requirements under section 745A(b)(3) of the FD&C Act (*i.e.,* standards, timetable, criteria for waivers of and exemptions), indicated by the use of the mandatory words, such as must or required, this document is not subject to the usual restrictions in FDA's good guidance practice regulations, such as the requirement that guidances not establish legally enforceable responsibilities. (See § 10.115(d).)

To the extent that this guidance describes recommendations that are not standards, timetable, criteria for waivers of, or exemptions under section 745A(b)(3) of the FD&C Act, it is being issued consistent with FDA's good guidance practices regulation (§ 10.115). The guidance represents the current thinking of FDA on Electronic Submission Template for Medical Device De Novo Requests. 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. This guidance contains both binding and nonbinding provisions.

II. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by downloading an electronic copy from the internet. A search capability for all Center for Devices and Radiological Health guidance documents is available at *https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products.* This guidance document is also available at *https://www.regulations.gov, https://www.fda.gov/regulatory-information/search-fda-guidance-documents* or *https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.* Persons unable to download an electronic copy of ''Electronic Submission Template for Medical Device De Novo Requests'' may send an email request to *CDRH-Guidance@fda.hhs.gov* to receive an electronic copy of the document. Please use the document number GUI00021027 and complete title to identify the guidance you are requesting.

III. Paperwork Reduction Act of 1995

While this guidance contains no new collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521). The collections of information in the following table have been approved by OMB:

21 CFR part; guidance; or FDA form	Topic	OMB control No.
807, subpart E	Premarket notification	0910–0120
860, subpart D	De Novo classification process	0910–0844
800, 801, and 809	Medical Device Labeling Regulations	0910–0485

Dated: August 20, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2024–18983 Filed 8–22–24; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2021–N–0874]

Final Decision on the Proposal To Refuse To Approve a New Drug Application for ITCA 650

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order under the Federal Food, Drug, and Cosmetic Act (FD&C Act) refusing to approve a new drug application (NDA) submitted by Intarcia Therapeutics, Inc., an i2o Therapeutics Business Unit, (Intarcia) for ITCA 650 (exenatide in DUROS device). FDA has determined that the approval criteria in the FD&C Act have not been met because Intarcia has failed to demonstrate that ITCA 650 is safe for its intended conditions of use.

DATES: This notice is applicable August 23, 2024.

FOR FURTHER INFORMATION CONTACT: Rachael Vieder Linowes, Office of Scientific Integrity, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4206, Silver Spring, MD 20993, 240–402–5931.

SUPPLEMENTARY INFORMATION:

I. Factual and Procedural Background

ITCA 650 (exenatide in DUROS device) is a novel drug-device combination product for human patients intended to deliver the active ingredient, exenatide, a glucagon-like peptide-1 receptor agonist (GLP–1 RA). Intarcia proposed that ITCA 650 be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. ITCA 650 is intended to provide continuous dosing of exenatide from an osmotic mini-pump implanted in the subdermal space of the abdomen for 3 months for initiation of therapy and every 6 months afterwards for maintenance therapy. ITCA 650 must be inserted and removed by a healthcare provider trained on the included placement tool and guide. ITCA 650 is proposed in two dosage strengths: 20 micrograms (mcg)/day for 3 months and 60 mcg/day for 6 months. The drug formulation used in ITCA 650 is a viscous, non-aqueous suspension. Each mini-pump of ITCA 650—20 mcg/day for 3 months and 60 mcg/day for 6 months—nominally contains 2.56 milligrams (mg) and 14.05 mg of synthetic exenatide, respectively.

On November 21, 2016, Intarcia submitted NDA 209053 for ITCA 650. In support of its NDA, Intarcia included three phase 3 clinical trials to establish substantial evidence of safety and effectiveness—CLP–103, CLP–105, and CLP–107. CLP–107, also known as FREEDOM, was a cardiovascular outcome trial (CVOT). On September 21, 2017, the Center for Drug Evaluation and Research (CDER) issued a complete response (CR) letter to Intarcia stating that the NDA could not be approved in its present form. On September 19, 2019, Intarcia resubmitted the NDA, and on March 9, 2020, CDER issued a second CR letter stating that the NDA could not be approved in its present form, describing specific deficiencies and, where deemed possible, recommending ways that Intarcia might remedy those deficiencies.

On March 16, 2021, after pursuing formal dispute resolution, Intarcia submitted a request under 21 CFR 314.110(b)(3) for an opportunity for a hearing on whether there are grounds under section 505(d) of the FD&C Act (21 U.S.C. 355(d)) for refusing to approve the NDA for ITCA 650. CDER subsequently published a notice of opportunity for a hearing (NOOH) regarding a proposal to refuse to approve the NDA (86 FR 49334

(September 2, 2021)). CDER highlighted six deficiencies with the NDA in the NOOH. CDER found that the clinical trial data raised concerns that ITCA 650 causes acute kidney injury (AKI), specifically that more subjects who received ITCA experienced AKI events than those who received the placebo. In addition to finding that those who experienced AKI events sometimes needed prolonged hospitalization, CDER also determined that ''a majority of the serious AKI events in participants randomized to ITCA 650 appeared to be associated with vomiting, diarrhea, and dehydration, which are known adverse reactions associated with exenatide therapy, supporting a causal relationship between ITCA 650 and AKI'' (86 FR 49334 at 49335). Further, CDER concluded that Intarcia's proposed risk mitigation measures were inadequate and that ''sufficient risk mitigation approaches could not be identified for the AKI risk identified in the clinical trial data, particularly because serious AKI events occurred in participants who received ITCA 650 who did not have known risk factors.'' (86 FR 49334 at 49336).

CDER's second deficiency noted that the cardiovascular risk assessment failed to provide sufficient assurances that ITCA 650 is not associated with excess cardiovascular risk. In particular, CDER stated that ''the clinical trial data suggested that ITCA 650 may be associated with an increased risk for major adverse cardiovascular events (MACE), defined as myocardial infarction, nonfatal stroke, and cardiovascular death.'' (86 FR 49334 at 49336). The other deficiencies related to concerns regarding the in vitro dose delivery performance data and drug-release specifications, delivery performance data and variability in daily in vitro drug-release (IVR) data, inadequate support of sterility assurance, and deficiencies regarding certain manufacturing practices. Key aspects of those deficiencies included that ''the in vitro device performance data demonstrated inconsistent day-to-day drug delivery and did not support that weekly and biweekly in vitro drug-release testing is adequate to ensure controlled in vivo drug release by the device constituent of ITCA 650,'' and that ''failure rate data was inadequate to support the safety and effectiveness of the device constituent of ITCA 650'' (86 FR 49334 at 49336).

Intarcia, through counsel, timely requested a hearing and subsequently submitted data, information, and analyses in support of that hearing request. Intarcia further argued that the risks identified by CDER are in line with the risks of the product class, as opposed to unique to ITCA 650, and that, provided there are appropriate restrictions included in ITCA 650's labeling, the safety profile for ITCA 650 falls in line with the product class. Intarcia stated that ITCA 650's benefits, including the new dosage form for patients, outweighs its risks and allows for a positive benefit-risk ratio that supports approval.

More specifically, Intarcia disputed CDER's determination that ITCA 650 led to higher AKI events in a controlled clinical setting compared to other products in its class. In support of its contention, Intarcia submitted an analysis of publicly available clinical review documents for Wegovy, an approved drug with a similar active ingredient, *i.e.,* a GLP–1 RA. Intarcia maintained that its analysis shows a comparable number of AKI events for Wegovy in the clinical trial setting but that FDA nonetheless approved Wegovy. Intarcia pointed to this analysis as evidence that ITCA 650's risks are in line with the drug product class risks and should also be able to receive approval, despite the AKI concerns. Intarcia made similar statements regarding adverse events (AEs) involving gastrointestinal (GI) issues stemming from AKI events in the clinical data for ITCA 650, in that their occurrence was in line with expectations for GLP–1 RA-containing drugs, including Wegovy.

