New FDA Commissioner, New Rules?
A Look into the Future of Orphan Drug Development

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September 14th , 2017

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Outline

01 **Orphan Drugs under Commissioner Scott Gottlieb**

02 **Regulatory Changes and Opportunities for Orphan Drug Development**

03 **Current Relevant Legislative Changes**

04 **Case studies on Model Informed Drug Development and Starting Dose Decision in Orphan Drug Approval**

Orphan Drugs under Commissioner Scott Gottlieb

Scott Gottlieb – New FDA Commissioner

positions

TOPIC	Position
PDUFA VI	• Supported fast passing of PDUFA VI
Drug Pricing	• Opposed negotiations in Medicare's prescription drug program • suggested changing the way Medicare pays for costly physician-administered drugs to try to bring down prices through private-sector bidding • Has been in favor of more transparency around drug pricing and ending the current system in which drug companies set high list prices but then give rebates to payers
Trial Design	• Advocate for new clinical trial designs and analyses—specifically the use of Bayesian methods to better evaluate trial results • Supports single arm trials and historical controls
Endpoints	• Likely to roll back rules related to pre-market development, most noticeably the cardiovascular outcomes studies • Potentially place emphasis on biomarkers as a surrogate endpoint along with an open embrace of simulation and modeling
Transparency	• Has backed the publication of Complete Response (CR) letters
FDA Organization	• May follow the course laid out by agency cancer czar Richard Pazdur • May set up a special Orphan unit at FDA • On FDA reviewers: thalidomide episode "fostered an idealization "lone reviewer championing an issue of safety against the prevailing orthodoxies, especially when it meant taking on corporate interests"
Gene Editing	• More and more, it's the product features of these novel technologies, and not necessarily their clinical applications

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Orphan Drugs under Commissioner Scott Gottlieb

Scott Gottlieb – New FDA Commissioner

positions

TOPIC	Position
Orphan Drugs	• Committed to clearing out a backlog of 200 orphan drug designation requests in 90 days. (expected mid-September) • "To help eliminate the backlog, we've created a special orphan-designated SWAT team. Moreover, we will never again develop a backlog." • FDA is also implementing a new, streamlined orphan drug designation review template. • FDA will focus on areas of strength for the agency based on Gottlieb's comments, rare disease and cancer therapies • FDA will be issuing new guidance on the clinical evaluation of targeted therapies for rare disease subsets in the next six months. "This new policy will address targeted drugs and how we can simplify the development of drugs targeted to rare disorders that are driven by genetic variations; and where diseases all have a similar genetic fingerprint even if they have a slightly different clinical expression." • Gottlieb noted that rare disease subsets "may be grouped by lab testing" in order to be studied in a single trial. "Our new policy will describe when we will approach drug review less by how a disease is expressed, and more by how it is driven by common sets of genetically-driven factors." • FDA will also reorganize the review staff and establish an FDA Orphan Products Council to help address scientific and regulatory issues • Other actions include: web-based training for sponsors, revising grant monitoring processes, and reduce the frequency of Orphan Cluster meetings with EMA and FDA's internal Rare Disease Council meetings.

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02 Regulatory changes and opportunities for orphan drug development

Regulatory Changes and Opportunities for Orphan Drug Development

On August 18th, President Trump signed the **"Food and Drug Administration Reauthorization Act of 2017" (FDARA)** into US law.

- ✓ FDARA reauthorizes FDA's user fee programs for prescription drugs and biologics, generic drugs, medical devices, and biosimilars for the next five fiscal years (October 2017 to September 2022).
- ✓ **Those user fee performance goals remain unchanged and will go into effect on October 1, 2017.**

