, and patients are exchangeable within studies. It is important to note that patients are not assumed to be poolable across studies.

The assumption of exchangeability facilitates borrowing among studies in a hierarchical model. Statistically, exchangeability implies that the variability of responses within each study is comparable (similar magnitude) to the difference in responses among the studies. This assumption might not hold for extrapolation because adults and children could respond differently to a treatment, and so the responses among studies could be quite different than the responses within each study. If this is true, then a weaker form of exchangeability (partial exchangeablity, discussed in Section 9.2) may hold. Ultimately, the actual extent of borrowing will depend on the data within the model. Therefore, if the device effect is actually observed to differ between adult and pediatric studies, the studies will not borrow much from each other, and the extent of extrapolation will be limited.

In order to determine whether studies are likely to have exchangeable device effects, the FDA review staff and sponsors should identify differences in the studies that could hinder exchangeability. They should compare previous studies with the proposed study for similarity in relevant factors, including the following:

- Device used

- Patient population, including anthropometric measurements, when relevant

- Protocol

- Inclusion/exclusion criteria

- Prognostic factors

- Patient management

872   • Ability of the patients to comply with instructions for safe and effective device
873   use

874   • Proximity in time

875   • Operator training/experience

876
877   Exchangeability is assessed by the clinicians and engineers from FDA as well as the
878   sponsor. The sponsor should be prepared to discuss exchangeability or partial
879   exchangeability among studies given covariates. Partial exchangeability may still hold
880   even if differences in any of the above factors (or others) limits or precludes the
881   assumption of unconditional exchangeability of adult studies with the proposed pediatric
882   study. However, if the identified differences are known to be associated with one or more
883   measured variables, and the measured variables have sufficient overlap between
884   populations, adjustments can be made to a hierarchical model so that the studies might
885   still be exchangeable after accounting for those variables. The next section provides an
886   overview of one commonly used adjustment when the adult and pediatric studies have
887   differences that affect the outcome of the study.   Appendix B provides more statistical
888   details as well as other adjustments.

889   9.2 Age-Related Covariates Associated With Device Outcomes

890
891   As mentioned above, there are likely to be one or more differences that could prevent the
892   assumption of exchangeability between adult and pediatric studies. If these differences
893   can be identified and measured, it is straightforward to account for them in a hierarchical
894   model. When this is done, we can say that the studies are exchangeable, except for
895   measured differences on certain variables. Often the differences will be related to the size
896   or growth of the patient. A simple example might be a new limb prosthetic. The
897   effectiveness and safety of the prosthetic might differ depending on the size or weight of
898   the patient. However, within a given patient size (e.g., height), the performance
899   characteristics might be the same, regardless of whether the patient is an adult or child.

900
901   It is imperative that FDA clinical reviewers and sponsors identify covariates that are
902   associated with device performance and that might be responsible for any perceived
903   differences in outcome for adults versus children or adolescents. A first step after
904   identifying potential covariates associated with device performance is to determine how
905   the covariate affects the primary outcome of the study, and then how age of the patient is
906   related to the covariate. Identified covariates should have sufficient overlap between
907   adult and pediatric populations so that the relationship between the covariate and age on
908   study outcome can be connected across populations.

909
910   For example, a device whose effect is related to hormone level may have very different
911   magnitudes of effect for adults than for children because they have different hormone
912   levels. If patients are categorized into low, medium, and high hormone levels, then within
913   each category, the adult studies might be exchangeable with the pediatric study.
914   Presumably, if hormone level is highly associated with the effect of the device, the

