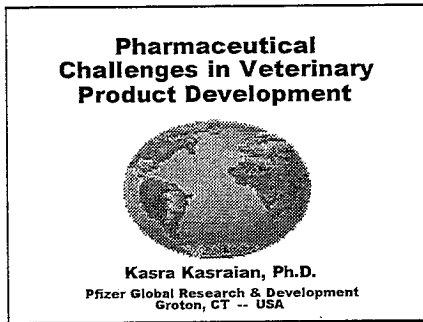


UNIQUE ASPECTS OF VETERINARY FORMULATIONS

Kasra Kasraian, PhD



Presentation Objective

To Highlight *Differences* between Human and Veterinary Formulations and *Challenges* Associated with Veterinary Formulation Development

I have not worked on all of these types of dosage forms, and I am not going to focus on them today. In order to try to compare and contrast human health and animal health formulations,

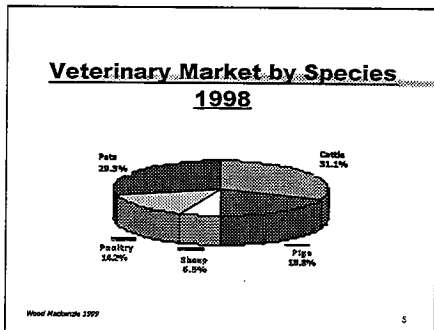
Dosage Forms Unique to Animal Health

- Feed additives
- Ear tags
- Flea collars
- Ruminal boluses
- Intra-mammary infusion
- Vaginal inserts (e.g. estrus control)
- Darts
- Bullet implant
- Pour-on/Spot on

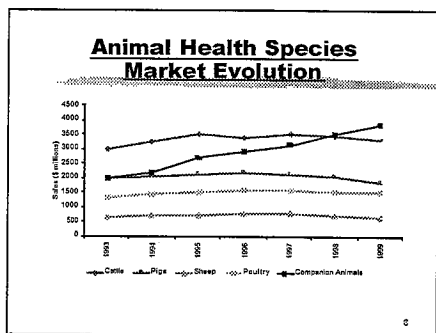
Dosage Forms Common to Both Human and Animal Health

- ⊗ IM, SC, IV injections
- ⊗ Oral solids (IR & MR)
- ⊗ Topical creams, ointments
- ⊗ Periodontal implants (new)

I'd like to focus on the traditional injectable formulation and oral tablets; that way you can get a much better picture of the differences between human health and animal health formulations. So basically I am going to focus on traditional injectables and oral solids, specifically talking about immediate release tablets.

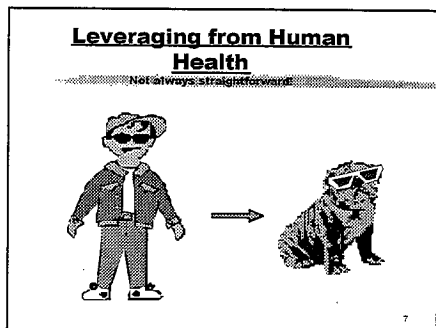


This pie chart basically just represents the veterinary market by species. As you can see, about 70% of the market is the livestock business, and about 30% is companion animals, and traditionally, most of the animal health companies have been focusing on the livestock business.



But over the last few years, as you can see, the companion animal market has grown. And a lot of companies, including Pfizer, have shifted some of their focus towards coming up with new drugs for companion animal uses. Again, back in '95, when I joined Pfizer, most of the formulation scientists, actually all of the formulation scientists were focused on injectable dosage forms; we didn't really focus on tablets as much for animals in general because it is difficult to dose herds with a tablet. But again as we got more focused on the companion animal market, there was a need for more oral dosage forms, again because a lot of times you have chronic therapy and it is easier to dose an animal with a tablet as opposed to giving them an injection frequently at home. And that was basically about two years ago I was asked to join what we call our solids group. And I have

been in the solids group for the past 2 years now, designing oral dosage forms for companion animal purposes.



I'd like to take a few minutes to talk about leveraging, actually, products from human health into animal health. A lot of companies try to leverage their human health portfolio and apply it to animals, and that makes all the sense in the world - it is very logical to try to maximize what you have in human health and try to make some use of it in the veterinary field.