Regarding the cardiovascular risk, Intarcia stated that CDER previously acknowledged that, ''due to the limited size and duration of the preapproval CVOT, the hazard ratio for cardiovascular risk was not definitive and would not constitute sufficient grounds for denial of the NDA, as long as a postmarketing CVOT would be completed.'' Intarcia stated that, because CDER overstated the AKI risk for ITCA 650 and admitted that the cardiovascular risk is not grounds for denial, ITCA 650 should be approved.

In accordance with 21 CFR 314.200, CDER then submitted a proposed order denying Intarcia's hearing request on the proposal to refuse to approve ITCA 650. In the proposed order, CDER provided findings that Intarcia had not raised a genuine and substantial issue of fact justifying a hearing regarding CDER's proposal to refuse to approve NDA 209053 in its present form. The proposed order found that the data and other evidence submitted in support of the NDA for ITCA 650 does not show the product to be safe under section 505(d)(2) of the FD&C Act:

> Intarcia's NDA fails to demonstrate that the novel combination of the DUROS pump device and exenatide (ITCA 650) is safe for use, in part because the IVR data do not demonstrate that ITCA is reliable and do not validate the limits of the dose delivery specifications for the device, the proposed acceptance criteria are too wide and would allow drug release that is not sufficiently controlled by the device to meet clinical needs, and the device hazards associated with failure modes have not been sufficiently addressed by new risk control measures.

The proposed order further described how the inaccurate dosing ''raises significant safety concerns because marked increases in [ ] exenatide increase the risk of gastrointestinal intolerability, AKI, and potentially MACE.'' In the proposed order, CDER noted how Intarcia's acceptance criteria for its dosing is ''unacceptably wide,'' indicating that the drug release is not well controlled and that, therefore, ITCA 650 is not safe for use under the proposed conditions.

Regarding the AKI events, the proposed order included analysis of Intarcia's clinical trials and concomitant findings that serious adverse events of AKI occurred in 14 study participants (0.5 percent) who received ITCA 650 (all requiring hospitalization) and 4 (0.2 percent) who received placebo. The proposed order found that this imbalance ''leads to an unfavorable benefit-risk assessment for ITCA 650 based on the data and information contained in the NDA in its present form.'' According to the proposed order, even a reanalysis of the data in a manner that would be most favorable to Intarcia would still raise a concern regarding the number AKI events for ITCA 650, leading to an unfavorable benefit-risk balance, which would preclude approval. CDER's proposed order accounted for Intarcia's Wegovy discussion and concluded that ''the numeric imbalance in serious AKI adverse events in [FREEDOM] suggests that ITCA 650 causes AKI to a greater extent than other members of the GLP–1 RA class, which did not show numeric imbalances in large, randomized clinical trials, and that the available data set ITCA 650 apart from the class with regard to AKI risk.'' The proposed order further included a conclusion that the AKI risk indicated by the data offered in support of approval cannot be adequately mitigated with post-approval measures because the AKI events occurred in patients who did not have known risk factors and they occurred in both the initial and maintenance dosing.

CDER's proposed order also addressed the cardiovascular risk, stating that the CVOT for ITCA 650, which was conducted in the population ''most

likely to reveal an adverse effect on MACE because of high baseline cardiovascular risk, had a hazard ratio (HR) for MACE alone of 1.24 (95 percent confidence interval: 0.90, 1.70).'' According to the proposed order, the HR was in the higher range, and, coupled with the AKI concerns, does not support approval. Additionally, the proposed order addressed Intarcia's contention that ITCA–650's status as a new dosing option tips the benefit-risk balance in favor of approval. CDER stated that Intarcia has provided no evidence that its new method would increase adherence among patients.

On October 10, 2022, Intarcia responded to CDER's proposed order. By letter dated February 7, 2023, the Office of the Commissioner (OC) provided Intarcia with an opportunity, pursuant to § 12.32 (21 CFR 12.32), to request a hearing under part 14 (21 CFR part 14) in lieu of a formal evidentiary hearing under part 12 (21 CFR part 12) and indicated that the Agency would conduct any such hearing before the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC). On February 20, 2023, Intarcia requested a public hearing before the EMDAC in lieu of a formal evidentiary hearing. On March 24, 2023, OC granted Intarcia's request and explained that, under § 12.32(f)(1), OC would treat the votes and discussion of the issues by the EMDAC as an initial decision under 21 CFR 12.120 and that both CDER and Intarcia could file exceptions to those votes and discussion pursuant to 21 CFR 12.125. OC further indicated that it would render a final decision for the Agency based on the public record.

On August 24, 2023, FDA published the notice of hearing before the EMDAC on the proposal to refuse to approve ITCA 650 and summarized the issues to be considered and addressed (88 FR 57958). CDER conducted the hearing before the EMDAC on September 21, 2023. After the EMDAC heard presentations from CDER, Intarcia, and the public participants, the EMDAC voted unanimously that, based on the available evidence, Intarcia had not demonstrated that the benefits of ITCA 650 outweigh its risks for the treatment of T2DM. The EMDAC members explained the reasoning behind their votes, which is summarized below. After the EMDAC meeting, Intarcia submitted timely exceptions to the EMDAC's votes and advice, and CDER responded to Intarcia's exceptions. Therefore, this matter is before the Principal Deputy Commissioner (PDC) on appeal under 21 CFR 12.130.

II. Relevant Statutory Framework

Pursuant to section 503(g) of the FD&C Act (21 U.S.C. 353(g)), for a combination product containing a drug and a device with a primary mode of action of a drug, Intarcia submitted an NDA for ITCA 650. Under section 505(d) of the FD&C Act, FDA may approve an NDA only if it contains, among other things, a demonstration of the safety and effectiveness of the product for the conditions prescribed, recommended, or suggested in the proposed labeling. FDA must deny approval if the evidence does not show that the drug is safe for use under the proposed conditions (section 505(d)(2) of the FD&C Act) or if there is insufficient information about the drug to determine whether it is safe for use under such conditions (section 505(d)(4) of the FD&C Act). In making these assessments, FDA ''implement[s] a structured risk-benefit assessment framework . . . to facilitate the balanced consideration of benefits and risks'' (section 505(d) of the FD&C Act).

III. Analysis

A. EMDAC's Votes and Discussion

At the hearing under part 14, both CDER and Intarcia made presentations consistent with their previous submissions in this matter with respect to CDER's proposal to refuse approval of ITCA 650. At the close of the hearing, in light of those presentations and the presentations by public participants, the EMDAC then considered two discussion questions and voted on whether, based on the available data, Intarcia had demonstrated that the benefits of ITCA 650 outweigh its risks for treating T2DM. The discussion questions focused on the safety profile of ITCA 650 with respect to AKI, ''cardiovascular safety'' and ''overall safety'' and the benefit-risk ''balance of ITCA 650 for the indication to improve glycemic control in patients with T2DM.''

