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FDA Approval Summary: Belzutifan for von Hippel-Lindau disease associated tumors

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Abstract

On August 13, 2021, the United States Food and Drug Administration (FDA) approved belzutifan (WELIREG, Merck), a first-in-class hypoxia-inducible factor (HIF) inhibitor for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. The FDA granted approval based on the clinically meaningful effects on overall response rate (ORR) observed in patients enrolled in Study MK-6482-004. All 61 patients had VHL-associated RCC; some also had CNS hemangioblastomas and/or pNET. For VHL disease associated RCC, ORR was 49% (95% CI: 36 to 62), median duration of response (DoR) was not reached, 56% of responders had DoR ≥12 months, and median time to response was 8 months. Twenty-four patients had measurable CNS hemangioblastomas with an ORR of 63% (95% CI: 41 to 81) and 12 patients had measurable pNET with an ORR of 83% (95% CI: 52 to 98). For these tumors, median DoR was not reached, with 73% and 50% of patients having response durations ≥12 months for CNS hemangioblastomas and pNET, respectively. The most common adverse reactions, including laboratory abnormalities, reported in ≥20% were anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea. Belzutifan can render some hormonal contraceptives ineffective and can cause embryo-fetal harm during pregnancy. This article summarizes the data and the FDA thought process supporting traditional approval of belzutifan for this indication.

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No potential conflicts of interest were disclosed.

Disclaimer: None

Introduction

Patients with VHL disease are at increased risk of developing benign or malignant lesions in multiple organs, including clear-cell RCC, CNS hemangioblastomas, pNET, retinal hemangioblastoma, pheochromocytoma, endolymphatic sac tumors (ELST), and cystadenomas of the epididymis and broad ligament (1).

RCC develops in up to 70% of patients with VHL disease and risk of metastasis is correlated with RCC tumor size. Surgery is recommended when tumor is ≥3.0 cm in diameter to prevent metastasis (2).

CNS hemangioblastomas are considered histologically benign tumors but can nonetheless cause serious morbidity or mortality due to mass effect (3). Surgical procedures are indicated when these lesions become large and symptomatic (4).

Most VHL disease associated pancreatic lesions are benign and generally asymptomatic. Approximately 10% of these lesions are pNETs (5). Tumor characteristics such as size (>3 cm), rapid growth, poor differentiation, and VHL missense or pathogenic variants are associated with higher risk of metastasis. For VHL disease associated pNETs, surgery is indicated to prevent metastasis when tumor size is ≥2 cm in the head of the pancreas or ≥3 cm when the tumor is in body/tail of the pancreas (6).

Retinal hemangioblastomas are one of the earliest presentations of VHL disease. Visual loss can be a complication of retinal hemangioblastomas due to retinal edema, tractional effects, and hemorrhage. Laser coagulation is the preferred approach in patients who require treatment for retinal hemangioblastomas (7).

Surgeries and procedures to treat VHL disease associated tumors may be associated with morbidity and mortality. Historically, there have been no available pharmacological therapies with activity directed towards VHL disease associated tumors, and treatment was generally limited to active surveillance and surgical intervention to alleviate symptoms from lesions or prevent tumor progression or metastasis. Belzutifan (WELIREG, MK-6482, PT2977) is a first-in-class oral small molecule hypoxia-inducible factor HIF-2a Inhibitor. On August 13, 2021, FDA approved belzutifan for adult patients with VHL disease who require therapy for associated RCC, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery (8). This article summarizes the FDA's review of data submitted in the new drug application (NDA), the issues identified during the NDA review, and the overall basis for approval.

Nonclinical pharmacology and toxicology

In VHL disease, VHL protein function is impaired, resulting in stabilization and accumulation of HIF-2α. HIF-2α translocates into the nucleus and dimerizes with HIF-1beta (HIF-1β) to form a transcriptional complex that induces expression of HIF-2α target genes, including genes associated with angiogenesis, cell proliferation, and tumor growth (9). Belzutifan binds to HIF-2α, and under conditions of hypoxia or impaired VHL

protein function, belzutifan inhibits the interaction of HIF-2α and HIF-1β, resulting in reduced expression of HIF-2α target genes.