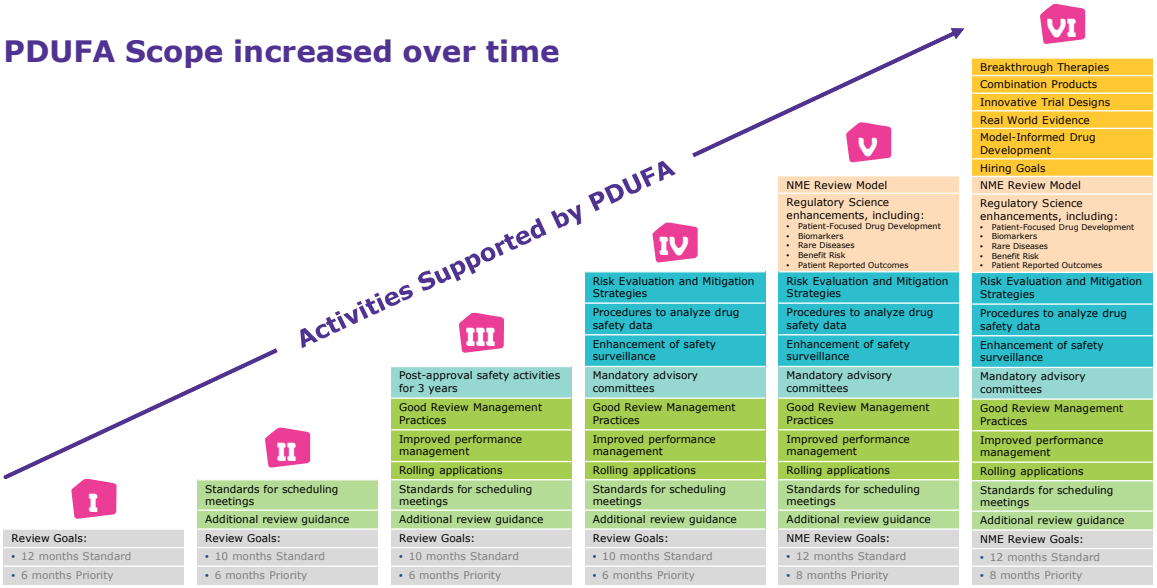
PDUFA VI

Basic PDUFA Construct

- Fee funds are added to appropriated funds and are intended to increase staffing and other resources to speed and enhance review process
- User fees pay for services that directly benefit fee payers*
- Fee discussions with industry focus on desired enhancements in terms of specific aspects of activities in "process for the review of human drugs".
  - What new or enhanced process will the FDA want or industry seek to include in the next 5 years?
  - What is technically feasible?
  - What resources are required to implement and sustain these enhancements?
  - No discussion of policy.
- Experience: Devil is in the Details

*OMB Circular A-25; direct benefit distinguishes user fees from tax

PDUFA Scope increased over time



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PDUFA VI Goals Letter

summary

Focus of the draft PDUFA VI agreement is to improve existing programs or optimize processes

- ✓ Accelerated development and availability of new medicines to patients
- ✓ Scientific and regulatory predictability
- ✓ Systematic integration of the patient perspective into drug development and regulatory review.
- ✓ Enhancing the FDA's access to state-of-the-art tools, processes, and expertise in drug development and regulation.
- ✓ Ensuring that FDA can hire and retain a strong scientific and medical workforce.

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High level summary (1)
PDUFA VI focus is on IMPROVING existing programs

TOPIC	PDUFA V	PDUFA VI
Product Development	**Drug review timelines** • Priority: 8 months • Standard 12 months	Same timelines **maintained**
Communication	**Office of Enhanced Communication Liaison** established	**Maintained** and best practice to be developed
EOP2 meetings	Scheduled 60 days from date of receipt meeting request	Scheduled 70 days from date of receipt meeting request
	Notification if meeting granted within 21 days	Notification if meeting granted within 14 days
All type A, B, C meetings	Written 'quality feedback' 2 days prior to scheduled meeting	Written 'quality feedback' 5 days prior to scheduled meeting
		Sponsor may request written response instead of meeting
	FDA may opt to provide written response instead of pre-IND and type C	Sponsor may request WRO

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High level summary (2)
PDUFA VI

TOPIC	PDUFA V	PDUFA VI
Patient focused drug development	Pilot patient-focused drug development meetings	**Workshop** to leverage learnings from pilots
		Develop **fit-for-purpose tool** to collect patient and caregiver input
		Develop **draft guidances**
Benefit/Risk Framework	Structured approach	**Implementation plan, workshop and draft guidance**
State of art tools, e.g.		Workshop and guidances (all topics)
• **Biomarkers**	**FDA biomarker qualification process**	Publish list of biomarker qualification submissions
		New dedicated meeting process (Type C) for early consultation
• **Real World Evidence**		**Pilot studies to address practical considerations**
• **Breakthrough therapy**	Not funded	**Dedicated resources to prioritise breakthrough medicines**

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High level summary (3)
PDUFA VI

TOPIC	PDUFA V	PDUFA VI
State of art tools, continued		Workshop and guidances (all topics)
• **Innovative clinical trial designs**		**2018: voluntary pilot for complex adaptive designs (2 proposals/Quarter)**
• **Model-Informed Drug Development Program (MIDD)**		Identify best practices
		Voluntary MIDD pilot program in 2018 (2-4 proposals selected per quarter)
Safety	Sentinel system	Expand data sources, enhance communication
		Assess agency's data systems and processes that support review
Resources and administration		Modernise human resource capabilities and hiring infrastructure
	Current exemptions remain	Simplified user fee structure
		Decreased growth rate annual costs
		Increasing transparency on fee use

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02

Regulatory changes and opportunities for orphan drug development

Accelerated development and availability of new medicines to patients

PDUFA VI New Meeting Management Goals (1/2)

New end-of-phase 2 (EOP2) Type B meeting classification

- EOP2 meetings scheduled 70 days from the date of receipt of the meeting request (was 60 days)
  - Extra time needed for internal alignment of reviewers and decision makers for "complex" meeting packages
  - Facilitates management of continued rise in requests for FDA meetings by sponsors overall.
  - Ensures FDA can provide sponsor with "quality feedback" 5 days prior to the scheduled meeting time
- Earlier sponsor notification: The Agency will provide notification to grant or deny the meeting request within 14 days of receipt (presently 21 days).
- Practical consequences for sponsors:
  - meeting package to be submitted earlier than today following the submission of the meeting request;
  - sponsors will still have at least a week (depending on receipt of the above notification) to finalize the EOP2 meeting package and submit it to FDA.