915 sponsor is likely to have patient-level data on the level of the hormone in adults. Patient-
916 level information in children as well would enable the sponsor to construct a model that
917 relates hormone level to outcome, and thus condition on hormone level to assume
918 exchangeability between the adult and pediatric studies. That is, except for hormone
919 level, there are no known (and measured) differences between adults and children that
920 would allow one to identify an outcome as belonging to either an adult or pediatric
921 patient. If there were, then these measured covariates would also be added to the model.
922 The structure of the model would be agreed upon by both the sponsor and FDA.
923 Moreover, once data become available, the assumed model would be checked against the
924 data to ensure it is still valid.
925
926 When premarket pediatric data are needed, there are several suitable study designs and
927 analyses to consider, depending on circumstances related to the feasibility of collecting
928 the data. The "Draft Guidance for Industry, Clinical Investigators, and Food and Drug
929 Administration Staff—Design Considerations for Pivotal Clinical Investigations for
930 Medical Devices,"[13] issued in 2013, discusses several concepts and principles related to
931 designing medical device studies.
932
933

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[13] Available at
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm
This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Appendix A. Examples of the Decision Process for Extrapolation

The examples in this section are intended to demonstrate the use of the Pediatric Extrapolation Decision Tree. The examples are not predictive of FDA decisions but may be considered guides for how FDA weighs the appropriateness of extrapolating existing clinical data to support pediatric indications.

A.1 A Hypothetical Example of Full Extrapolation for Effectiveness

A gel that is used as a pleural air leak sealant is proposed to be indicated for a pediatric population (aged 2–21). The gel is currently approved for adults in the closure of remaining visible air leaks incurred during open resection of lung parenchyma, after standard sutures have been applied; the same condition can occur in pediatrics. Suppose that extrapolation of effectiveness from adults to pediatrics is under consideration. The measure of device effectiveness used to gain approval was that the patient remained free of air leaks 1 month post-surgery, after application of the gel. The same measure would be used for pediatrics. Therefore, the first two questions in the decision tree (A. and B.) are answered yes.

The gel is intended to be applied in the body in the same location for both age groups, for roughly the same duration (eventually the gel gets resorbed and excreted). Furthermore, the gel itself does not have different characteristics for adults than for children. With respect to the purpose of the gel, the disease characteristics (air leaks) are similar for both adult and pediatric patients. However, the size of the air leak and therefore the amount of gel used and perhaps the size of the syringe to deploy the gel could differ between adult and pediatric patients. In this example, the Agency has determined that these differences do not impact device effectiveness in the pediatric population in a clinically meaningful way. The gel has been demonstrated to be equally effective when covering smaller areas as larger areas, and the size of the syringe is not relevant to effectiveness. Therefore, the answers to Box C were all "NO", and full extrapolation of effectiveness data could be considered for this device. In this case, the FDA might decide that adult effectiveness data could be substituted for prospective pediatric study (i.e., full extrapolation) if the adult studies are of sufficient quality.

In separately assessing whether the existing data could be extrapolated to demonstrate safety in the pediatric population, the potential for adhesions was felt to be of concern due to the expected needs for reoperation in this population, based on the preclinical testing results. For this reason, safety extrapolation was not performed and a separate study for safety in pediatrics was recommended.

975
976

A.2 A Hypothetical Example of Partial Extrapolation with Relevant Age-Associated Differences between Populations Accounted for Via Modeling