In repeat-dose toxicity studies, oral administration of belzutifan to rats and dogs for up to 3 months resulted in reduced red blood cell mass consistent with anemia observed in trial participants receiving belzutifan. In rats, belzutifan caused adverse effects on male reproductive organs, including degeneration or atrophy of the testes and hypospermia and cellular debris in the epididymis. Findings in the testes and epididymis were associated with abnormal sperm morphology and reduced sperm count and motility.

In an embryo-fetal development study, oral administration of belzutifan to pregnant rats during the period of organogenesis resulted in embryo-fetal mortality, reduced fetal weights, and fetal skeletal malformations at exposures below the human exposure at the recommended clinical dose. Belzutifan may also impair fertility in males and females based on animal findings. Belzutifan was not genotoxic in vitro or in vivo.

Clinical pharmacology

The recommended dosing regimen of belzutifan of 120 mg once daily (QD) was selected based on the evaluation of pharmacokinetics, pharmacodynamics, and safety information from the first-in-human dose escalation study MK-6482-001 (NCT02974738) in patients with advanced solid tumors. The recommended Phase 2 dose of 120 mg QD was chosen based on pharmacodynamic response, maximum suppression of EPO at dose ≥120 mg.

There was no statistically significant relationship between belzutifan exposure and ORR; however, there was a numerical trend for improved efficacy at higher exposure. Exposure-response relationship for safety suggested a trend of increased probability of Grade ≥3 anemia with increased belzutifan exposure; however, the relationship was shallow, and the probability of Grade ≥3 anemia was low (<20%) even at the highest exposure range in patients with VHL disease.

Belzutifan is primarily metabolized by the polymorphic enzymes UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. Population pharmacokinetic analyses predict poor metabolizers of both UGT2B17 and CYP2C19 to have 3.2-fold higher belzutifan steady state AUC0-24hr compared to UGT2B17 normal metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers.

Belzutifan is an inducer of CYP3A4. The co-administration of belzutifan may substantially decrease the exposure of drugs that are substrates of CYP3A4 (e.g., oral contraceptives), which may lead to loss of efficacy of these CYP3A4 substrates.

Clinical trial MK-6482-004

Trial Design

The efficacy database for this NDA was derived from the ongoing single arm open label phase 2 Study MK-6482-004, which enrolled patients with localized VHL disease associated RCC. The diagnosis was confirmed by the presence of a VHL germline alteration, and at

least one measurable kidney-confined solid tumor on radiographic imaging, with all images reviewed by IRC at baseline. Patients with RCC greater than 3.0 cm requiring immediate surgery were excluded. Patients could have additional VHL disease associated tumors in other organs and the diagnosis of VHL disease associated tumors could be radiologic. The primary endpoint was ORR in the RCC target lesions as assessed by Independent Radiologic Review Committee (IRC). Key secondary endpoints included DoR and time to response (TTR) in RCC, and ORR, DoR, and TTR in VHL disease associated non-RCC tumors as assessed by investigator.

After study enrollment was completed, the Sponsor pursued additional retrospective IRC review of existing images for enrolled patients in an attempt to also assess responses for CNS hemangioblastoma, retinal hemangioblastoma, and pancreatic tumors including pNET. This was attempted in a subset of patients who had available images captured for each of these tumors. ORR for these additional tumor types in patients in whom they were identified was then determined by IRC per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. This retrospective review of images via IRC was added as a protocol amendment to the study.

Patient Demographic and Disease Characteristics

MK-6482-004 enrolled 61 patients with a median age of 41 years (range, 19 to 66). The median diameter of RCC target lesions per IRC was 2.2 cm (range, 1.0 to 6.1) [9 patients per investigator and 18 patients per IRC (7 patients in common) had at least one RCC tumor ≥3.0 cm in diameter]. In addition to RCC, all patients had VHL disease associated non-RCC tumors (Table 1).