Leveraging from Human Health

Oral Dosage Form

Formulation Challenges

- Lower Doses
- Multiple Strengths
- Palatability Requirements

However, what I want to point out here today, is that we all know that a drug that works in animals may not necessarily work in humans and vice-versa, something that works in humans may not be really safe and efficacious in animals. The same thing holds true for dosage forms. A dosage form that was originally designed for human health is not always easy to commercialize for veterinary use, and a lot of work has to be done, in trying to customize the dosage form to fit the animal health needs, and I would like to use some example on the oral side to illustrate that point.

Stability Challenges
Leveraging from Human Health

	Initial	Total Impurities		
		3 weeks (40C/75%RH)	6 weeks (40C/75%RH)	12 weeks (40C/75%RH)
Larger Dose (Human)	0.10%	0.08%	0.20%	0.20%
Lower Dose (Animal)	0.10%	0.66%	1.00%	1.70%

some theories that you might be getting more drug excipient interaction, or that there is maybe more water available to interact with the drug substance and hence make it more mobile and reactive with some of the excipients present in the formulations. So lower doses basically increase the risk of stability issues.

Again, as I said, I am going to focus on oral dosage forms to illustrate my point about the complexities of leveraging from human health formulations. Typically, on animal health sides, we are dealing with lower doses. That is not always the case, but in general, as I think Dr. Martinez alluded to yesterday, we dose animals on a mg/kg basis, and humans on a milligram basis. And a lot of times, we are dealing with very small animals, or small cats and dogs, so we have to adjust to our formulation to lower doses. And while that seems pretty easy, it is not always the case. Whenever you drop the dose and lower the dose of the formulation, you run into issues such as stability. Traditionally, what we have seen as we have lowered the drug concentration, and make a more dilute formulation, we typically run into some stability issues. The reasons for that aren't really known, there are

Impurity Threshold for Drug Product
Human Health vs Animal Health

	Human Health	Animal Health
Report	0.1%	0.3%
Identify	0.5%	1.0%
Qualify	0.5%	1.0%

ICH Guidelines

illustrates my point in that just dropping the dose can have on the stability of the product. And those are some of the issues that we typically see when we try to take a human health tablet and apply it to animal health.

To illustrate this point, I'll take a real example of a formulation that was originally developed for human use, and then what we ended up doing was trying to leverage this formulation for use in animal health. And what we did was, basically it is the same exact formulation except the dose was decreased- I don't know how much by, but by probably an order of magnitude, the dose was lowered. And, as you can see we put up these formulations up on stability- these are accelerated stability conditions, we typically use accelerated stability conditions for screening purposes. At 40 degrees and 75% relative humidity. And what you see, is after 12 weeks storage of the human health tablets, at 40/75, we saw a total impurity of about .2% in that tablet. Whereas the same formulation except at a lower dose, we saw about 1.7 % impurities, so that just kind of

Leveraging from Human Health

Oral Dosage Form

Formulation Challenges

- ⌘ Lower Doses
- ⌘ **Multiple Strengths**
- ⌘ Palatability Requirements

mean do tox work. When we hit the .5% threshold for the human health products, whereas for the animal health, that level again is 1%. Now at Pfizer, we start to worry, because most of our portfolio is human health, we start to worry when we even hit the .1%. So we treat our animal health formulations similar to the human health, but the rules are a little bit wider for the animal health impurity threshold.

The other factor is that the animal health formulations are typically subject to more environmental stresses; you can imagine a product being in a barn in the middle of the winter, versus in the back of a pickup truck in the heat of the summer. So, the veterinary products are typically subject to more environmental stresses and hence stability issues. More so than the human health formulations. Probably the only thing that I found easier on the animal health part than on the human health part is some of the impurity threshold we have on the drug product side. Basically, on the human health side, if a single impurity is greater than .1 %, we typically have to report it. Whereas on the animal health side, that number is about .3 %, so it makes our life a little bit easier, we don't really have to react if we are below .3%. We typically have to identify and qualify; by qualifying we