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PDUFA VI New Meeting Management Goals (2/2)

- For all Type A, B, and C meetings, if a meeting is granted, FDA will provide written preliminary feedback 5 days before the scheduled meeting (presently 2 days).
- After receipt of the feedback, sponsors can notify the FDA if the meeting is still needed or inform the FDA that different personnel will be attending the meeting.
- Sponsor can request a written response in lieu of a Type A, B, and C meeting
- FDA cannot a provide a written response in lieu of holding the meeting without the permission of the sponsor. However, FDA can opt to provide a written response to a pre-IND (Type B) and Type C meeting request vs. actually holding a meeting.
- FDA to issue revised Meetings Guidance consistent with the Goals Letter by September 30, 2018.

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PDUFA VI Facilitates Enhanced FDA-Sponsor Communication

- PDUFA VI Promotes Innovation by Continuing to Enhance Timely Interactive Communication Between FDA and Sponsors.
- Office of Enhanced Communication Liaison (established under PDUFA V) will be maintained:
  - to provide answers on procedural questions,
  - to assist sponsors who are having difficulty in obtaining timely responses to "simple scientific" and clarifying questions from the review Division.
- Independent contractor to assess current practices and identify best practices and areas of improvement for IND communications between FDA and sponsors.
  - By March 31, 2021: public workshop to discuss the findings of the assessment
  - One year after the workshop: Guidance on Best Practices for Communication between IND Sponsors and FDA during Drug Development updated if necessary.

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02 Regulatory changes and opportunities for orphan drug development

Systematic integration of the patient perspective into drug development and regulatory review

PDUFA VI Supports Integration of the Patient Voice in Drug Development and Regulatory Decision Making

- FDA will invest resources and strengthen staff capacity for Patient-Focused Drug Development (PFDD).
  - Dedicated experts within the review divisions
  - Advance the science of patient input, including the use of patient-reported outcome measures.
- FDA to develop a series of draft guidances with stakeholder engagement from September 2018 to September 2021 (to be finalized (or revised) within 18 months following the close of their respective comment periods).
  - **Guidance #1:** Comprehensive and representative patient and caregiver data collection
  - **Guidance #2:** Processes and approaches to determine most important impacts to patients
  - **Guidance #3:** Measuring disease impact to facilitate meaningful patient input in clinical trials
  - **Guidance #4:** Revise or supplement guidances on patient-reported outcome (PRO) measures and address the incorporation of clinical outcome assessments into endpoints
- FDA will hold a patient engagement public workshop by September 30, 2019, leveraging the learning from the 20+ PFDD disease-specific meetings held under PDUFA V.

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PDUFA VI Further Enhances a Structured Approach to Benefit-Risk Assessment

PDUFA VI will further enhance a structured approach to benefit-risk (BR) assessments in the regulatory review process, i.e.:

- **By March 31, 2018:** Publish implementation plan for benefit: risk (BR) assessment
- **By September 30, 2019:** Public workshop on the utilization of the BR framework throughout the drug life-cycle starting early in drug development, including the translation and incorporation of PFDD into the BR framework, and the communication of a drug's BR assessment to the public
- **By September 30, 2020:** Publish a draft guidance, on utilizing above-mentioned structured BR framework
- **By September 30, 2021:** conduct evaluation of above-mentioned structured BR framework

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02

Regulatory changes and opportunities for orphan drug development

Enhancing FDA's access to state-of-the-art tools, processes, and expertise in drug development and regulation

PDUFA VI Promotes Increased Use of Drug Development Tools, Including Biomarkers

PDUFA VI enhances the FDA biomarker qualification process and facilitates the use of biomarkers as new surrogate endpoints. FDA will:

- Develop staff capacity and pilot processes to engage external experts to support review of biomarker qualification submissions.
- Convene a public workshop (September 2018) and draft guidance on standards, approaches and other essential elements of biomarker qualification (2018-2020)
- Publish and update a list of biomarker qualification submissions.
- Establish a dedicated meeting process for early consultation:
  - "New" dedicated Type C meeting to discuss the feasibility and determine how the new surrogate may be adopted as surrogate endpoint.
  - Type C meeting request must include preliminary human data indicating impact of the drug on the biomarker at a dose that appears to be generally tolerable.