The median time from initial radiographic diagnosis of the RCC lesion that initially qualified patients to enroll on MK-6482-004 to the time of treatment with belzutifan was 18 months (range, 2.8 to 97). The target RCC lesion was histologically confirmed in 62% of patients. All patients had a germline VHL mutation identified by a variety of local tests. VHL gene alterations were retrospectively confirmed by Sanger sequencing (central testing), however, central testing was not required for eligibility.

Efficacy Results

As of the data cutoff date of December 1, 2020, the median follow-up was 22 months.

RCC

The ORR per IRC for RCC was 49% (30 of 61 patients) (95% CI: 36 to 62) (Table 2). Median DoR had not been reached (range, 2.8+ to 22.3+ months). Two patients who achieved an objective response subsequently had progression of disease and six others with stable disease as best overall response had disease that increased by at least 20% but because their measurable lesions were small, they had not reached the minimum 5 mm increase needed to qualify as progression per RECIST v1.1. The median TTR was 8 months (range, 2.7 to 19).

To assess the natural history of VHL disease associated RCC, and to put these responses into context, an analysis was conducted of the linear growth rate (LGR) of these RCC tumors. This analysis found that the overall median LGR before and after treatment with belzutifan was 3.63 mm/year and −4.48 mm/year, respectively. This served as a supportive analysis to the efficacy results and demonstrated an overall slowing of the growth of RCC tumors.

CNS hemangioblastoma

CNS solid tumors and cysts were measured together on (retrospective) IRC assessments and 50 (82%) of 61 patients were identified as having CNS hemangioblastoma at baseline. However, further review of the CNS procedures document and images provided in response to an information request by the FDA suggested that IRC review included brain and spine edema in tumor volume measurements. The FDA therefore requested that the Sponsor provide a re-review of the CNS hemangioblastoma imaging data by IRC with the following changes:

- Define maximal tumor diameter as the maximal contrast-enhancing diameter measured using post-contrast T1-weighted MRI. Do not include peri-tumoral cyst diameter in tumor measurements.
- Include patients with measurable disease at baseline only.

The Applicant provided this now read of the CNS imaging data by IRC on July 8, 2021, identifying 24 (39%) of 61 patients with measurable disease at baseline. In 24 patients with a measurable solid lesion in CNS per IRC, ORR was 63% (95% CI: 41% to 81%) and median DoR was not reached (range, 11+ to 19+ months) (Table 2). There was one complete response. The median TTR was 8 months (range, 2.7 to 11).

Pancreatic tumors

The same abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) images that were initially acquired for RCC assessment were then retrospectively used for evaluation of pancreatic lesions by IRC. Therefore, the images were not optimized for pNET detection on a number of parameters, including contrast timing and slice thickness, which led to high discordance in diagnosis of these tumors at baseline between the investigator and IRC as well as between the IRC readers, and further adjudication was needed on a high proportion of the patients.

Among 61 patients with pancreatic lesions, 22 (36%) patients had pNET identified by IRC in the NDA submission; however after adjudication, only 12 (20%) of 61 patients had pNET at baseline as determined by at least two blinded radiologists.

For 12 patients with evaluable pNET based on IRC, ORR was 83% (95% CI: 52% to 98%) and median DoR was not reached (range, 11+ to 19+ months) (Table 2). There were two complete responses and eight partial responses. The median TTR was 8 months (range, 2.7 to 11).

Reduction in tumor size was seen in patients with non-pNET pancreatic lesions. However, there was high discrepancy between the number of pancreatic lesions at baseline per

investigator and IRC. Additionally, these lesions may undergo spontaneous regression and resolution which limited the interpretability of the efficacy results in these lesions.

Other VHL disease related tumors

Retinal photographs were available in 16 (26%) of 61 patients. Of these 16 patients (32 eyes) theoretically available for retinal evaluation, 3 did not have any images in one or both eyes. Of the 28 eyes with images, 13 eyes did not have any lesions at baseline. Of 15 eyes with available retinal photographs and at least one retinal lesion at baseline, one eye had no light perception (completely blind) at baseline, seven eyes had laser treatment which could have been the reason for lesion improvement and thus presented a confounding factor in evaluating efficacy of belzutifan, and two eyes without laser treatment were already showing fibrosis, a stage of improvement. The remaining five eyes followed in this trial appeared to have improvement per IRC without potentially confounding circumstances.