Leveraging from Human Health

Multiple Strengths: Body Weight Comparison-Adult Animals

Species	Weight Range (kg)
Cat	1 - 4
Dog	3 - 43
Horse	408 - 433
Cattle (Beef)	266 - 641
Dairy Cow	600 - 700
Sheep	54 - 66

The next factor one has to consider when trying to leverage from human health is the fact that when you are trying to target animals, you have to develop multiple strength tablets. Again, you have a wide variety of weights and this slide just illustrates the weight range for the different species. So we are targeting quite a wide weight range, and even within a species, such as dogs, you can see weight ranges, ranging from 10 lbs. to 100 lbs. And so again, in order to accommodate the market needs, we have to develop tablets in dosage forms, which can basically hit these weight ranges.

Tablet Design for CA

Dog Weight Range (lb)	Marker (%)
10 lbs	2-3%
11-25 lbs	8-10%
26-50 lbs	20-25%
51-100 lbs	Rest

Typically, formulators like to work with what is known as a common blend. A common blend, basically you have the same drug to excipient ratio. So, you do one stability on one formulation, and if you need multiple strength, you just change the tablet size. In other words, let's take for example, a 10 mg/kg does and basically you've got the animal body weight ranging from 5 to 40, that would indicate that you need tablet strength bearing from 50 mg all the way to 400 mg. Simply what we would do is, set up this formulation on stability, make a 50 mg tablet, and the total tablet weight is 200 mg. And basically, in order to increase the dose, we just make bigger tablets. That way, that one stability study will cover all of these weight ranges.

Tablet Design for CA

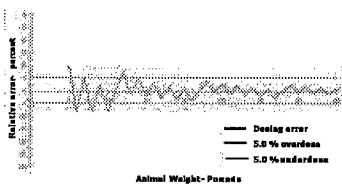
- Tablet
 - Common blend
 - Tablets can be divided

Animal Weight		Tablet Weight	Tablet Potency	
kg	pounds	mg	10 mg/kg or 5 mg/lb	15 mg/kg or 7.5 mg/lb
5	10	200	50	75
10	20	400	100	150
20	40	800	200	300
40	80	1600	400	600

This is traditionally done in the animal health world, because again, you don't want to set up multiple stability programs because they cost more. And so, what you want to leverage is the fact you can work with common blends. And when you are working with large animals, typically, they can handle taking 1 or 2 gram tablets. Not a big issue, whereas again, on the human health side, our tablet size does not exceed 600 mg tablet weight, because it is hard to swallow. Then again, on the animal health side, we basically try to work with the common blend. Again, we try to develop tablets that are, what we call, scored, meaning they can be broken easily into halves for more accurate dosing.

Dosing Error

30 mg/kg dosing: 100 and 25 mg active tablets
5.0% dosing error target; low strength tablets



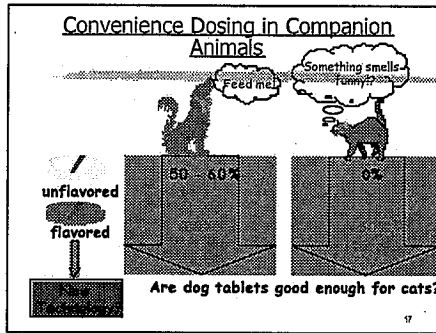
And what I want to point out here, is despite the fact that we want to design multiple strength tablets, we still run into the problem of not always trying to hit the target, because of the wide weight ranges, we sometimes underdose or overdose, and that is just a fact of life. So even with multiple strength and being able to score, you are not always going to get your exact dosage you wanted on a mg/kg basis.

Leveraging from Human Health

Oral Dosage Form

Formulation Challenges

- ! Lower Doses
- ! Multiple Strengths
- ! Palatability Requirements



I'd like to talk a little bit about palatability. Some people might consider palatability as a marketing gimmick, that may be so, but the reality is, in my opinion, it is more of a compliance issue and it is a real need.