980
981 A diagnostic device is approved in adults as an aid to diagnosing a particular disease or
982 condition through the quantitative measurement of a particular measurand. This
983 measurand is the same one used to diagnose both adults and children. In the adult study,
984 the device was compared to the currently used diagnostic test, which is generally
985 considered a reference standard method, to provide reasonable assurance of safety and
986 effectiveness. This reference standard method requires the collection of a large amount of
987 blood. An indication is sought for pediatric patients as young as 2 years old. Use of the
988 reference standard method as the comparator for the pediatric population was considered
989 an unsafe option, due to the need to collect large amounts of blood from young children.
990
991 When referencing the flow chart to decide whether or not extrapolation is appropriate, it
992 is apparent that the condition occurs in both adults and pediatrics and that there is an
993 endpoint that is relevant to both populations. It is not known whether the values obtained
994 from the comparator reference standard are the same between adult and pediatric patients.
995 Because these values could differ, the difference in results between the device and the
996 comparator method may have a different magnitude for adults than for children.
997 Accordingly, the difference in blood volume that precludes use of the reference standard
998 method as the comparator is a unique characteristic of the intended pediatric population,
999 which could have a clinically meaningful impact on the safety or effectiveness of the
1000 device. Specifically, the difference in the use of the reference standard may change the
1001 diagnostic result which, if erroneous, could impact patient safety. Therefore, full
1002 extrapolation is not appropriate. We thus proceed to consider whether partial
1003 extrapolation is appropriate.
1004
1005 In this example, the device characteristics, device matrix, and interfering substances are
1006 considered the same for the adult and pediatric population. It is also known that the
1007 reference standard values expected for adults and children can be calibrated to be
1008 comparable by accounting for body size, among other measured patient-level variables
1009 that may be correlated with age. Because calibration using measured variables is possible,
1010 the Agency and sponsor agree that the adult reference standard data can be borrowed
1011 statistically to bolster the expected reference information in pediatrics. To the extent that
1012 the calibrated reference standard values are similar between the adult and pediatric
1013 populations, more adult data can be borrowed. Therefore, because the observed
1014 differences between the adult and pediatric populations can be accounted for in a
1015 statistical model, the extrapolated data may be used in support of demonstrating a
1016 reasonable assurance of the safety and effectiveness of the device. Because the data from
1017 the adult population was of high quality in terms of study design, these data are

1018   considered a viable candidate for partial extrapolation.
1019
1020   This example highlights that borrowing from adult data can be done not only for the
1021   device group in a clinical study, but also for control groups or reference standard values.
1022   In many cases, a control or comparator is not available for pediatrics but it is available for
1023   adults. As illustrated, partial extrapolation can potentially be used in these cases.

A.3 A Hypothetical Example of Partial Extrapolation

1025
1026   Suppose a company wishes to extend an indication to adolescents for their marketed
1027   device X to treat a condition Y. The device is approved for use in adults. There are
1028   several available adult data sets from the US pre-market application as well as from
1029   marketing applications in other regions of the world. The endpoint used in the available
1030   studies is identical to the endpoint desired in the adolescent population. However, the
1031   adults were followed for eight months, and the FDA recommends following adolescents
1032   for at least 12 months. There are no other identified differences between populations
1033   with respect to the anticipated effectiveness or safety of the device. Thus, Box C has
1034   been answered "no". However, full extrapolation is not recommended because the eight-
1035   month adult data are not sufficient to serve as a substitute for twelve-month pediatric
1036   data.
1037
1038   Based on additional information from studies published in medical journals about how
1039   the device performs beyond eight months in adults, the sponsor was able to borrow from
1040   the adult studies and use statistical modeling to predict adolescent response at 12 months.
1041   The predictive model also incorporated some prospectively collected adolescent data out
1042   to 12 months. Thus, the data quality when paired with the statistical model was
1043   determined to be sufficient to allow for partial extrapolation. However, with the
1044   leveraged adult data the sample size estimated for the adolescent study was smaller than
1045   it would have been otherwise. Once the adolescent study is completed, the model will be
1046   verified to ensure that assumptions are met and borrowing is indeed appropriate.

A.4 Hypothetical Examples where Extrapolation is not Recommended

1049
A.4.1 Hypothetical Example where Extrapolation is not Recommended because of Quality of Data

1052
1053   A pre-amendment device is not indicated for pediatric use. When submitting their
1054   device's annual report to FDA, the sponsor cites case report studies which the sponsor
1055   believes suggest an indication for pediatric use may be appropriate. The disease to be
1056   treated is essentially the same in adults and pediatric patients, and the endpoints used to
1057   evaluate clinical outcomes are also the same. There are also no apparent expected
1058   differences between the pediatric and adult response to device. Therefore, the answer to
1059   Box C is "no."