Per investigator assessment, all three patients with pheochromocytoma had stable disease; two of 10 patients with epididymal cystadenoma had improvement in size of lesions; and the only patient with ELST had stable disease.

Safety results

The safety evaluation for belzutifan was based primarily on patients with VHL disease associated RCC in MK-6482-004 (N=61). Additional supportive safety data were analyzed from patients who received belzutifan at 120 mg in MK-6482-001 (N=58), a Phase 1, dose-escalation and dose-expansion study in patients with advanced solid tumors that had progressed on or were intolerant to standard of care and/or approved treatment options. No patients died from study drug toxicity on either study (one patient died of a fentanyl overdose on MK-6482-004). In MK-6482-004, one patient (1.6%) had hypoxia and 90% of patients had anemia (7% had grade 3 anemia). The most common (≥25%) adverse reactions were anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

Regulatory Insights

VHL disease associated tumors are rare and conducting randomized controlled clinical trials to assess time-to-event endpoints in each VHL disease associated tumor type would be extremely challenging (10). Additionally, morbidities such as metastasis, pain, neurologic deficits, and requirement for surgical resection of VHL disease associated tumors, are strongly correlated with size of the tumors. In oncology, response rate and duration of response are commonly used endpoints to support Accelerated Approval and can be assessed in single-arm non-randomized studies. In certain clinical contexts a meaningful response rate with longer durations of response can demonstrate a direct clinical benefit and support traditional approval (11). In this case, the review team concluded that the substantial reduction in size of multiple tumors associated with VHL disease for a prolonged time as demonstrated in the single-arm multinational trial MK-6482-004, provided substantial evidence of clinical benefit from treatment with belzutifan in this rare biomarker-driven

disease and therefore recommended a traditional approval despite relatively small patient numbers and absence of a control arm.

While all the enrolled patients had VHL disease associated RCC, other VHL disease associated tumors were also studied as the disease manifests in many organs. In particular, the data in CNS hemangioblastomas and pNETs were also deemed supportive of approval, based on an understanding of the biology of the HIF2-alpha pathway across different VHL disease associated tumors, re-review of imaging, the durable and clinically meaningful ORR demonstrated, and consideration of the rarity of these tumors. However, the limited efficacy data in retinal hemangioblastoma, non-pNET pancreatic lesions, pheochromocytoma, epididymal cystadenoma, and ELST did not provide sufficient evidence to support a favorable benefit-risk assessment and inclusion in the indication statement. Specifically, the data in retinal hemangioblastoma was lacking due to missing and incomplete assessments and lack of baseline disease, the non-pNET pancreatic lesion assessment was not optimized for assessment which decreased accuracy of tumor measurements, and almost no responses were observed in the very small number of patients with pheochromocytoma (0/3), epidydimal cystadenoma (2/10) and ELST (0/1).

To further assess the efficacy of belzutifan in patients with VHL disease associated non-RCC tumors, FDA issued three post-marketing commitments (PMCs) for extended follow up of efficacy in MK-6482-004, to conduct a clinical trial further evaluating efficacy of belzutifan in patients with VHL disease associated non-RCC tumors, and to submit efficacy results in the subgroup of patients with VHL disease from the phase 2 study of belzutifan for treatment of advanced and metastatic pheochromocytoma/paraganglioma or pNET (12)

In MK-6482-004, the initial diagnosis of VHL disease associated RCC was made radiologically in all patients via CT scan or MRI. Although all patients had a germline VHL mutation (by a variety of local tests), histologic confirmation was not required for trial enrollment. This is consistent with current clinical practice where patients with known germline VHL alteration and typical tumor characteristics on imaging often do not have a biopsy performed to histologically confirm RCC (13).

Unlike classic companion diagnostic devices in oncology generally used to diagnose mutations at the time targeted treatment is required, VHL disease is a syndrome where diagnosis is often established many years prior to the point where treatment is required. Thus no companion diagnostic device was approved concomitantly with the approval of belzutifan.