	Plain White Tablet (no flavor)	Tablet w/ Flavor
Bland Drug	~60%	~100%
Bitter Drug	~40%	~90-100%
Odoriferous Drug	~20%	~55%

If anybody tried ever to pill a cat, you know how difficult that is, and so one of our principle headaches and challenges in designing an oral dosage form, especially for chronic treatment is trying to design a palatable formulation. This should be a white tablet, doesn't show very well here. The easiest approach, I guess, in trying to make a palatable dosage form is just to take your original formulation and substitute it with maybe 5 to maybe 20% of some sort of flavoring agent. Our traditional favorites are yeast and pork liver seems to work really well in dogs. Our traditional method is just by direct flavor addition and with that typically in dogs, we can improve the free choice acceptance to about 80%, I would even say 90% free choice acceptance. And by free choice, I mean either you offer the tablet in a pan, or you offer it by hand or something like that. Whereas if

you take pretty much a bland tablet or a bland drug and offer it to the dog, most of the time you are going to get 50 maybe 60% free choice. Just a direct flavor addition, you can get pretty good palatability numbers. However, on the cat, it is a lot more difficult, forget about trying to give a white tablet to a cat, they'll never take it free choice. And even with addition of flavors, we haven't seen, but we see a great improvement from 0 to 50%, but still, it is not where we would like to be from a convenience standpoint. And the other factor is, typically, when we design a formulation, we want to develop one formulation that covers both dogs and cats. And a lot of times, what works in dogs may not necessarily give you the desired palatability requirement in cats. Now, I have been focusing on direct flavor addition that is the simplest approach that sometimes does not work. And here you can see some data we have on percent acceptance in dogs, if you take pretty much a bland drug, and offer it to the animal, this is in about 30 dogs, and if you give a bland tablet to an animal with no flavoring, you are probably going to get somewhere in the 60% acceptance range.

- 1) compatibility of active with flavor base
- 2) global acceptability (regulatory approval)
- 3) acceptability by dogs and cats
- 4) stability of flavor
- 5) ease of characterization of flavor and
- 6) precedence

If you flavor the tablet with something like yeast or pork liver, somewhere in the range of 5 to 20%. You are going to get pretty good palatability numbers, somewhere in the 100% range. Likewise, if you take bitter drug, you can pretty much mask the bitter taste by adding a flavor. And we have typically seen numbers in the 90 to 100% free choice, so we have been successful in masking bitter taste just by flavor addition. This number of 40% is deceiving; I think that number should be lower.

***Question from crowd, "Are those lab dogs or client owned animals?"** * Those are client owned animals. **Can you speak to the in what you experience in the lab versus client?** Yes it was a hard lesson, we have tried both and one thing that I would say is never do any sort of palatability studies on lab animals. Some of them might give you great palatability numbers and others might give you very poor numbers. I remember one study we did in a clinical setting, and these dogs, because they had not been used to being given treats. They would not even take things like Pupperoni, which most dogs love. We got very low scores, so you can get false negatives and positives when you go into lab animals. So typically, we try to go into client owned dogs. Again, the bitter drug here, I think the numbers should be higher, a lot of times the dog just inhales the tablet, and doesn't have time to taste the bitter taste. So, I would imagine if the dog actually chewed the tablets, these numbers would be close to zero. Because you could sense that the dogs we actually saw when the dogs chewed the tablet, they would actually spit it out. But there were some dogs that were eager to take a tablet, and they would just inhale it, so that is why the

numbers are a little bit high. The biggest challenge I find in palatability is when you are working with drugs that are not only bitter, but they are odorous to the dogs, no matter how much flavor you put in them, really they won't come near it. I guess they have a stronger sense of smell. So in the case of odorous drugs, you may have to go with more unique technology cites, such as microencapsulating the drug, and sometimes even the some of the odor may be associated with the recrystallizing solvent used for the drug substance, so you might have to figure out ways of washing the drug and treating the drug substance differently to minimize the odor associated with the drug. So for the most part, I would say in dogs, you can get away with just adding a direct flavor, and you can get pretty decent palatability numbers. I focused quite a bit on percent acceptance or the free choice acceptance, but there are a lot of other things one needs to consider when trying to develop a palatable dosage form. And I think the biggest issue that I find is the compatibility of the active with the flavoring agent. The flavoring agent isn't one single entity, it is a combination of a bunch of amino acids and fats, and each one of those could go rancid or react with your active ingredients and cause all sorts of headaches. We have even seen cases where things like pork liver could affect dissolution. The protein will denature and slow down the dissolution and subsequently could affect your bioavailability, so there is a lot of things to consider- it is not just simply adding the flavor into the tablet, there is a lot of other things one needs to consider. Global acceptability is obviously another issue, a lot of these flavoring agents are animal derived, and so a lot of the European countries and agencies don't want to deal with animal byproducts, and in some cases, we have even had to irradiate some of our flavoring agents, which again, add some more complexity to the development, time wise.