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PDUFA VI Enhances the Use of Real-World Evidence in Regulatory Decision-Making

- Real World Evidence (RWE) means data regarding the usage, benefits or risks of a drug derived from sources other than randomized clinical trials.

PDUFA VI supports the appropriate use of RWE in regulatory decision-making to encourage greater efficiencies in drug development. FDA will:

- Conduct public workshops with key stakeholders, including patients, industry, and academia, on the use of RWE in regulatory decision-making.
- Initiate activities, including pilot studies, aimed at addressing practical considerations related to RWE use.
- Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness

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PDUFA VI Enhances FDA's Capacity to Review Innovative Clinical Trial Designs

The following FDA activities are foreseen:

- a public workshop by March 31, 2018
- draft guidance on complex adaptive design by September 30, 2018.
- a voluntary pilot program for complex adaptive design starting in 2018. FDA plans to accept 2 proposals per quarter (e.g., one per Center [CBER/CDER]).
  - pilot program experiences **will be discussed** as case studies in FDA-sponsored public workshops (pilot applicants to agree before entry into pilot on information to be made public)
  - Sponsors not participating in the pilot can utilize existing FDA's meeting procedures and guidance(s) e.g. Critical Path Innovation Meetings

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PDUFA VI Advances the Application of Model-Informed Drug Development ("MIDD") Program

MIDD Program intended to foster the use of exposure-based biological and statistical models derived from preclinical and clinical data vs. the traditional clinical trials based model. FDA will:

- Convene a series of public workshops to identify best practices on:
  - Physiologically-based pharmacokinetic modeling,
  - Design analyses and inferences from dose-exposure-response studies,
  - Immunogenicity and correlates of biologics.
- Issue a draft MIDD guidance by September 30, 2019.
- Initiate a voluntary MIDD pilot program (2018). FDA plans to accept 2-4 proposals quarterly each year. Selected, sponsors will be granted a pair of meetings to occur within a span of 120 days.

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One More Thing…

- CDER is hosting a "CDER Rare Diseases Public Workshop: Strategies, Tools, and Best Practices for Effective Advocacy in Rare Diseases Drug Development."
- When: Monday, Oct. 30, 2017
- Who should go: While this workshop is primarily for the rare disease community to help them effectively understand what FDA needs to enhance drug development, this may be of interest to industry.
- This effort is consistent with FDA's efforts to support the integration of patient experience in drug development programs, including through implementation of the ''Patient Focused Drug Development'' provisions of the 21st Century Cures Act (Cures Act).
- This public workshop will include case studies demonstrating the beneficial overlap of effective advocacy techniques and FDA regulations in rare disease drug development.

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03 current relevant legislative changes

Current Relevant Legislative Changes

Legislative Action

PDUFA Reauthorization

+

RACE for Children Act

- The RACE Act ends the current PREA exemptions for orphan drug status and allows for FDA to require certain studies for pediatric populations
- The key RACE provisions are included in
  - Section 503- Early meeting on pediatric study plan
  - Section 504- Development of drugs and biological products for pediatric cancers
  - Section 505- Additional provisions on development of drugs and biological products for pediatric use.

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Current Relevant Legislative Changes

Key Highlights of Sec 503

- ✓ Section 503 amends PREA to enable a sponsor of a drug intended to treat **serious and life-threatening disease/condition to request a meeting with FDA to discuss preparation of initial Pediatric Study Plan (iPSP) prior to end of Phase I or within 30 days of such request, whichever is later**.
- ✓ Allows **sponsor to discuss an iPSP as soon as practicable but no later than 90 days after receipt**.
- ✓ Enable a sponsor to request a meeting with FDA to discuss any scientific or operational challenges that may be the basis of a deferral or partial/full waiver.

Current Relevant Legislative Changes

Key Highlights of Sec 504

- ✓ Amends PREA and **orphan indication** that would otherwise be exempt from PREA would, in fact, be subject to the **requirement to conduct a molecularly targeted pediatric cancer investigation**
- ✓ Requires a **"molecularly targeted pediatric cancer investigation"** for
  - o an original application for a new active ingredient submitted **at least 3 years after** enactment of FDARA
  - o if the product **is intended for treatment of an adult cancer** and
  - o **"directed at a molecular target that [FDA] determines to be substantially relevant** to the growth or progression of a pediatric cancer."
- ✓ Pediatric investigation must be "**designed to yield clinically meaningful pediatric study data regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling**" and **shall be required at the time of application submission** (unless a waiver or deferral has been granted).