1060
1061   However, the adult data available for extrapolation are decades old. Both the practice of
1062   medicine and relevant study design considerations have significantly changed. As such,
1063   despite the similarities between the adult and pediatric populations, it is likely that FDA
1064   would determine that the adult data in this case are not of sufficient quality for either full
1065   or partial extrapolation.
1066
1067   **A.4.2 Hypothetical Example where Extrapolation is not recommended because of**
1068   **Relevant Differences**
1069
1070   Consider a generic device which is indicated for a rare adult disease. A sponsor would
1071   like to extend the indication to a pediatric subpopulation because the endpoints between
1072   the two groups are similar. The only difference in the response to device intervention
1073   relates to how pediatric growth may impact the safety and effectiveness of the device.
1074   However, the device may need to be removed or adjusted for growth, which requires
1075   surgical intervention and introduces additional risk for pediatric patients. In addition, the
1076   anticipated impact of pediatric growth on device safety and effectiveness is largely
1077   unknown, and there is limited clinical experience in adults so the data are not sufficient to
1078   reliably inform modeling. Partial extrapolation is not feasible because the differences
1079   between the adult and pediatric populations cannot be accounted for, clinically or with
1080   modeling. Therefore, extrapolation is not recommended in this scenario.

A.5 An Example of an Actual Extrapolation

1081

1082
1083   Patients with systemic, left-sided, congenital heart valve disease pose significant
1084   challenges for physicians. There are limited technological solutions available for these
1085   patients. Few replacement heart valves are indicated for pediatric patients, and
1086   commercially available bioprosthetic valves for aortic and mitral valve replacement may
1087   not be available in sizes appropriate for infants and children.
1088
1089   The clinical impact of congenitally deformed valves is significant and often lifelong.
1090   Treatment decisions are almost always impacted by the effects of rapid growth,
1091   active lifestyle, and accelerated deterioration of biological prostheses. Pediatric valve
1092   replacement is a high-risk procedure involving higher operative mortality, high
1093   reoperation rate, and late morbidity compared to adult patients undergoing the same
1094   operation.
1095
1096   The reasons for the higher operative mortality are multiple and complex. Most often, the
1097   available prosthesis is too large for the child's anatomy, resulting in delay in referral for
1098   surgery. When surgery is undertaken, additional steps are often required to enlarge the
1099   site of implantation to accommodate the prosthesis.
1100
1101   Clinical studies have routinely been conducted on the adult patient population. However,
1102   pediatric patients have typically been excluded from replacement heart valve trials for
1103   several reasons, including:

1104
1105   • Limited patient pool requiring a replacement heart valve, which can lead to
1106   prolonged recruitment to achieve required enrollment numbers

1107   • Complex health histories (many leading to early mortality)

1108   • Co-morbidities confounding the adverse event profiles for the study, making it
1109   very difficult to assess overall safety of the valve

1110   • Limited valve sizes available

1111   • Following valve replacement, the pediatric patient continues to grow, ultimately
1112   necessitating reoperation and the placement of a larger valve

1113   • Uniformity of an identifiable patient population is extremely challenging to
1114   achieve, again leading to prolonged study recruitment

1115
1116   Below we trace the pathway to extrapolation of adult data using the decision tree,
1117   beginning with effectiveness. First, the disease is identified as being the same for
1118   pediatrics as for adults. Additionally, the primary endpoint for effectiveness would be
1119   similar in both a pediatric study and adult study (Decision Tree Questions A and B).
1120   Therefore, the adult data is considered relevant.

1121
1122   While a heart valve for a pediatric patient is implanted in the same location as for an
1123   adult, the duration of implantation of a particular size will be shorter for a pediatric
1124   patient due to normal pediatric patient growth. This could influence the effectiveness of
1125   the device for pediatric use. Therefore, the answer to question #1 in Box C is "yes".
1126   Furthermore, one of the most important patient characteristics unique to pediatrics is that
1127   the patient continues to grow after valve replacement, necessitating additional operations
1128   to implant larger valves. This difference can also influence effectiveness. Question #3 is
1129   also answered yes because pediatric patient growth could impact effectiveness of the
1130   heart valve. Therefore, there are some differences related to effectiveness.