With respect to the discussion question regarding ITCA 650's safety profile, including the risk of AKIs and cardiovascular events, the EMDAC Chair summarized the views expressed by the committee as follows:

> [R]egarding whether the safety profile of [ ] ITCA 650 has been adequately characterized based on available data with respect to the AKI safety signal, what I heard is that panel members expressed concerns about the imbalance in AKI. Although some panel members also noted the low incidence, there were concerns expressed about this risk being increased while on metformin, or ACE [angiotensin-converting enzyme] inhibitors, or ARBs [angiotensin receptor blockers], which are therapies that patients with [T2DM] are likely to be taking. * * * Regarding cardiovascular safety, there were a lot of comments about this, and I think, in general, the panel expressed a lot of concerns about the point estimate of cardiovascular risk being above 1 and felt that the cardiovascular safety signal needs to be further investigated before consideration for approval. * * * Then lastly, in terms of overall safety, the panel did have concerns. Some of the concerns expressed were related to, really again, AKI cardiovascular risk[,] but also all-cause mortality was mentioned. A few panel members expressed concerns about lack of information about glycemic excursions and rate of hyper- and hypoglycemia with concerns about variability in the release of the drug.

A review of the transcript confirms the accuracy of this summary. Of note, multiple EMDAC members expressed concerns about the AKIs and cardiovascular risks given how little is known about the drug delivery and the variability of the delivery levels. In general, the EMDAC expressed a need for more data related to AKIs, cardiovascular risks, and overall safety to assess whether ITCA 650 is sufficiently safe for the indicated population.

With respect to the discussion question regarding the benefit-risk balance of ITCA 650, the EMDAC Chair summarized the committee's stated views as follows:

> Regarding the panel's assessment of the benefit-risk balance of ITCA 650 for the indication to improve glycemic control in patients with [T2DM], what I heard was that, in general, panel members felt that the benefits of ITCA 650 didn't outweigh the risks. Panel members commented on the moving testimonies during the open public hearing. [T2DM] is a devastating disorder to live with. We need to do better with available therapies and other treatments, but right now there are other options for [T2DM] treatment, and several of them reduce cardiovascular risk and risk for kidney outcomes. * * * Furthermore, I heard the panel members talk about adherence being a very complex problem, and the management of [T2DM] is not just about taking a single medication; there are many other factors. Right now, we really don't have evidence for improved adherence or adequate data to alleviate the safety concerns. The benefit of [ ] lowering [blood sugar levels] is not enough for a [T2DM] medication necessarily now; we need to also be looking at cardiovascular benefits, heart failure, and kidney outcomes, among others.

A review of the transcript again confirms the accuracy of the Chair's summary. Of additional note, several EMDAC members expressed concerns that variability in drug delivery by ITCA 650, as suggested by the data, could lead to patients receiving less reliable dosages of the drug on a regular basis than they would if they were using an

analogous drug regimen not delivered via an osmotic drug-delivery device.

The hearing concluded with the EMDAC's consideration of a voting question: ''Based on the available data has the [sponsor] demonstrated that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of T2DM?'' As noted above, the EMDAC members voted unanimously—by a vote of 19 to 0—that Intarcia had failed to make such a showing, and each provided a rationale for their vote. The Chair summarized the EMDAC members' stated rationales as follows:

> As you heard, none of the panel members voted yes[,] and all 19 panel members voted no. What I heard is that panel members mentioned the uncertainty about AKI and cardiovascular safety, as well as the variability in drug delivery being the greatest concerns, and then whether or not this is the best version of the device was questioned. * * * I think, overall, the panel acknowledged the work that has gone into ITCA 650 and this innovative approach[ ] but felt that it would be a disservice to our patients to recommend approval with the safety and drug delivery concerns that exist, and panel members voiced their understanding of the negative impact of [T2DM] and the hope that the applicant can do [ ] additional safety studies because of the great potential for this device.

Of note, the EMDAC consistently voiced safety concerns about ITCA 650 based on the data presented at the hearing, including the potential for cardiovascular complications and AKIs and the variability of the dosages provided by the device component of the product. Several EMDAC members also observed that resolving these safety concerns before approval of ITCA 650 would be essential and that post-approval studies would be inadequate to ensure the safety of the product for patients.

B. Procedural Objections Raised by Intarcia on Appeal

On appeal, Intarcia's arguments regarding the procedural aspects of the EMDAC hearing generally question the overall fairness of the proceeding. In general, Intarcia presented concerns related to the scope of the meeting and the voting question, specifically that the EMDAC did not focus solely on the issues identified in CDER's NOOH and that the considerations before the EMDAC were ''unjustly expanded'' beyond the scope of the NOOH. Furthermore, Intarcia states that the EMDAC Chair did not let Intarcia address certain ''inaccurate statements'' made by CDER and the EMDAC regarding: (1) the death narratives for certain subjects in the clinical studies of ITCA 650 and (2) a comparison of AKI events in the clinical data for ITCA 650 in relation to the clinical data for other products in the same class that received FDA approval. Intarcia also argues that CDER's presentation approach ''did not allow the EMDAC to engage in a fact-based and evidence-based deliberation and voting discussion that was supported to address the comparative GLP–1 safety assertions in CDER's proposed order under dispute.'' Where procedural objections and factual objections intertwine, the PDC addresses the core of the factual disputes below. Here, the analysis focuses on the overall fairness of the hearing.

After considering Intarcia's procedural objections, the PDC finds that they are unfounded. When Intarcia requested the part 14 hearing in lieu of a formal evidentiary hearing under part 12, the PDC did not limit the scope of what would be reviewed by the EMDAC. CDER appears to have followed its standard processes for advisory committee meetings and presented its full assessment of Intarcia's NDA to enable the EMDAC to render an initial decision on whether the data offered in support of the NDA show that the benefits of ITCA 650 outweigh its risks. Intarcia received proper notice of the issues before the EMDAC, including the voting question. As was borne out at the EMDAC meeting itself, Intarcia had the opportunity to shape the issues for the advisory committee meeting through its briefing materials and presentation.

As to Intarcia's contentions regarding the EMDAC Chair's meeting facilitation the PDC does not find any evidence of unfairness or prejudice against Intarcia after reviewing the EMDAC transcript. Both CDER and Intarcia had opportunities to present their views on the issues, ask clarifying questions of the other, and answer questions posed by the EMDAC. Intarcia argues that there were instances when the EMDAC Chair did not allow it to properly rebut certain assertions by CDER or the EMDAC members and when the EMDAC Chair made allegedly inaccurate statements. The PDC does not find that the inability to further respond to certain issues created an unfair hearing or any prejudice in this instance. The statements that Intarcia claims it was unable to rebut or challenge, namely statements regarding the death narratives for certain clinical study subjects and AKI rate reflected in the clinical data for ITCA 650 compared to the data for other products in the same class, were addressed in both CDER and Intarcia's presentations, as well as in the EMDAC's briefing documents. Intarcia had ample opportunity throughout the hearing to address both topics. Therefore, the EMDAC Chair's decision not to give Intarcia an additional opportunity to address either matter does not persuade me that the hearing was unfair. Further, as the PDC will explain in more detail below—after considering the additional information Intarcia presented on appeal, including statements on the death narratives and examples of what Intarcia states were ''inaccuracies''—the PDC does not believe that any of the procedural issues to which Intarcia points prejudiced it in a meaningful way or materially affected the advice and recommendations provided by the EMDAC. Perhaps more importantly, the PDC concludes that any alleged deficiency in the hearing process before the EMDAC would not affect her judgment with respect to the substantive issues discussed next.

C. Substantive Objections Raised by Intarcia on Appeal

Intarcia's factual challenges center on three areas: the AKI discussion and conclusions, the necessity of a post-approval CVOT, and the IVR data and performance. Intarcia disputes numerous assertions and findings related to AKI events in the clinical data offered in support of approval, including: (1) whether the number of serious adverse events (SAEs) in the clinical studies cited by CDER was accurate, (2) whether the AKI events are a product-class issue, as opposed to an issue specific to ITCA 650, and (3) whether the GI-related events are also a drug-class issue related to the AKI events. Intarcia further disputes the EMDAC's findings on the necessity of another pre-approval CVOT, largely by suggesting that CDER's presentation on the issue was incomplete or misleading. Intarcia states that CDER misrepresented conclusions related to the necessity of another CVOT and that CDER presented conclusions conflicting with statements from its own dispute resolution process. Intarcia also asserts that there were multiple areas where CDER either did not provide proper context or provided false information regarding ITCA 650 and other products in the drug class. Regarding ITCA 650's device performance and dose variability, Intarcia claims that CDER's presentation was misleading in that it relied on hypotheticals while discussing the device.