Many patients with VHL disease do not require any treatment for VHL disease associated tumors for several years after diagnosis as the LGR of these tumors is just 3–4 mm/year. Indeed, most patients in MK-6482-004 were not diagnosed immediately prior to enrollment, with a median time from diagnosis of VHL disease associated RCC to enrollment of 17.9 months (range 2.8 – 96.7). The review team therefore inserted the qualifier in the indication statement that belzutifan is approved for "*the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy*," since there may be many instances where observation alone is suitable.

Anemia and hypoxia are on-target adverse effects of belzutifan and are labeled as Warnings and Precautions in belzutifan product labeling. The rate of hypoxia on Study MK-6482-004 was lower than the frequency of this adverse reaction reported in studies of belzutifan in patients with advanced solid tumors on Study MK-6482-001. The observed difference is likely due to the differences in patient characteristics such as older age, presence of co-morbidities (e.g., chronic obstructive pulmonary disease), or presence of lung metastasis in patients with advanced or metastatic cancer. The presumed mechanism of belzutifan-induced anemia suggests that erythropoiesis-stimulating agents (ESAs) would be expected to provide mitigation; however, secondary malignancies are a known adverse effect of ESAs, and patients with VHL disease are already at heightened risk for a variety of new malignancies. Because of this risk, the use of ESAs in patients who develop anemia while taking belzutifan was not recommended in Prescribing Information for belzutifan. To mitigate the risk of severe anemia and need for frequent blood transfusion in patients with VHL disease, Hb ≤9 mg/dL is the threshold for holding belzutifan. Due to potential increases in belzutifan exposure, patients who are dual UGT2B17 and CYP2C19 poor metabolizers should be closely monitored for an increased risk of incidence or severity of anemia. Regarding the relatively short duration of exposure and safety follow up on Study MK-6482-004, a post-marketing requirement (PMR) was issued to further assess the toxicities associated with long-term use of belzutifan, and rate of blood transfusion, ESA use, and secondary malignancies.

The degree of embryo-fetal toxicity seen in non-clinical studies of belzutifan was comparable to that observed with many oncology drug products approved in recent years; however, the patient population for whom belzutifan is indicated is young, and prolonged duration of exposure is expected compared to other oncology products. Furthermore, drug-drug interactions with belzutifan may render some hormonal contraceptives ineffective. Because of these considerations, the review team placed a boxed warning for embryo-fetal toxicity in the Prescribing Information in addition to having this as a Warning and Precaution.

Conclusion

Results from Study MK-6482-004 demonstrate a favorable benefit-risk profile for belzutifan for the treatment of patients with VHL disease associated RCC, CNS hemangioblastoma, and pNET (Table 3). Belzutifan is the first-in-class HIF inhibitor and the first systemic treatment approved by FDA for patients with VHL disease associated tumors providing a novel therapy in an area of high unmet need. The magnitude of response and likelihood of symptomatic improvement, long duration of response, biologic rationale and rare tumor type allowed for granting of a traditional approval. Additional VHL disease associated tumors will be studied in belzutifan post-marketing trials to further describe benefit.

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Table 1.

Patients' baseline and disease characteristics

	MK-6482 (N=61)
Age (years)	
Median	41.0
Min, Max	19, 66
Sex, n (%)	
Male	32 (52)
Female	29 (48)
Race, n (%)	
American Indian or Alaska Native	0
Asian	1 (2)
Black or African American	2 (3)
Native Hawaiian or Other Pacific Islander	1 (2)
White	55 (90)
Unknown	2 (3)
ECOG Performance Status, n (%)	
0	50 (82)
1	10 (16)
2	1 (2)
VHL Subtype, n (%)	
Type 1	51 (84)
Type 2A	2 (3)
Type 2B	6 (10)
Type 2C	0
Missing	2 (3)
VHL disease associated non-RCC tumors [1], n (%)	
Pancreatic Lesions[2]	31 (51)
Pheochromocytomas	3 (5)
CNS Hemangioblastoma[3]	51 (84)
Endolymphatic Sac Tumors	1 (2)
Epididymal Cystadenomas	10 (16)
Retinal Lesions	17 (28)
Other	2 (3)
Median number of Prior Surgeries per patient [4]	5 (range: 1 to 15)
Median time from initial radiographic diagnosis of VHL disease associated RCC tumors that led to enrollment to MK-6482-004 to the time of treatment with belzutifan	18 months (range: 3 to 97)

Note: Table adapted from FDA's Multi-Discipline Review; there are no restrictions on its use (14).