1131
1132   However, despite the various differences that could influence effectiveness, these can be
1133   explained clinically as associated with valve size rather than age per se. Additionally,
1134   there is extensive relevant adult data of sufficient quality available for the sizes of interest
1135   and the different positions (aortic, mitral) to inform a statistical model to account for this.
1136   It was thus possible to incorporate a clinical relationship between valve size, position and
1137   device effectiveness into the statistical model used for extrapolation, which could be used
1138   to fairly and responsibly support demonstration of a reasonable assurance of effectiveness
1139   of the device in the pediatric population. Therefore, a partial extrapolation was
1140   considered plausible for effectiveness. FDA agreed that a sample size of 15 pediatric
1141   patients per size per position (aortic, mitral), when combined with the borrowed adult
1142   data, could potentially suffice for demonstrating clinical effectiveness of the device for
1143   the proposed pediatric indication.

1144
1145   In assessing whether the existing data could be leveraged to extrapolate for safety, the
1146   primary difference with pediatric device use is that patient growth after valve

1147   replacement necessitates additional operations to implant larger valves. As such, the
1148   answer to question #2 in Box C would be "yes". This exposes pediatric patients to
1149   additional operations, which pose an incremental risk. Therefore, safety data adequate to
1150   evaluate this incremental risk for pediatric patients was necessary. FDA concluded that
1151   the number of pediatric patients that would be prospectively enrolled to confirm
1152   effectiveness would be sufficient to evaluate safety as well. In addition, a post-approval
1153   study was recommended to assess the long-term safety and effectiveness of the device in
1154   pediatric patients.
1155
1156   This example illustrates how available relevant adult clinical data were leveraged to
1157   bolster new pediatric data in a manner that constitutes valid scientific evidence. When
1158   considered alongside other forms of scientific evidence from assessments of safe device
1159   functioning (e.g., preclinical testing, engineering models, biocompatibility, etc.),
1160   appropriate partial extrapolation was used to support demonstration of safety and
1161   effectiveness of new pediatric heart valves.
1162

Appendix B: Details on Statistical Modeling for Extrapolation
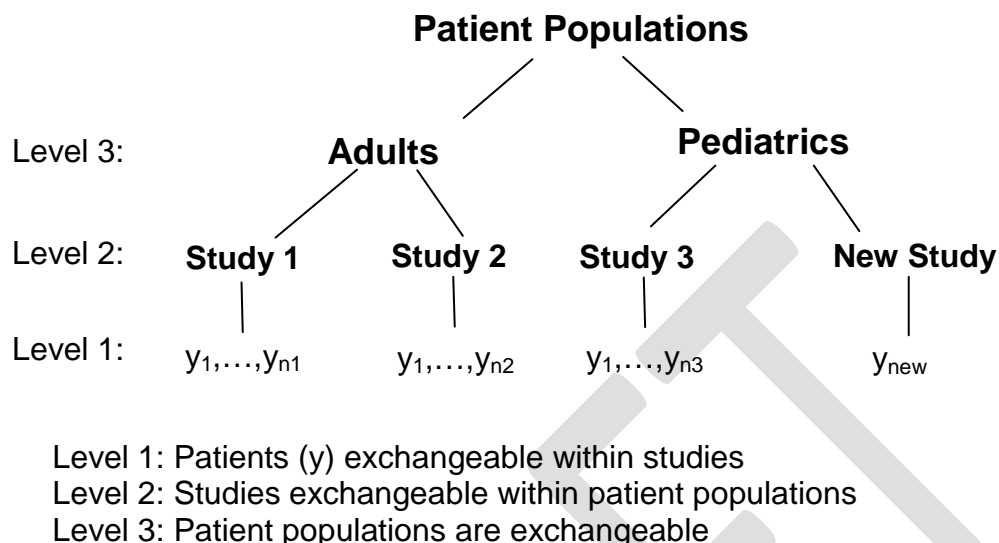
1163
1164
1165
1166 In this appendix, we present further details of statistical modeling that might be
1167 performed for partial extrapolation. As described in the text, a goal for partial
1168 extrapolation is to borrow strength or information from adult data while still accounting
1169 for the important differences between adult and pediatric populations. Accounting for
1170 baseline characteristics is a common way to distinguish studies that should not be
1171 considered exchangeable. This technique was described above. However, if there are
1172 multiple adult studies from which to borrow, then placing another level in the two-level
1173 hierarchy to include subgroups of studies might further temper borrowing between adult
1174 and pediatric studies when they should not be considered on the same level.
1175
1176 We introduce a simple three-level hierarchical model, followed by an overview of other
1177 possible methods for borrowing strength along with pros and cons of the methods.