Beyond these specific challenges, Intarcia generally argues that the data provided in ITCA 650's NDA shows that the combination product would have a

positive benefit-risk profile if (1) the labeling included an AKI warning consistent with other products in its class and (2) Intarcia conducts a post-approval CVOT study. Intarcia presented a letter from 12 experts stating that (1) ITCA 650 addresses an unmet need by promoting adherence to the therapy though its implant, (2) the AKI imbalance issue is well-known and there is no ''meaningful difference'' between ITCA 650's occurrences and others in the drug class, and (3) the cardiovascular data meet the requirements for approval with a post-marketing study to ''further narrow the confidence interval around MACE events.'' Furthermore, Intarcia asserts that CDER made ''numerous misrepresentations of fact'' and that the EMDAC was given ''materially false and misleading information'' in the CDER briefing documents, which ''did not allow the EMDAC to engage in a fact-based and evidence-based deliberation and voting discussion that was supported to address the comparative GLP–1 safety assertions in CDER's proposed order under dispute.'' [1]

Before addressing the specific factual challenges, the PDC first addresses the allegations that CDER made misrepresentations of facts and presented materially false and misleading information. In support of this position, Intarcia points to alleged inconsistencies in CDER's position during the review process and in its presentation to the EMDAC. For example, Intarcia states that CDER made misrepresentations related to the MACE data and the intersection of that data with the AKI imbalance by citing what it claims are differences in CDER's position in the formal dispute resolution process and the current process. In both the proposed order and its presentation to the EMDAC, CDER has consistently described its concerns with the MACE data and maintained that, taken together with its other concerns with ITCA 650, the data do not support approval because the benefit-risk profile presented by the clinical data offered in support of the NDA does not support approval. The documents associated with the prior dispute resolution process are not part of the record before the PDC in this proceeding. Nevertheless, even if Intarcia's allegations of inconsistency are accurate, a mere evolution in thinking by CDER, including statements in previous decisions by specific officials within CDER, would not establish that CDER misled the EMDAC.

In support of its position that CDER misled the EMDAC, Intarcia also includes a list of allegedly inaccurate claims that misled the EMDAC, including but not limited to the number of AKI-related deaths, the AKI imbalance calculation, and hypothetical device graphs used during CDER's discussion of the IVR concerns. Intarcia's disagreement with CDER's assessments do not even approach establishing that CDER made an effort to mislead the EMDAC, and a review of Intarcia's arguments and the underlying record bears out that Intarcia merely disagrees with CDER's interpretation of the evidence in many instances.

Regarding the AKI disputes, the differences in interpretation of the data regarding AKI events were central to the presentations by Intarcia and CDER, and their divergent views do not establish an effort by CDER to mislead the EMDAC. The PDC addresses the disputes regarding AKI events in the clinical data in detail below but finds nothing in the record before her to indicate that CDER misled the EMDAC or included inaccurate information in its briefing materials for or its presentation to the EMDAC. As to the IVR dispute, CDER affirmatively disclosed that its presentation used hypothetical graphs, negating the argument that the data used in those hypothetical graphs were inaccurate or misleading. CDER appears to have presented those graphs to demonstrate the effect of inconsistent dose delivery in hypothetical devices as a means of providing context and enabling a fuller understanding of the clinical data presented. While the PDC does not explicitly address each aspect of Intarcia's claims that CDER misled or misrepresented the evidence or data to the EMDAC, the record before her establishes that Intarcia's arguments along those lines reflect disagreement with CDER's interpretation of the data and do not show that the CDER's presentation to the EMDAC or its briefing materials were misleading or inaccurate. Further, as previously discussed, Intarcia had ample opportunity to challenge CDER's interpretation of the data and frame the scientific issues for the EMDAC.

After reviewing the information presented by Intarcia on appeal and documents contained in the public record, the PDC finds that CDER's presentation, while at odds with Intarcia's own interpretation of the underlying data, contained appropriate conclusions. As to the allegedly inaccurate statements by the EMDAC Chair, a review of the evidence and the meeting transcript supports that the EMDAC's overall assessment was amply reasoned and supported based on the underlying record. In short, the PDC finds that the data presented and evaluated by the EMDAC regarding the safety of ITCA 650 precludes a finding that the drug is safe for use under the proposed conditions.

Intarcia urges FDA to consider ITCA 650's NDA based on a comparison to approved drug products, rather than on its own standalone merits. The PDC finds that the benefit-risk profile of ITCA 650, as reflected in the data and other information presented at the hearing, is inadequate to support approval. In so finding, the PDC is aligned with the conclusions of the EMDAC, whose stated views on the safety of ITCA did not, to any meaningful degree, hinge on comparisons to the benefit-risk profile of other therapies. The evidence presented to the EMDAC highlights serious safety concerns that have not been adequately addressed by the information contained in ITCA 650's NDA. Based on the multiple safety concerns addressed below, the NDA in its present form does not support a determination that ITCA 650 is safe within the meaning of section 505(d)(2) of the FD&C Act. As discussed in more detail below the PDC has further concluded, based on the data, information, and arguments presented to the EMDAC, that Intarcia has failed to show that the benefit-risk profile of ITCA 650 compares favorably to drug products currently on the market.

The PDC now addresses each area of concern identified by Intarcia with respect to EMDAC's conclusions regarding the clinical data offered to support approval of ITCA 650, namely issues related to concerns expressed by CDER with respect to AKI and cardiovascular events and variability in the dosing provided by the product.

[1] After the EMDAC meeting, the PDC received comments from former Intarcia employees who claimed that CDER made misleading claims during the EMDAC meeting. These documents are available on the docket at *https://www.regulations.gov,* docket numbers FDA–2021–N–0874–0081 and FDA–2021–N–0874–0082. Specifically, the individuals challenged hypothetical information that CDER provided the EMDAC related to device performance and CDER's failure to address certain analysis related to the IVR data. Consistent with the analysis included in this section, the PDC has considered the claims and, after reviewing information contained the public record, the PDC finds that CDER did not mislead the EMDAC by presenting to the EMDAC hypothetical information. CDER explicitly stated that the information provided was based on a hypothetical. Nor does the PDC find it problematic that CDER failed to address aspects of the IVR data submitted in support of the NDA for ITCA 650. CDER need not address all aspects of an NDA file to support its position; rather, CDER may determine what it feels are the key aspects underlying its determination and present on those topics accordingly.

1. AKI Events

As described above, the EMDAC highlighted concerns related to AKI events reflected in the data, including the number of AKI events observed in the clinical data and the likelihood that the AKI risk would increase if the patient were also taking common T2DM therapies while using ITCA 650. The EMDAC also expressed concerns about the number of reported AKI events in the clinical data even with a low proportion of participants with significant chronic kidney disease. The EMDAC expressed concerns about how the AKI rates would translate in a real world setting when the indicated population would likely have higher, or more serious, rates of chronic kidney disease.