Summary

Formulation Challenges

- Lower Doses
 - Stability
 - Dose Uniformity
 - Analytical Challenges
- Multiple Strengths
 - Dog/Species weight range (wide range)
 - Accurate dosing (critical if narrow T.I.)
- Palatability Requirements
 - Chronic treatment

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So in summary, I'd like to point out that when you are trying to customize a human health formulation for animal health, you are typically going to deal with lower doses which carry the risk of increased instability, there could also be manufacturing issues; things such as dose uniformity, as your drug concentration goes down, there is increased chance that your dose won't be uniform. Obviously, there are analytical challenges, extraction, and things like that. Furthermore, sometimes even adding these flavoring agents make manufacturing a lot more difficult. Things like yeast, when it is put into the tablet, what we see are the mechanical properties of the tablets are compromised when you add things like yeast. You get very soft tablets. So these are all of the things one needs to consider, also multiple strength, we talked about that. And again, palatability as

another big aspect that one needs to consider.

Other Factors: Biological

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I spent some time now talking about the formulation, things like chemistry and formulation challenges that one faces when trying to develop an animal health dosage form. But there are obviously other factors, which I lumped in as biological factors, and I am not going to spend a lot of time here because most of the audience here is an expert in this field.

Food Effects

Compound	Ratio of Fed AUC to Fasted AUC
A	1.9
B	1.3
C	2.4
D	3.9
E	2.6
F	5.1

•Convenience issue
•Exposure/Efficacy/Safety issue

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One of the things one needs to worry about, both on the human and animal health side is food effects. This table just illustrates a series of compounds here and compares the ratio fed AUC to fasted AUC, and within this class of compounds, you see a wide range of affect that food has on the bioavailability of the drug. Again, on the human health side, it is still an issue, but you can control the eating habits of a human. You can tell them to take it on an empty stomach, or take it with food, whereas on the animal health side, that is not always very convenient. And trying to control the eating habits of an animal, especially a sick one, isn't that easy, so a lot of times we try to minimize food effects by altering the formulation, if we can.

Half-life Comparison in Representative Species

(Hours)

	Ruminant	Horse	Dog	Cat	Human
Pentobarbital	0.8	1.5	4.5	4.9	22.3
Amphetamine	0.6	1.4	4.5	6.5	10-15
Salicylate	0.8	1.0	8.6	35	4-8
Sulfadimethoxine	9	11.3	13.2	10.2	40
Trimethoprim	0.8	3.2	3		10.6
Phenylbutazone	43	3-6	2.5-6		72

Reppel, J. D., Controlled Release 6, (1991) 5 - 13

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This slide right here, again, compares the half-life of different drugs in different species, and the point I want to make here is that this is actually half-lives, OK, so this is the half-life of various drugs in different species. And you can see, there are some great differences, and the point I want to make here is that you can't really extrapolate the half-life from one species to another. Not one single formulation fits all species, so you have to consider some of the biological factors and some of the absorption, distribution and metabolism factors in designing your formulations.

Species Differences and Metabolism

Species	Reaction	Major Target Groups	Comment
Cat	Glucuronide synthesis	- OH, - COOH, - SH, - NH ₂	Present, slow rate
Dog	Acetylation	- Ar - NH ₂	Absent
Pig	Sulfate Conjugation	- Ar - OH - Ar - NH ₂	Present, low extent

Reppel, J.D., The State of Veterinary Clinical Pharmacology (1977) 144 - 216.

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This slide is similar, it illustrates the difference in the metabolism between the different species and again, sometimes you may even have interspecies differences. You may even have differences just within a species; there have been cases where we've tried formulations in beagles, and they work fine, and then we go to mongrels and we see totally different behaviors. So it is not just within different species, but intraspecies differences is not uncommon.