B.1 A Three-Level Hierarchical Model

1178
1179
1180 In the proposed three-level hierarchical model (see Figure 2), the third level involves the
1181 two patient populations (adults and children), each having studies that are exchangeable
1182 with one another. The adult studies are exchangeable among themselves, and the
1183 pediatric studies are exchangeable among themselves. To facilitate borrowing between
1184 the adult and pediatric studies, they are connected by assuming exchangeability between
1185 the two patient populations regarding the device effect on the endpoint of interest. That
1186 is, prior to knowing anything about what type of effect a device will have, it is presumed
1187 that if there is evidence of the effect of the device on a population, it would not be
1188 possible to tell which population it was, adult or pediatric.
1189
1190
1191

1192 **Figure 2. Three-Level Hierarchical Model Structure Example: Studies Within**
1193 **Patient Populations Have Different But Related Effects**
1194

1195 **Patient Populations**

1196

1197 Level 3: **Adults**   **Pediatrics**

1198

1199 Level 2: **Study 1**   **Study 2**   **Study 3**   **New Study**

1200

1201 Level 1: $y_1,\ldots,y_{n1}$ $y_1,\ldots,y_{n2}$ $y_1,\ldots,y_{n3}$ y_{new}

1202

    Level 1: Patients (y) exchangeable within studies
1203   Level 2: Studies exchangeable within patient populations
1204   Level 3: Patient populations are exchangeable

1205

1206 In Figure 2, patients are represented by their values (y) on the endpoint of interest. There
1207 are n_1 patients in Study 1, n_2 in Study 2, and n_3 in Study 3. (For simplicity, the figure
1208 represents single-arm studies). The adult population produced Studies 1 and 2, and the
1209 pediatric population produced Study 3. The two patient populations are assumed to come
1210 from a common superpopulation of patient populations. The figure also includes a branch
1211 for a future pediatric patient from the pediatric population. With Bayesian hierarchical
1212 models, not only is it possible to borrow strength to estimate individual study means and
1213 their population means, but it is also possible to estimate a predicted value for a new
1214 pediatric patient from the pediatric population, using the Bayesian predictive distribution.
1215 The Bayesian predictive distribution is the distribution of an unknown outcome, which
1216 can potentially be observed in the future. It is essentially the posterior distribution of a yet
1217 to be observed outcome (Carlin & Louis, 2009).

1218 ## B.2 Age-Related Covariates Associated With the Device Effect
1219 ## or Outcome

1220

1221 Figure 2 above is highly simplified because it assumes no differences across patient
1222 populations that would affect the safety or effectiveness of the device. As with the two-
1223 level model, in practice, there are likely to be one or more differences that could prevent
1224 the assumption of exchangeability between adult and pediatric populations (the third
1225 level in the hierarchy). If these differences can be identified and measured, it is
1226 straightforward to account for them in the model. Essentially, the model will dictate that
1227 the populations are exchangeable, except for measured differences on certain variables.
1228 Differences could be static or dynamic (time-varying) over the trial period. Often the
1229 differences will be related to the size or growth of the patient. The structure of the model
1230 should be agreed upon by both the sponsor and FDA. Moreover, once data become

1231   available, the assumed model would be checked against the data to ensure it is still valid.
1232   Section 9.2 also discusses accounting for covariates.
1233

B.3 Extrapolation From a Single Adult Study

1235

1236   When extrapolating from adult studies, it is advantageous to have several prior studies to
1237   use in an analysis to facilitate more precise estimation of the device effect in pediatrics.
1238   However, it is often the case that only a single prior adult study exists. Although the
1239   example above described borrowing from two adult studies, similar methodology can be
1240   used when there is a single prior adult study available. FDA's "Guidance for the Use of
1241   Bayesian Statistics in Medical Device Clinical Trials" (2010) discusses limitations with
1242   the use of Bayesian hierarchical models with a single prior study.
1243