CDER has stated that, based on the evidence included in the NDA, clinical trial subjects who received ITCA 650 had more AKI events than the control group. CDER, relying on individual and pooled analyses of the three ITCA 650 phase 3 clinical trials and the resulting analyses, found a numeric imbalance in serious AKI events:

> Baseline eGFR category was coded as mild renal impairment (baseline eGFR 60 to 89 mL/min/1.73m2) for 9 subjects and moderate renal impairment (baseline eGFR 30 to 59 mL/min/1.73m2) for 5 subjects who had AKI SAEs in the ITCA 650 treatment arm. As shown in Table 30 (Section 5.2) among these 5 subjects categorized as 48 moderately renally impaired at baseline, two subjects had baseline eGFRs of 57 and 58 mL/min/1.73m2, respectively, and no subject had baseline eGFR. . . . Only a limited number of subjects with chronic kidney disease (CKD) stage 3 or worse were enrolled in any of the trials, including FREEDOM: as previously noted, only one subject in CLP–103 had a baseline eGFR under 60 mL/min/1.73m2, fewer than 5% of subjects in CLP–105 had a baseline eGFR under 60 mL/min/1.73m2, and fewer than 10% of subjects in CLP–107 had a baseline eGFR under 60 mL/min/1.73m2 at baseline. The AKI signal in FREEDOM was observed in a population less susceptible to AKI I, whereas no AKI signal was observed in the other [GLP–1 RA] CVOTs which studied populations more susceptible to AKI . . . further indicating that the risk of AKI associated with use of ITCA 650 is greater than the risk of AKI associated with currently marketed [GLP–1 RAs].

The crux of Intarcia's argument related to the AKI events reflected in the clinical data for ITCA 650 is that AKI concerns expressed by both CDER and the EMDAC are a drug-class risk and no worse for ITCA 650. Intarcia points to data from various other drug products to support its assertions. Intarcia also disputes the number of AKI events presented by CDER, claiming that there are 11 AKI events instead of the 14 counted by CDER.

In its presentation to the EMDAC, CDER discussed a key concern contained within the data—namely, an increase in AKI events in trial subjects who received the drug, particularly in Intarcia's largest study, FREEDOM, which had a relatively low proportion of subjects with significant chronic kidney disease:

> All but one serious AKI event and all but 4 nonserious AKI events occurred in Study CLP–107 (FREEDOM), the largest study with the longest median follow up time. Baseline eGFR is associated with risk of AKI events (Grams et al. 2010); *e.g.,* patients with eGFR below 60 mL/min/1.73m2 have greater risk than patients with higher eGFR. Only a limited number of subjects with chronic kidney disease (CKD) stage 3 or worse were enrolled in any of the trials, including FREEDOM: as previously noted, only one subject in CLP–103 had a baseline eGFR under 60 mL/min/1.73m2, fewer than 5% of subjects in CLP–105 had a baseline eGFR under 60 mL/min/1.73m2, and fewer than 10% of subjects in CLP–107 had a baseline eGFR under 60 mL/min/1.73m2 at baseline. The AKI signal in FREEDOM was observed in a population less susceptible to AKI, whereas no AKI signal was observed in the other [GLP–1 RA] CVOTs which studied populations more susceptible to AKI (see Table 21)—further indicating that the risk of AKI associated with use of ITCA 650 is greater than the risk of AKI associated with currently marketed [GLP–1 RAs].

The EMDAC appears to have agreed with this analysis.

Having a low proportion of participants with significant chronic kidney disease would lead to the expectation that there is a lower baseline risk for AKI events. Renal impairment is common for those with T2DM. Therefore, if an AKI safety concern is present for those who do not have significant renal concerns, it raises serious questions regarding the potential AKI risk to those in the patient population for ITCA 650 that Intarcia has proposed. The indicated population would generally have underlying renal impairment concerns. The higher risk observed in the clinical data for ITCA 650 raises issues about the potentially greater risk in the postapproval setting. In the monitored setting of a clinical trial, some AKI events may be prevented or mitigated, but doing so is more difficult in the real world. As explained in CDER's proposed order, ''sufficient risk mitigation approaches could not be identified for the AKI risk, particularly because serious AKI events occurred in participants who did not have known risk factors, could occur at unpredictable times, and were observed with both the initial (20 mcg/day) and maintenance dose (60 mcg/day) of ITCA 650'':

> [T]here is no evidence to support Intarcia's assertion that the AKI events occurred in ''well-defined windows'' of treatment initiation and dose escalation. Although some of the AKI events in the treatment group occurred proximate to implantation and dose escalation, others occurred at unpredictable time points thereafter. The unpredictable timing of these events makes it impossible to adequately warn providers as to when patients may be most likely to experience serious AKI. Accordingly, the clinical trial data support CDER's conclusion that the AKI risk cannot be adequately mitigated through labeling.

The PDC further finds that, if serious AKI events are occurring in individuals without significant renal concerns and at variable times, there is insufficient reason to believe that the potential for AKI events stemming from ITCA 650 can be addressed through risk mitigation measures, such as labeling or patient monitoring, because healthcare providers would not have adequate information to identify patients requiring additional monitoring or education.

Additionally, throughout the process, CDER also responded to Intarcia's contentions that the increase in AKI events was observed in those in the study who were also using metformin. As CDER and the EMDAC correctly noted, metformin usage is a first line treatment for patients with T2DM, and therefore this signal would apply to the majority of the intended patient population for ITCA 650. Given that metformin is not believed to be associated with an increased AKI risk, the increase in AKI events for ITCA 650 for those patients being treated with metformin simply reinforces the conclusion that ITCA 650 poses an increased AKI risk, especially for those in the intended patient population. Indeed, as CDER explained in its briefing materials for the EMDAC, study subjects in both the control and test groups were often taking metformin:

> Study CLP–105 was a multicenter, randomized, double-blind (subjects randomized to ITCA 650 and placebo pill or to sitagliptin and placebo ITCA 650 device), active comparator trial that compared efficacy, safety, and tolerability of ITCA 650 to sitagliptin, both as add-on to metformin.

Regardless of the AKI risk associated with approved products whose active ingredient is a GLP–1 RA, the evidence underlying the NDA for ITCA 650 highlights a concerning AKI risk arising in subjects that did not have significant renal impairment. The PDC notes that neither in its recommendations nor its underlying reasoning, did the EMDAC

address the risk comparisons that Intarcia included in its presentation. The EMDAC's focus in those recommendations on the data for ITCA 650—as opposed to comparisons of the data underlying ITCA to that for GLP–1 RA-containing products—effectively conveys the EMDAC's view that it is not necessary to reach such comparisons to conclude that ITCA 650 is not safe for its intended use. Indeed, the PDC agrees with the EMDAC's overall conclusions that the AKI events observed in the clinical data are a significant safety concern regardless of comparisons to other available therapies.

Additionally, even if the PDC was to view Intarcia's arguments regarding the number of AKI events in its favor and find that there were only 11 AKI events for subjects being treated with ITCA 650, it would still not address the overriding concern of the AKI risk appearing in a subject population with low significant chronic kidney disease. Regardless of which count is used, although the number of AKI events in the ITCA 650 Phase 3 trials was small, there is an overall, and serious, increase in AKI events for ITCA 650.

Separately, despite the concerns just described, were the PDC to consider Intarcia's arguments regarding ITCA 650's risk relative to the risk of similar products with an analogous indication, the evidence presented to the EMDAC supports that ITCA 650 in fact presents a higher risk than approved drug products containing GLP–1 RA as an active ingredient. After analyzing the CVOTs for other products in the class, CDER summarized its findings in its EMDAC briefing materials:

> CDER interrogated the CVOTs of the approved [GLP–1 RA] products with the same censoring schemes, [standardized MedDRA queries] (SMQs), and [FDA MedDRA queries] (FMQs) as were applied to FREEDOM. . . . CDER notes that the imbalance in AKI seen in FREEDOM (labeled ITCA in Figure 12) was not observed in other CVOTs in the [GLP–1 RA] class. This imbalance in AKI was observed despite FREEDOM enrolling a lower proportion of subjects with baseline moderate-to-severe renal impairment compared with other CVOTs in the [GLP–1 RA] drug class, such that the FREEDOM population would be expected to have lower baseline risk for AKI events (Table 21).