Current Relevant Legislative Changes

Key Highlights of Sec 504 (continued)

- ✓ FDA must, **within one year of the enactment of the FDARA**,
  - o develop and regularly update a list of molecular targets, that may trigger requirement to conduct a molecularly targeted pediatric cancer investigation.
  - o FDA must also include molecular targets for which the pediatric cancer investigation requirement will be automatically waived.

- ✓ **FDA must, within two years after enactment,** Issue **final guidance** on implementation of provisions regarding molecularly targeted cancer drugs, including
  - ▪ considerations for determining whether a molecular target is substantially relevant to the growth or progression of a pediatric cancer,
  - ▪ regulatory considerations for trial designs,
  - ▪ and approaches to streamline the amendment process.

Current Relevant Legislative Changes

Key Highlights of Sec 505

- ✓ No later than 1 year of enactment, FDA shall develop and implement a plan to achieve, when appropriate, earlier submission of pediatric studies.
  - o The plan should include recommendations to achieve earlier discussion of proposed pediatric study requests with sponsors and written request (including for investigational new drugs);
  - o Earlier issuance of written requests for a pediatric study prior to the submission of a study; and shorter timelines (when appropriate) for the completion of studies pursuant to a written request.

- ✓ Requires FDA to provide to the internal pediatric review committee any response issued to an applicant or holder with respect to a proposed pediatric study request.

- ✓ **Requires FDA to review and act on pediatric study requests and proposed amendments to written request within 120 days of receipt.**

04 case studies

Case Study - QSP Based Analyses in Regulatory Review of Natpara

FDA approved Natpara (Parathyroid hormone; PTH) for following specific indication:

NATPARA is a parathyroid hormone indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. (1)

1 Natpara Approved Label (BLA125511)

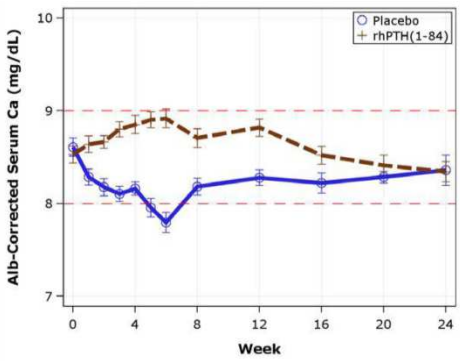
2 Case study slides are based on: *Natpara BLA12551 Reviews and Label from drugs@fda and Advisory Committee Materials*

- *http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125511s000lbl.pdf*
- *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm386727.htm*
- *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm416167.htm*

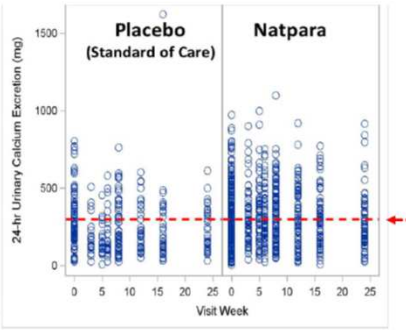
Case Study - QSP Based Analyses in Regulatory Review of Natpara
KEY Results

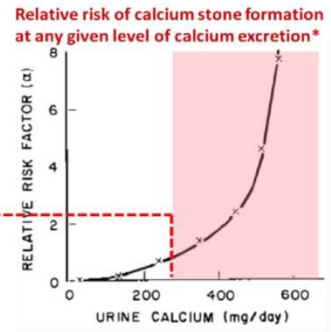
Pivotal Trial Results met Pre-specified Objectives

- ~50% Reduction in calcium daily dose
- ~80% reduction in Vitamin D daily dose



Control on 24-hour Urinary Calcium was Not Apparent in the Pivotal Trial





*Andrew F. Stewart and Arthur E. Broadus. Ann Rev Med. 32: 457-73 (1981).

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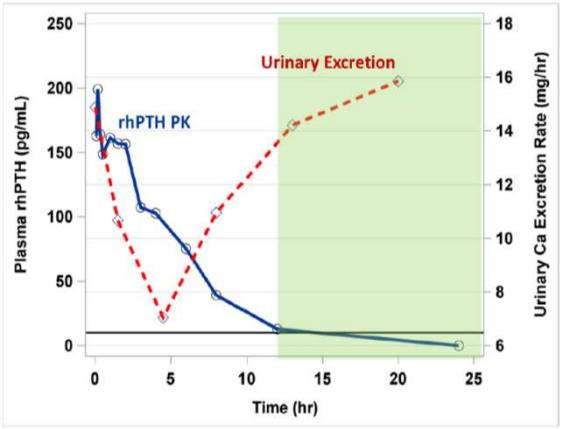
Clinical Pharmacology - PK/PD Data Revealed that Short-lived Renal Effect is a Reflection of PK Profile

Single-dose study in 7 patients with hypoparathyroidism

- 50 µg (Period 1) and 100 µg (Period 2) dose
- PKPD
  - Serial PK
  - Serial serum calcium
  - Timed urine collection over 24-hr