1244   Several authors have developed methods for incorporating a single historical study as
1245   prior information in a Bayesian model, where the weight placed on the historical study
1246   varies with the similarity of the historical study and the current study data as they are
1247   collected (e.g., Hobbs et al., 2011, 2012). Some of these methods have similar limitations
1248   with hierarchical models in that fairly informative priors must be used to describe the
1249   relationship between the historical and current studies. However, the specification of the
1250   priors might be conceptually easier than with a hierarchical model.
1251

1252   In limited cases it might be reasonable to prespecify, as a percentage, the amount of
1253   borrowing from the prior adult data set(s). The method of power priors (Ibrahim & Chen,
1254   2000) uses a prior that is constructed from the likelihood of the prior data raised to a
1255   power, where the power falls between 0 and 1. The power indicates the downweighting
1256   of the prior data, so that a power of 0.5 implies that 50% of the information from the prior
1257   likelihood is borrowed. Unfortunately, when the power must be fixed in advance, it
1258   cannot change based on later observed data from a new pediatric trial. Placing a prior on
1259   the power parameter itself, thereby potentially allowing the data to determine the amount
1260   of borrowing, has been shown in practice to have limited success (see, for example, the
1261   discussion in Hobbs et al., 2011).

B.4 Additional Methods for Extrapolation

1263

1264   While Bayesian methods are described in this document, non-Bayesian methods can also
1265   be used for borrowing strength. The structure of the hierarchical model is not inherently
1266   Bayesian, and it can be used without the interpretation of posterior probability. However,
1267   in many cases the overall conclusions will remain the same, and the Bayesian
1268   interpretation of posterior probability is often simpler to understand.
1269

1270   As mentioned above, the Bayesian hierarchical model can be difficult to use when there
1271   is only one observed prior adult study. The between-study variance either must be
1272   prespecified (and just like with the prespecified power parameter for the power prior, it
1273   cannot be changed once the pediatric trial is run), or an informative prior must be placed

1274   on the between-study variance, potentially limiting the range of values it can realize once
1275   the pediatric study is run.
1276
1277   In addition to hierarchical models, one could use propensity score methods for
1278   extrapolation from adult data (Rosenbaum & Rubin, 1983; Yue, 2007, 2012). A
1279   propensity score for a subject is the probability of the subject being assigned to the device
1280   group in a medical device clinical trial, rather than to the control group, conditional on a
1281   set of measured baseline covariates (but not on the measured outcome variable). In a
1282   randomized trial, with 1:1 randomization, this probability is by definition 0.5,
1283   independent of any covariates. In a nonrandomized study, the probability often depends
1284   on observed covariates. If it depends only on observed covariates, then for the same
1285   values on those covariates, two subjects have the same probability of being assigned to
1286   the device group. For a set of subjects with the same probability of receiving the device
1287   over the control, an estimate of the treatment effect will be unbiased, just as it would be
1288   in a randomized trial. Accounting for the propensity score in a regression model or
1289   matched analysis can then yield an overall estimate of the device effect that is unbiased
1290   despite the trial being nonrandomized.
1291
1292   If adult data are available from a previous trial, adult subjects could be grouped with
1293   pediatric subjects based on their propensity scores (say, in quintiles). Those subjects with
1294   the same propensity score quintile would be compared (device versus control) to obtain a
1295   device effect within each propensity score grouping. An overall estimate of the device
1296   effect can be obtained using regression adjustment. In general, this adjustment is similar
1297   to that described in Sections 9.2 and B.3 (Age-Related Covariates Associated With
1298   Device Effect). However, the propensity score is a single representation of all measured
1299   baseline covariates. The single-dimensional representation makes it easy to use in
1300   modeling, but the form of the model might be difficult to determine from a summary
1301   measure rather than from individual covariates. Moreover, there is no simple way to
1302   account for variability across studies that the hierarchical model can incorporate.
1303

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