[1] Per investigator assessment

[3] All 61 patients had at least one pancreatic lesion per IRC assessment.

[2] Twenty-four patients had a measurable solid lesion in CNS per IRC assessment.

[4] Forty-seven (77%) patients had prior surgical procedures for RCC.

Table 2.

Efficacy results (IRC assessment) for belzutifan for VHL disease associated subgroups with RCC, pNET, or CNS hemangioblastoma

	Belzutifan 120 mg daily		
Endpoint	**Patients with RCC N=61**	**Patients with pNET N=12**	**Patients with CNS Hemangioblastomas N=24**
Overall Response Rate			
ORR, % (n) (95% CI)	49% (n=30) (36% to 62%)	83% (n=10) (52% to 98%)	63%, (n=15) (41% to 81%)
Complete response	0	17% (2)	4% (1)
Partial response	49% (30)	67% (8)	58% (14)
Duration of Response ‡			
Median in months (range)	Not reached (2.8+ to 22+)	Not reached (11+ to 19+)	Not reached (4+ to 22+)
% (n) with duration ≥ 12 months	56% (17/30)	50% (5/10)	73% (11/15)
Time to Response			
Median in months (range)	8 (2.7 to 19)	8 (2.7 to 11)	3.1 (2.5 to 11)

Note: Table adapted from FDA's Label; there are no restrictions on its use (15).

Table 3.

Overall benefit-risk assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with VHL disease have a genetic predisposition putting them at high risk for developing various tumors including RCC, CNS hemangioblastoma, pNET, and retinal hemangioblastoma.	Patients with VHL disease have a serious and potentially life-threatening condition with limited treatment options.
Current Treatment Options	• Surgery and other procedures may treat individual VHL disease associated tumors, often with substantial associated morbidity. • While small studies describe the use of kinase inhibitors to treat localized VHL disease associated RCC tumors, these data have not been FDA-reviewed and this represents off-label use. • Efficacy data for use of kinase inhibitors in other VHL disease associated tumors is even less well-characterized.	There are no approved therapies for VHL disease associated tumors despite an unmet medical need.
Benefit	• In a single-arm trial, the confirmed response rate by IRC for belzutifan in 61 patients with RCC evaluated at the proposed dose was 49% (95% CI: 36 to 62). The median duration of response was not reached (range 3+ to 22+ months). • Responses were also seen in other VHL-associated tumors, including an ORR of 83% (95% CI: 52 to 98) for 12 patients with evaluable pNET and an ORR of 63% (95% CI: 4 to 30) for 24 patients with evaluable CNS hemangioblastomas.	Belzutifan has demonstrated a substantial ORR and DOR for VHL disease associated RCC and other tumors that represents direct clinical benefit.
Risk and Risk Management	• The most commonly reported treatment emergent adverse events were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose and nausea. Anemia, Hypoxia, and Embryo-Fetal Toxicity are labeled as Warnings and Precautions. Embryo-Fetal Toxicity is also a boxed warning due to the young age of patients and long-term use in the otherwise relatively healthy approval population. • The Applicant will submit extended follow-up of patients on MK-6482-004 as post-marketing information to further characterize safety and describe efficacy. An additional study will further evaluate and describe efficacy of belzutifan in patients with VHL disease associated non-RCC tumors.	The risk-benefit profile of belzutifan is acceptable in the approved patient population. Additional post-marketing trial data may further inform belzutifan labeling.

Note: Table adapted from FDA's Multi-Discipline Review; there are no restrictions on its use (14).