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Inspiration to use QSP was hidden in the Very Nature of PTH driven "Calcium Homeostasis"

- **Is less than optimal control on hypercalciuria due to QD dosage regimen?**
- **How do we show alternate regimen is needed?**
- How do we integrate PTH exposure-serum calcium-urinary calcium accounting for PTH effects on gut absorption renal re-absorption?
- PTH driven "calcium homeostasis" provided the clue

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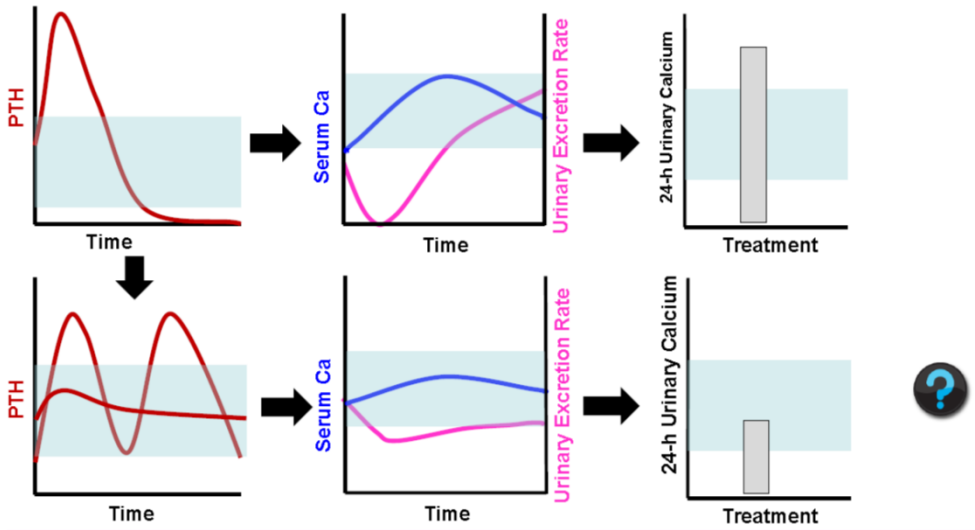
Optimizing the PKPD – Conceptual Framework



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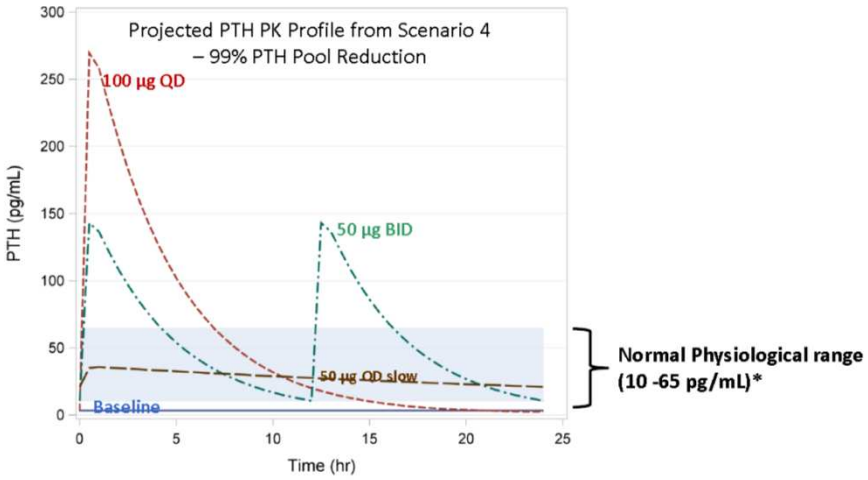
Altering Regimen (QD to BID) or Release Profile Bring PTH levels Close to the Physiological Levels



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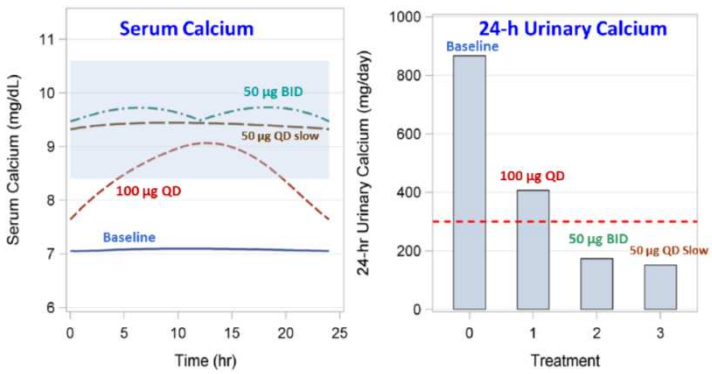
QSP Based Simulations helped us in Conveying the Idea and Hypothesis Generation

Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria while Maintaining Normocalcemia