U.S. Animal Health Market by Dosage Form Based on Sales

- Oral (52%)
 - Feed premixes (35%)
 - Oral dosage forms (17%)
- **Injectable (33%)**
- Topicals (5%)
- Others (7%)

Based on 1987 Sales: Cardinal 20, 1992

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I'd like to now shift the focus onto the injectable formulation. Again, this slide was based upon 1987, but shows that 33% of the dosage forms used in veterinary products are injectable formulations. So I would like to spend a little bit of time comparing the human health and animal health injectable formulations.

Injectable Formulations

Formulation Challenges

- ⌘ **Injection Site Toleration (IST)**
- ⌘ Multi-dose Formulation
- ⌘ In-vivo Stability

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One of my favorite topics is injection site toleration.

Injection Site Toleration (IST)

IST is common issue for injectable formulations for both Human Health (HH) and Animal Health (AH)

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Injection site toleration is common for both animal health and human health formulations. So the question is, why is the injection site toleration a bigger challenge or animal health products? The reason is, on the human health side, typically if we find that we have a major injection site toleration issue, you can maybe overcome it by changing the route of administration, going from a subcutaneous or an intramuscular injection to an IV route. You can also overcome it by maybe administering less drug, and maybe having to go multiple times.

Why Is IST a bigger Challenge for Animal Health Products?

Human Health

- ⊗ overcome by changing route of administration (i.e. IV)
- ⊗ overcome by administering less drug (multiple injections)

Animal Health

- ⊗ Economic Issue
 - ⊗ IV route is not always feasible (labor cost/management practice)
 - ⊗ multiple injections not desirable
 - ⊗ one-shot therapy (formulation with high drug loading—ex. Advocin 18%)
 - ⊗ sustained release (depot)
 - ⊗ restricted to "cheaper" formulation technology

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Whereas, on the animal health side, it is more of an economic issue. The IV route is not always feasible. Multiple injections, again for economic reasons aren't desirable, either. A lot of times, we are looking for these one shot therapies, an example of this is a product I worked on that is currently on the market. It is advocin 18% that is a dosage form that is like 180 mg/ml, so it is a very concentrated formulation, very complex formulation. And to get that much drug into solution, we had to complex it with magnesium and use organic solvents to try to solublize 180 mg of this drug in solution. And, again, we did that because the market wanted a one shot therapy. And you can imagine that what sort of injection sight toleration you can have when you have that much drug at the injection site. However, with advosin 18%, the drug is well tolerated because we

optimize the formula, but in early screening, injection site toleration was a major issue because of the high drug loading. The other issues are the fact that a lot of clients want some kind of one shot therapy, or sustain released depo and then whenever you have a depo formulation, you are bound to run into more injection site toleration issues, just by the fact that the drug is staying around at the injection site. And finally, we are restricted to cheaper formulation technology, so we can't, say microencapsulate the drug, because that is an expensive process. So again, these are some of the issues that make injectable formulations for animal health a bit more complex.

IST Companion Animals (CAVs) Livestock

Companion Animals

- ⊗ Issues
 - ⊗ pain on injection
 - ⊗ swelling

Livestock

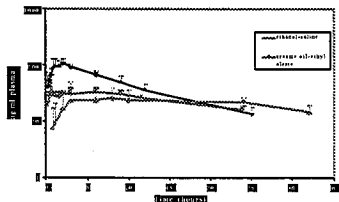
- ⊗ Issue
 - ⊗ meat quality



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Injection site toleration for companion animals, basically, we want to minimize pain on injection and any sort of swelling. Whereas on the livestock side, if there is pain on injection or twitching during administration, or swelling, we don't really worry about that. What we are really worried about more is the meat quality.

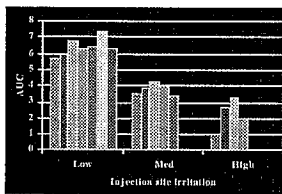
Plasma concentrations following subcutaneous administration of 1 mg/kg (n=4)



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The first two formulations here are an ethylene-saline formulation, and a sesame oil-ethylolate formulation. And this formulation I cannot disclose, but it is a different formulation of these two. And these two formulations, again form a nice sustained activity, and it was more of a depo formulation, but they are very poorly tolerated, whereas this formulation was very well tolerated, but again, it is not as sustained as one may want in some cases. Basically what I want to try to illustrate here, is that if you want a sustain release type depo, you are probably going to run into more of an injection site toleration, then if you had something that was rapidly absorbed.