CDER concluded:

> The higher risk observed in the preapproval database for ITCA 650 raises concern about the potentially greater risk versus other [GLP–1 RA] products in the postapproval setting: in the monitored setting of a clinical trial, some AKI may be prevented or mitigated, while this may not consistently occur in clinical practice. Moreover, the number of patients exposed to the ITCA 650 product would be much higher postapproval, and both of these factors differentiate the preapproval from the postapproval setting.

CDER reiterated in its presentation to the EMDAC that ''no approved [GLP–1 RA-containing] product had an AKI imbalance in their premarket or postmarket clinical trials.'' In response, Intarcia points to the AKI warning included in Wegovy's labeling, which it claims refutes the notion that no AKI imbalances occurred in the clinical trials for GLP–1 RA products. Intarcia's argument conflates AKI occurrence with an AKI imbalance. CDER does not claim that AKI events never occurred in GLP 1- RA related clinical trials, but rather that the number of events that occurred in FREEDOM led to an imbalance that was not seen for any other GLP–1 RA products in a randomized clinical trial. The relative number that occurred in FREEDOM distinguishes ITCA 650 from the other clinical trials for approved products containing a similar active ingredient, which may have had instances of AKI events but in a smaller proportion than ITCA 650 in the preapproval setting.

Intarcia specifically points to Wegovy as an example of another GLP–1 RA product that had an AKI imbalance in its randomized clinical trials and still received approval; however, that argument is not borne out by the data. As explained in CDER's proposed order:

> Intarcia asserts that there was an imbalance in serious AKI events during titration in both Wegovy arms (1.0 mg and 2.4 mg) in Trial 4374 (STEP 2). Intarcia states that the percentage of participants with serious AKI for each arm in STEP 2, and in STEP 2 overall, was ''identical'' to the percentage of treatment-emergent serious AKI in [FREEDOM]. The STEP 2 trial demonstrated a rate of serious AKI adverse events of 0.5% for both the 2.4 mg and 1 mg arms (2 participants with serious AKI events per arm), and 0.2% for the placebo arm (1 participant with serious AKI events). Although Intarcia claims these percentages are comparable to the AKI risk demonstrated in [FREEDOM], there are too few events (*i.e.,* just two versus one event) for a meaningful analysis, in contrast to the larger serious AKI imbalance observed in the ITCA 650 development program.

The PDC agrees with CDER's analysis. Indeed, considering that ITCA 650 showed an AKI imbalance in a preapproval trial, where no others in the class presented similar concerns, the PDC finds that ITCA 650 presents a higher risk than approved products containing a GLP–1 RA.

GI-related issues. Intarcia makes additional arguments on appeal relating to the incidence of GI events in the study subjects using ITCA 650 and again focuses on how the GI events are a drug-class risk and whether the GI events observed for ITCA 650 in the clinical data are comparable to those observed for other products in the class in the clinical data or otherwise. Intarcia includes arguments surrounding the GI events and dose titration and contends that, after dose escalation, the number of GI events decreased. As stated, the pivotal question here is whether the data offered in support of the NDA for ITCA 650 yields a positive benefit-risk profile adequate for a finding of safety.

CDER described the connection between GI events to AKI occurrence in its briefing materials, stating that ''CDER's review of the narratives of serious AKI events that occurred in the ITCA 650 treatment arms revealed 11of 14 events described GI symptoms (*e.g.,* nausea and vomiting) and dehydration that preceded development of AKI.'' Intarcia does not contest CDER's findings that serious AKI events in FREEDOM were preceded by GI symptoms. Given the concerns outlined in the AKI discussion, the PDC finds that these GI events and the connection to the AKI risk are yet another indication that ITCA 650's NDA has not provided enough evidence and data to show a benefit-risk profile that would support a finding that ITCA 650 is safe within the meaning of section 505(d)(2) of the FD&C Act. Regarding the relationship between dose titration and GI events, as the PDC will discuss in the IVR-related section, the PDC finds that the wide variability in dose accuracy does not support that the GI issues would necessarily be adequately controlled after the initial titration period.[2]

2. Cardiovascular-Related Issues and the Necessity of a Pre-Approval CVOT

Both CDER, and later the EMDAC, expressed concerns regarding cardiovascular safety. Specifically, the EMDAC felt that, after looking at the various data analyses, the CVOT did not adequately exclude the possibility that ITCA 650 is associated with an excess risk of cardiovascular harm. The EMDAC disagreed with Intarcia's view that, because its CVOT met the primary end point requirements and conformed to FDA guidance, those findings are sufficient alone to support approval of ITCA 650. The EMDAC concluded that,

[2] Insofar as Intarcia argues that the GI issues associated with ITCA 650 compare favorably to approved products containing a GLP–1 RA, Intarcia ties those arguments to the occurrence of AKI and cardiovascular events in the clinical data for the products at issue (including ITCA 650). Thus, the PDC finds that the analysis in the previous and next sections adequately addresses those arguments.

given the MACE point estimate was above one, the cardiovascular safety signal should be further investigated before ITCA 650 receive approval. Some members of the EMDAC found that, regardless of point estimates or HRs, a concerning cardiovascular signal in a preapproval trial is itself enough to warrant further investigation before approval. Further, in addressing the discussion question on the cardiovascular risks, the EMDAC found that the current data, as a whole, did not establish that ITCA 650 was sufficiently safe to warrant approval and recommended that Intarcia perform another pre-approval CVOT.

On appeal, Intarcia contests both the need for another pre-approval CVOT, stating that its original pre-approval CVOT meta-analysis met CDER's primary end point requirements, and the comparison of its CVOT results to post-approval CVOTs for other products. Intarcia also contends that CDER's current analysis conflicts with previous statements. Lastly, Intarcia states that a ''larger, longer, *post-approval* CVOT is warranted and would be performed.''

Intarcia does not, however, dispute that the CVOT showed an HR estimate of 1.12, with a 95 percent confidence interval. Moreover, Intarcia does not challenge the number of MACE incidents or contend that collecting additional CVOT data is warranted. But the fundamental question is whether the data submitted with the NDA show a benefit-risk profile sufficient to establish the safety of ITCA 650 for approval. Whether, if ITCA 650 were approved, FDA would require a postmarketing CVOT is a separate issue. In the PDC's view, the cardiovascular data for ITCA 650 are troubling and do not characterize the risks associated with the product, including the cardiovascular risk, in a manner adequate to support the finding of safety necessary for approval.

Additionally, were the PDC to consider Intarcia's CVOT comparisons to other GLP–1 RA products, the PDC still finds that the ITCA 650 data does not adequately characterize the cardiovascular risks associated with ITCA 650. CDER analyzed FREEDOM in its EMDAC briefing materials and summarized its findings:

> Notably, Table 21 [,which compared baseline subject characteristics across CVOTs in the GLP–1 RA class,] demonstrates that at baseline, a smaller proportion of subjects enrolled in FREEDOM had moderate or severe renal impairment than the trial populations of any other CVOT in the class, and the proportion of subjects with baseline [cardiovascular] disease was lower relative to most of the other [GLP–1 RA] CVOTs. This observation is reflected in the lower incidence of MACE in the placebo arm of the trial compared to the placebo arms of the other trials (Table 22). As noted above, imbalances in MACE events unfavorable to ITCA 650 were most pronounced in susceptible subgroups (*i.e.,* subjects ≥65 years of age, and subjects with baseline moderate to-severe renal impairment), as interventions that increase risk of MACE cause the greatest harm among the highest-risk populations.