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Normocalcemia and Normocalciuira is Achievable with Different Dosing Regimens

Scenario #	Assumption of 50% loss in PTH gland pool (Similar to Mosekilde-IIT Population) 6 month treatment simulation			Assumption of 99% loss in PTH gland pool (Extreme Clinically Realistic Scenario) 6 month treatment simulation		
	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration (d)	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration(d)
1	0 QD	50	1.5	0 QD	50	1.5
2	0 QD	25	1.5	0 QD	25	1.5
3	0 QD	50	0.5	0 QD	50	0.5
4	0 QD	25	0.5	0 QD	25	0.5
5	100 QD	50	1.5	100 QD*	50	1.5
6	100 QD	25	1.5	100 QD*	25	1.5
7	100 QD	50	1.5 / 120 d	100 QD*	50	1.5 / 120 d
8	100 QD#	25	0.5	100 QD*	25	0.5
9	50 QD**	25	0.5	50 QD*	25	0.5
10	50 BID#	50	1.5	50 BID*	50	1.5
11	-			50 BID**	50	1.5 / 120 d
12	-			50 BID**	25	1.5 / 120 d
13	50 BID**	25	0.5	50 BID**	25	0.5

Hypercalciuria with hypocalcemia

Hypercalciuria with noromocalcemia

Calciuria and serum calcium ~ ULN

Normocalciuria with noromocalcemia

Source: Table 15 Clinical Pharmacology Review BLA125511 drugs@fda

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Putting Pieces of Information Together

Summary

- Proposed QD regimen was able to control serum calcium, reduce oral calcium and vitamin D requirement
- Proposed QD regimen was not optimal in control on hypercalciuria
- Natpara QD administration does not produce PTH levels to cover the entire 24 hours
- The effect on urinary calcium excretion is short-lived
- Using systems pharmacology model we showed that control on hypercalciuria is feasible with more frequent regimen or a slow release PTH profile at lower systemic exposure than 100 µg QD
- For hormone replacement therapy, applying PKPD data for optimization of dosing regimen is important

Source: Summary Slide From Clinical Pharmacology Sep 12, 2014 EMDAC Meeting FDA Presentation

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QSP Based Analysis - Impact on Regulatory Decision

- Following Post-marketing Requirements were issued

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of hypercalciuria in patients treated with Natpara (parathyroid hormone).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2856-3	A clinical pharmacology trial to assess the pharmacokinetics (PK) and pharmacodynamic effects (PD) of Natpara (parathyroid hormone) dose and dosing regimen on the control of serum calcium and normalization of calcium excretion in urine. Modeling and simulation using mechanistic model-based assessment of prior PK/PD data should be used to design this trial.

2856-4	A 26-week randomized, controlled clinical trial to evaluate the longer term safety and effect of an alternative dose(s) and/or dosing regimen(s) of Natpara (parathyroid hormone), including longer term safety with respect to hypercalciuria. This trial should not be initiated until the results from the clinical pharmacology trial (PMR 2856-3) and the nonclinical rat study (PMR 2856-1) have been submitted to and reviewed by the Agency.

Natpara BLA 125511 Approval Letter:
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125511Orig1s000ltr.pdf

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Key Learning Points in Retrospect

- Modeling and simulation using PK/PD would have been useful to guide the Phase 3 trial design
  - need for a better groundwork is even more critical
- Too early to say QSP Model is answer to everything
  - discipline seems to be in its infancy – from a regulatory perspective
  - regulatory experience is limited
- Hypoparathyroidism (Only known application presented here)
- Commitment for time and resources
  - wisely identify key areas where this is feasible/applicable
  - prioritize efforts and resources
- Sharing of information
  - proprietary nature of data and/or model

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Starting Dose Decision for Signifor (Pasireotide Diapartate)

Indication:

SIGNIFOR is a somatostatin analog indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative

Dosing:

Recommended initial dosage is either 0.6 mg or 0.9 mg by subcutaneous injection twice a day; recommended dosage range is 0.3 mg to 0.9 mg twice a day

Titrate dosage based on treatment response [clinically meaningful reduction in 24-hour urinary free cortisol (UFC) and/or improvements in signs and symptoms of disease] and tolerability

Source: Signifor Label
Signifor Clinical Pharmacology Review NDA 200677
Signifor Division Director's Memo NDA 200677