Impact of IST on AUC from various suspensions



This slide, basically, is trying to make the same point. It shows the impact of injection site toleration on AUC from various suspension formulations. These are similar formulations, which had very low injection site toleration issues, but we had higher blood levels whereas when we saw less blood levels, it was more accompanied by injection site toleration issues. Again, it is just because the drug is sitting at the injection site a lot longer. So it is a balancing act, a lot of times you want sustained release depo formulations, but you are going to run into injection site formulation, so it is a balancing act.

Injection Site Toleration

(Impact of Formulation Design)



This picture just illustrates the impact that formulation development has on injection site toleration. On the right here, you see a formulation which caused considerable amount of swelling and actually, it was one of the ethyloleate formulations that I just illustrated, whereas with the new formulation, basically we saw no signs of swelling or edema. It was basically clean as normal saline.

Injectable Formulations

Formulation Challenges

- ⌘ Injection Site Toleration (IST)
- ⌘ Multi-dose Formulation
- ⌘ In-vivo Stability

When you are trying to develop an injectable for animal health, one needs to consider the fact that a lot of times, our marketing folks would like to have multi-dose formulations. On the human health side, we typically develop what is called a single use vial; you use it once, you throw it away. On the animal health side, veterinarians would like to have multi-dose formulations, and that adds another level of complexity to our jobs.

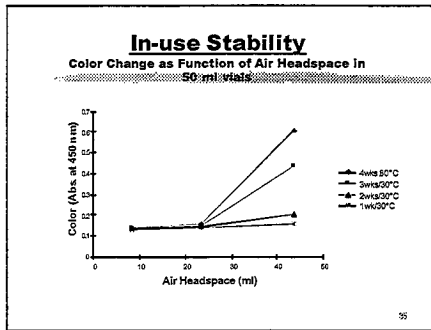
Injectable Formulations (Multi-Dose Requirements)

- ⌘ *Need for preservative (if aq./not self-preserving)*
- ⌘ *Need to pass PET (preservative efficacy requirements)--meeting EU criteria is sometimes a challenge*
- ⌘ *Need to pass max multi-puncture study (issue with large needle gauge; large volume package)*
- ⌘ *In-use stability: how to design study, O2 sensitive products*

Typically, we need to identify a preservative. A preservative sounds easy enough, but it is not easy to identify the right preservative that is both stable and meets some of the preservative efficacy requirement tests. Again, when you add in another ingredient into the formulation, you run the risk that preservative itself is not stable, or that it could carry in something, some impurity, that could render the active unstable. So a lot of effort has to be spent on trying to identify the right preservative. As I said, trying to meet a preservative efficacy test both in the US and Europe is very difficult, trying to meet the European preservative efficacy test criteria is pretty challenging. The fact that you are going to make this a multi-dose vial, we need to do some testing to see if the stopper can pass a multi-puncture study in other words, we go into the stopper several times and find out at what

point the stopper basically shatters. Injectables for animal health, you need to design, again, formulated with different ranges of package sizes could vary from 10 ml all the way up to 5 gallons, so that again makes a formulation scientist's job a lot more challenging because the stability of fluids, believe it or not can vary as a function of packet size, because the head space to the volume ratio changes, so in fact, a product that I worked on that was very much the case. The product, when it was put into 500 ml volume, was pretty stable, but when it was placed in a 10 ml volume, it showed some oxidation issues, just because of the nature of the ratio of the headspace to the volume exposed. And finally, when you have multi-dose vial, you

need to assess the in-use stability. How is the formulation going to behave upon stability when half of it is removed? And trying to design an in-use stability study is a challenge.