CDER concluded:

> The primary and secondary endpoint analyses and all other prespecified analyses of CV risk, regardless of pooling or censoring strategy utilized, support the same conclusion: the results of FREEDOM, a dedicated CVOT which enrolled patients with T2DM at high CV risk, do not adequately exclude the possibility that ITCA 650 is associated with excess risk of CV harm.

On appeal, Intarcia merely dismisses CDER's analyses as scientifically unsound and reiterates that a postapproval CVOT is warranted because the preapproval CVOT met the primary endpoint requirements. However, the PDC agrees with CDER's analysis regarding comparisons between the preapproval clinical data offered in support of approved GLP–1 RA products and the data presented in support of ITCA 650 in this proceeding.

Diabetes is associated with an elevated risk of cardiovascular disease. The PDC finds that, while the original CVOT met the primary end point requirements, the PDC agrees with CDER's and EMDAC's concerns that the HR, especially in light of the other findings, does not provide adequate assurance that ITCA 650 is not associated with an increase in cardiovascular risk. Contrary to Intarcia's assertions, meeting the primary endpoints in the original CVOT is not sufficient, standing alone, to show that the existing clinical data adequately characterizes the cardiovascular risks associated with ITCA 650 to conclude that the product is safe. Meeting the primary endpoints is merely one data point in the overall assessment of the overall benefit-risk assessment of a medical product. As described by CDER in the briefing materials to the EMDAC and highlighted through tables 20–22 in those materials, the primary and secondary endpoint analyses, regardless of pooling strategy, supports that the data generated by FREEDOM, the only CVOT conducted thus far, do not adequately exclude the possibility that ITCA 650 is associated with excess risk of cardiovascular harm. As described in CDER's briefing materials to the EMDAC, ''imbalances in MACE events unfavorable to ITCA 650 were most pronounced in susceptible subgroups (*i.e.,* subjects ≥65 years of age, and subjects with baseline moderate to-severe renal impairment), as interventions that increase risk of MACE cause the greatest harm among the highest-risk populations.'' Intarcia's concession that a postmarket CVOT is warranted aligns with the PDC's view that more data is necessary to adequately characterize the cardiovascular risk associated with ITCA 650 for a full assessment of the product's benefit-risk profile and a determination of safety. The question is when that CVOT should occur, and the PDC agrees with CDER and the EMDAC that the data available for ITCA 650 does not satisfy the requisite threshold for safety under section 505(d)(2) of the FD&C Act. Therefore, discussion of a postmarket study is premature.

3. IVR-Related Concerns

Finally, in considering whether the benefits outweigh the risks for ITCA 650, the EMDAC also expressed concerns about the variability in drug delivery and the device itself. CDER's review of the data found that the IVR ranges for ITCA 650 are unacceptably wide, leading to concerns with dose accuracy. On appeal, Intarcia's states that its daily IVR testing meets the acceptance criteria and necessary confidence intervals and offers comparisons to other products on pharmacokinetic variability. Focusing on the issue of variability, the PDC finds that Intarcia has not presented adequate information to ensure that ITCA 650 would be safe for the proposed indication.

In its previous submissions, and in its appeal, Intarcia lists its proposed IVR range for each dosage target: for the 20 mcg/day device, from days 0 to 14, the proposed IVR range is 2 to 40 mcg/day, which represents 10 percent to 200 percent of the target dose. From days 14 to 91, the IVR range is 10 to 36 mcg/day, which represents 50 percent to 180 percent of the target dose. For the 60 mcg/day device, the IVR range for days 0 to 28 is 2 to 120 mcg/day, which represents 3.3 percent to 200 percent of the target dose. The IVR range for days 28 to 182 is 25 to 110 mcg/day, which represents 50 percent to 180 percent of the target dose. Intarcia states that these ranges are within a 95 percent confidence interval with 80–90 percent reliability, but they nonetheless reflect very wide acceptance criteria. For both the 20 mcg/day device and the 60 mcg/day device, after day 14, a patient could receive anywhere from 50 percent to 180 percent of the exenatide dose, which could also result in rapid shifts

between either end of the spectrum on a daily basis. A device that might deliver 3.3 percent, 10 percent, or 200 percent of the target dose would be expected to cause clinical adverse events related to irregular daily dosing when administering exenatide. As noted by CDER in its proposed order,

> Such wide acceptance criteria would allow for daily exenatide release that is not controlled sufficiently by the ITCA 650 device to safely meet clinical needs for the proposed indication. For example, because in steady state both ITCA 650 devices can deliver on a daily basis anywhere from 50% to 180% of the target dose of exenatide, rapid shifts in exenatide exposure could result. Increasing exposures to exenatide are known to result in gastrointestinal adverse reactions such as vomiting and diarrhea leading to dehydration, decreased intravascular volume, and AKI.

Intarcia argues that the GI concerns lessen after dose titration and escalation, but such a wide dosing range undermines that position. If patients are never assured of how much exenatide they are receiving, if they receive too little or too much, there is always an elevated risk of GI events with ITCA 650 in its present form.

In general, applicants propose acceptance criteria, and FDA may agree or disagree with the proposal, depending on the data. The data submitted by Intarcia are intended to show that the device meets the proposed acceptance criteria to a specific confidence interval. Even if the specific ITCA 650 performance data submitted are within a tighter range than the acceptance criteria proposed by Intarcia, those acceptance criteria are inappropriate because they would allow for manufacture of the device with unacceptably wide criteria. As stated in CDER's proposed order, ''[t]he wide acceptance criteria specifications for both the 20 mcg/day and the 60 mcg/day devices would allow for drug release that is unreliable and not controlled sufficiently by the device to meet clinical needs.'' The IVR acceptance criteria proposed by Intarcia are very wide and thus indicate that drug release is not well controlled by the device.

Additionally, given that the IVR ranges are so wide, the confidence interval and reliability percentages are low for ITCA 650. As CDER described in its proposed order,

> CDER typically recommends that dose accuracy requirements are met with 95% confidence and 95% reliability. In this context, reliability is the probability that the device will perform satisfactorily for a specified period of time for the intended use. Because ITCA 650 is an implantable device that does not communicate device failures to the end user (*e.g.,* device occlusion, free flow, etc.), an even higher level of reliability is expected (>99%).

It is even more imperative that ITCA 650 doses reliably because it does not communicate device failures to the user. As explained by CDER in its briefing materials,

> A patient may only discover that a device failure occurred during use due to the onset of symptoms related to the device failure. This lack of user awareness regarding the status of drug delivery necessitates a high degree of device reliability to ensure that use of the device is safe in patients.

Intarcia's analysis does not support its claims related to dose accuracy, given the low reliability percentages as well as the wide IVR specification ranges. The wide acceptance criteria specifications for both the 20 mcg/day and the 60 mcg/day devices would allow for drug release that is unreliable and not controlled sufficiently by the device to meet clinical needs. Given the rates of adverse events in the clinical trials for ITCA 650, as discussed above, it is reasonable to interpret those safety signals as potentially flowing from dosing variability. In short, the data do not support that the intended patient population would receive an accurate dose of exenatide each day, thereby leading to adverse health events.