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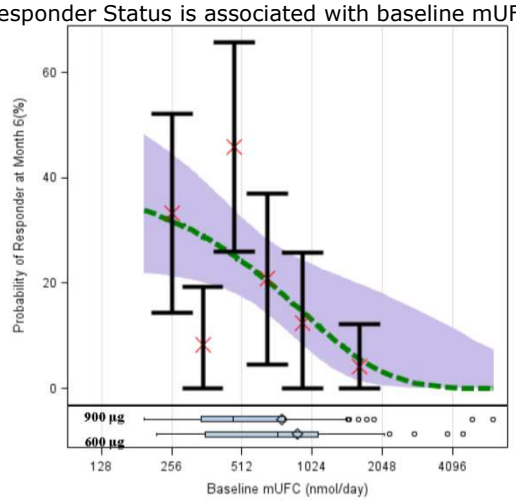
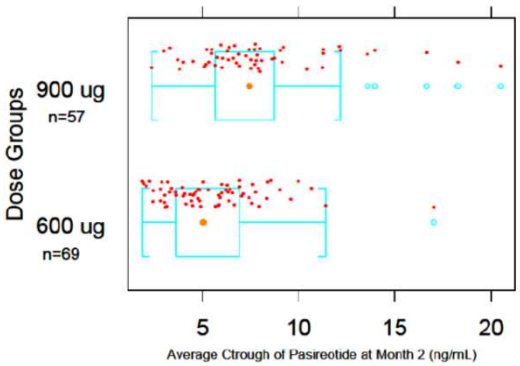
Does the exposure-response relationship for efficacy support the proposed initial dose of 900 µg b.i.d.?

Responder Status is associated with baseline mUFC



Two dose groups have substantial overlap in exposure



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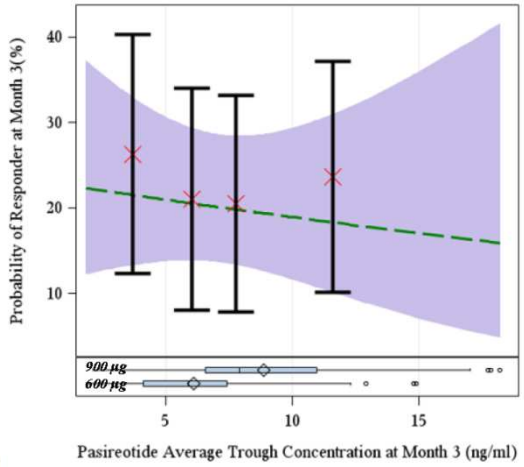
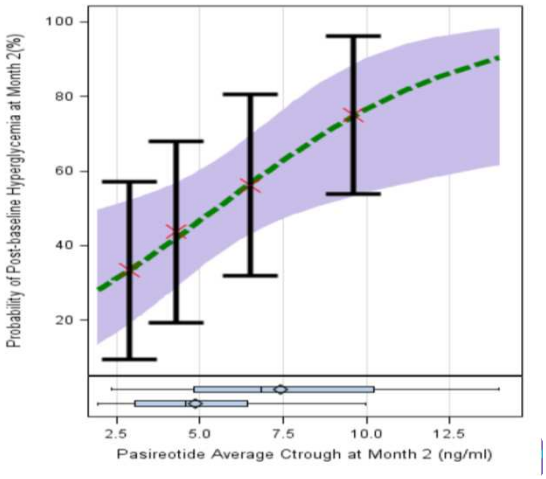
Does the exposure-response relationship for efficacy support the proposed initial dose of 900 µg b.i.d.?

No evident relationship between exposure and response rate after adjusting for baseline mUFC



Increase in probability of developing post-baseline hyperglycemia



Final Regulatory Decision

- 900 ug bid dose met the pre-defined criterion for declaring a statistically significant treatment effect
- The criterion for declaring a statistically significant treatment effect was an arbitrarily set one and the absence of a placebo arm precludes from declaring that the effect observed with the 600 ug bid dose was also significant
- A numeric imbalance in the baseline UFC might also contribute to the lower rate of UFC normalization in the 600 ug bid group
- Additional exploratory analyses were performed with results supporting a conclusion that the 600 ug bid dose could also be considered a clinically effective dose option
- After discussions with the review team there was agreement that the label does not need to be prescriptive in a recommended start dose but that a dose range with guidance for clinicians would be appropriate

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Take Home Points

- Important changes are coming in the orphan and rare disease development space with the arrival of the new Commissioner
- FDARA presents several opportunities for interaction, commenting and novel approaches in the orphan drug space
- RACE may present some new challenges but also opportunities in the orphan oncology space
- FDA seems to be opening up to the idea of modeling and simulation and more exposure-response analysis also or in particular in the orphan drug space

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Acknowledgements

OCP

- Nitin Mehrotra
- Liang Li (Fellow)
- Jeffery Florian
- Chandra Sahajwalla
- Vikram Sinha
- Sang Chung
- Jingyu (Jerry) Yu

OND

- Naomi Lowy
- Dragos Roman
- Jean-Marc Guettier
- Curtis Rosebraugh

EMD Serono

- Mark Bokelman
- Ritesh Jain
- Chun-Pyn Shen
- Christine Mayer-Nicolai

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