I actually have an example of that here, this is a product that was sensitive to oxidation, and as it oxidized, there was a color change associated with that. And what we saw was basically, this is an unbroached vial, so after 4 weeks at 30 degrees, you saw no color change, but if you remove even half the vial, again you'd still have a pretty stable formulation. But if you took more than half the contents of the vial, you would start to see some severe color change. Again, just by the nature of the fact that the oxygen level in the vial was higher than the amount of anti-oxidants that was present in the formulation. Again, due to the changes in the headspace to actual volume ratio changes, we saw differences in stability. I have spent quite a bit of time talking about *in vitro* stability; there are some cases, especially when you are trying to formulate biologicals and proteins,

where you have to consider *in vivo* stability. I have actually worked on two protein formulations while I have been at Pfizer, where we were trying to design a depo type formulation, and the biggest challenge was that the actual protein wasn't stable at the injection site, and so you couldn't prolong the duration of action of the active ingredient.

Injectable Formulations

Formulation Challenges

- ☐ Injection Site Tolerant (IST)
- ☐ Multi-dose Formulation
- ☐ **In-vivo Stability**

Again, proteins are obviously bigger than small molecules; they have a tertiary, secondary structure, which if changed, could lead into aggregation or loss of bioactivity. So there are a lot more complications to deal with, and I have an example of a product that I worked on, and I won't go into all the detail. This is PST, or porcine somatotropin, a growth enhancer, and the objective, I believe, if I remember correctly, was to try to come up with a protein formulated as a pellet in some sort of waxy matrix, and was implanted into the swine and the objective was try to get a three week delivery system out of it. And even with several formulation tries, we never exceeded 9 days of delivery, and that was simply due to the fact that the protein itself, at those higher temperatures, basically, body temperature of about 40 degrees and the subcutaneous space being moist. We

basically couldn't get beyond 9 days, again, because the protein was aggregating and forming a mass. So, the pellet that was released in the drug for 9 days stopped working after 9 days simply due to the fact that the protein was denaturing and forming an insoluble material. I have highlighted some of the technical challenges associated with developing animal health products, there is obviously some non-technical challenges and I guess the biggest one from my perspective is that we deal with much shorter time lines in animal health world than we do on the human health side. From the time a candidate enters development from our discovery colleagues to the time they start phase 3 or pivotal studies, I want to say is about 18 months to 2 years, which is very rapid and pretty much by the time we start pivotal studies, we have to have our commercial bulk finalized, our dosage forms have to be as finalized as possible, and our methods have to be finalized. Because we want to try to avoid any bridging studies down the line. So the time lines are much more compact, whereas on the human health side, from the time a candidate comes into developmental to the time you start phase 3 could be as long as 7 to 8 years. So there is a lot more time there to try to develop your processes and your methods. So.....End of lecture.

CHALLENGES IN DEVELOPMENT OF SUSTAINED RELEASE PARENTERAL FORMULATIONS

Scott A. Brown, DVM, PhD, DACVCP

Slide 1

Challenges in development of sustained release parenteral formulations

Scott A. Brown, DVM, PhD
Senior Director
Preclinical Development

PHARMACIA Animal Health

Slide 4

The Conundrum

- Oral administration is one of the preferred routes of administration
 - dose every day in monogastrics
 - dose every 2-3 days in ruminants (except rumen retention devices)
- Sustained release injectables
 - dose once every 2-5 days (or more)
 - absorption-rate limited
 - high drug residues at injection sites
 - localized residues of varying geometry

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Slide 2

Introduction

- Production agriculture consolidation
- Many effective antibiotics and endectocides
- Convenience driving therapeutic choices
 - reduced animal handling
 - enhanced animal welfare
 - fewer injection sites

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Slide 5

Problem areas for SR injectables

- Manufacturing control
- Pharmacokinetic pitfalls
- Prediction of injection site residues
- Safety of injection site residues
- Injection site residue variability

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Slide 3

Ideal Pharmaceutical Product

- Administered once
- Lifelong therapeutic/disease prevention properties
- Ease of manufacture; shelf stable
- Safe and minimal drug residues in edible tissues

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Slide 6

Manufacturing Control

- Consistency of manufacture is more critical, since formulation governs in vivo profile
 - solid dosage forms
 - geometry
 - amount/consistency of disintegrant
 - compression force
 - surfactant/lubricant
 - injectable dosage forms
 - salt/crystal form
 - viscosity/wettability
 - particle size/surface area of bulk drug

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