Intarcia on appeal compares ITCA 650's IVR data to other products' data. The PDC does not find Intarcia's arguments regarding such comparisons to be persuasive. On appeal, Intarcia references another exenatide product, Byetta, which it says, ''is known to have large swings in pharmacokinetic variability.'' As noted in the proposed order, however, ''Byetta is not an implanted device. Byetta (exenatide) is a twice daily injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'' CDER, in the proposed order, further explained, ''The timing of the injections is specific and clearly outlined in the prescribing information. In contrast, as discussed in detail above, Intarcia's proposed IVR acceptance criteria are very wide and as such would allow for drug release that is not sufficiently controlled by the device.'' Similarly, Bydureon, which Intarcia points to as an example of an exenatide product with comparable pharmacokinetic variability, is also not an implantable device but instead is a weekly injectable. CDER compared ITCA 650 and Bydureon's variability in its briefing materials and summarized the findings:

> Quantification and comparison of within-subject variability (WSV) in pharmacokinetics is challenging for a few reasons. First, clinical trials do not typically collect frequent pharmacokinetic samples, particularly in time periods relevant to detect rapid concentration excursions. Secondly, the estimate of variability is sensitive to the nature of the chosen time window (duration of window, time between samples). Lastly, even if ideal data were available, within-subject variability does not quantify infrequent but dramatic spikes, but rather average variability (*e.g.,* the ''spread'' of the data over a specified sampling window). In other words, WSV reflects usual variability, but is insensitive to infrequent abrupt concentration increases. Nonetheless, CDER reanalyzed the PK data from Study CLP–109 and CLP–103SS and estimated the WSV in individual exenatide concentrations collected over 24 hours (*i.e.,* within-day WSV) as well as the between-day WSV in individual exenatide concentrations data collected across multiple days proximal to each other [*i.e.,* within 72-hours of each other and compared to the WSV of Bydureon (from Studies 104 and 105)]. The results of the within-day WSV and between-day WSV are summarized below in Table 5. These values reported in Table 5 for ITCA 650 are similar to the WSV of 65% (using individual concentrations over 24 hours in Study CLP–109) reported by the Applicant in their Summary of Clinical Pharmacology Studies. In comparison, Bydureon showed a lower estimated within-day and between-day WSV of 20% and 30%, respectively.

Even if the PDC was to consider these other products, which are not implantable devices like ITCA 650, the PDC agrees with CDER and the EMDAC that the evidence and data presented in this proceeding suggests that ITCA 650 raises concerns with drug delivery variability that compare unfavorably to approved products with a similar or identical active ingredient.

The studies supporting ITCA 650's NDA, which were conducted in a controlled environment to measure drug delivery rates, demonstrated that the ITCA 650 does not provide an accurate and predictable release of exenatide. Given the information discussed above, the PDC finds that Intarcia's IVR data does not support the safety of the product given the wide IVR acceptance ranges and lower reliability percentages.

4. Potential Benefits of ITCA 650

Having already addressed the safety-related concerns, the PDC will turn briefly to the benefits of ITCA 650. Intarcia states that the benefits of ITCA 650 include (1) an extended maintenance therapy option, (2) a dosing option with ''unequivocal sustained efficacy with 6-month dosing,'' and (3) safety in-line with other GLP–1s. Intarcia presented a letter signed by 12 experts in support of its arguments related to the benefits of ITCA 650.

The main benefits that Intarcia highlights relate to its position that ITCA 650 is a valuable new dosing option because it may increase medication adherence. Intarcia has not provided data in support of its argument but instead bases this assertion on the fact that ITCA–650 is an implantable device that lasts for 3 or 6 months. However, the evidence offered in support of approval undermines Intarcia's position. As previously discussed, ITCA 650 has dose reliability and variability issues. As previously outlined in the EMDAC discussion summary, multiple EMDAC members expressed concern that the drug delivery variability issue could lead to patients receiving less reliable drug doses than if they were using an analogous drug regimen that was not delivered via an implanted osmotic pump. Therefore, if ITCA 650 does not provide the proper dose, a patient would become nonadherent to their medication, regardless of the patient's intentions. The PDC therefore disagrees with Intarcia and its experts that the mode of drug delivery inherently equates to medication adherence. Furthermore, as found by CDER in its proposed order, ''Intarcia has provided no evidence that demonstrates patients prescribed ITCA 650 are more likely to continue the treatment than patients prescribed other approved treatments for type 2 diabetes.'' Given the lack of concrete information to support its theoretical argument, the PDC gives little weight to this benefit in the overall assessment of whether the benefit-risk assessment supports approval of ITCA 650 in its present form.

D. Conclusion

While Intarcia correctly points out in its appeal that more therapies are needed for patients with T2DM, FDA will only approve NDAs when the data shows that the benefits outweigh the risks. After reviewing the information contained in the public record, the PDC finds that the benefits of ITCA 650 do not outweigh its risks. The PDC agrees with the EMDAC's conclusions and find that there are too many unanswered questions regarding risks associated with ITCA 650 to find that it has a positive benefit-risk profile and is safe under section 505(d)(2) of the FD&C Act. For the reasons described above, Intarcia has not presented adequate evidence to show that the drug is safe for use under the proposed conditions; therefore, the PDC cannot approve the NDA for ITCA 650.

IV. Findings and Order

For the reasons described above, FDA finds that the record shows that the approval criteria set forth in section 505(d)(2) of the FD&C Act have not been met, as ITCA 650's risks outweigh its benefits; therefore, Intarcia has not demonstrated that ITCA 650 is safe for its intended use. Therefore, under section 505(d) of the FD&C Act, FDA hereby denies approval to Intarcia's NDA in its current form.

Dated: August 16, 2024.

Namandjé N. Bumpus,

Principal Deputy Commissioner.

[FR Doc. 2024–18898 Filed 8–22–24; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2020–N–1584]

Authorization of Emergency Use of Certain Medical Devices During COVID–19; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the issuance of Emergency Use Authorizations (EUAs) (the Authorizations) for certain medical devices related to Coronavirus Disease 2019 (COVID–19). FDA has issued the Authorizations listed in this document under the Federal Food, Drug, and Cosmetic Act (FD&C Act). These Authorizations contain, among other things, conditions on the emergency use of the authorized products. The Authorization follows the February 4, 2020, determination by the Secretary of Health and Human Services (HHS), as amended on March 15, 2023, that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of U.S. citizens living abroad and that involves the virus that causes COVID–19, and the subsequent declarations on February 4, 2020, March 2, 2020, and March 24, 2020, that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the virus that causes COVID–19, personal respiratory protective devices, and medical devices, including alternative products used as medical devices, respectively, subject to the terms of any authorization issued under the FD&C Act. These Authorizations, which include an explanation of the reasons for issuance, are listed in this document, and can be accessed on FDA's website from the links indicated.

DATES: These Authorizations are effective on their date of issuance.

ADDRESSES: Submit written requests for single copies of an EUA to the Office of Policy, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5431, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the Authorization may be sent. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the Authorization.

FOR FURTHER INFORMATION CONTACT: Kim Sapsford-Medintz, Office of Product Evaluation and Quality, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3216, Silver Spring, MD 20993–0002, 301–796–0311 (this is not a toll-free number).

SUPPLEMENTARY INFORMATION:

I. Background

Section 564 of the FD&C Act (21 U.S.C. 360bbb–3) allows FDA to strengthen the public health protections against biological, chemical, radiological, or nuclear agent or agents. Among other things, section 564 of the FD&C Act allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product in certain situations. With this EUA authority, FDA can help ensure that medical countermeasures may be used in emergencies to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a biological, chemical, radiological, or nuclear agent or agents when there are no adequate, approved, and available alternatives.

Section 564(b)(1) of the FD&C Act provides that, before an EUA may be issued, the Secretary of HHS must declare that circumstances exist justifying the authorization based on one of the following grounds: (1) a determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents; (2) a determination by the Secretary of Defense that there is a military emergency, or a significant potential for